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ORIGINAL ARTICLE

Three-dimensional modeling of the umbilical artery Doppler and its applications in preeclampsia assessment: a case-control study

Short title: Three-dimensional modeling applications in preeclampsia

Wisam **Akram**[1], Wassan **Nori**[1,*], Muna Abdul Ghani **Zghair**[2]

[1] Obstetrics and Gynaecology Department, Mustansiriyah University, Baghdad, Iraq.

[2] Radiology Department, Al Yarmouk Teaching Hospital, Mustansiriyah University, Baghdad, Iraq.

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*** Corresponding author:** Wassan **Nori**, Obstetrics and Gynecology Department, Al-Yarmouk Teaching Hospital, Mustansiriyah University, Baghdad, Iraq.

E-mail: Dr.wassan76@uomustansiriyah.edu.iq.

ORCID: 0000-0002-8749-2444.

ABSTRACT

Ultrasound and Doppler indices were implemented to screen high-risk pregnancies as preeclampsia, a unique pregnancy syndrome that imposes many challenges on the mother and her unborn child. Since there is currently no conscience of what parameter is best for screening, this study was designed to examine if a 3-dimensional re-modeling of a 2-dimensional Doppler wave will perform better in PE screening and evaluating its severity.

A case-control study enrolled 90 eligible primigravida's age and body mass index-matched screened and followed till 34 weeks, where they were re-grouped into controls; and preeclampsia (PE) cases (45/90) each. Demographic, biochemical, and hematological parameters were tested; followed by ultrasonic parameters [amniotic fluid index, estimated fetal weight, resistance, and pulsatility index (RI and PI)].

From Doppler strip, 5 heights were taken from a heartbeat for every patient to measure the volume under the surface (VUS) of 3 dimensional modeled Doppler.

VUS was significantly low among PE cases, with strong significant associations; ($P < 0.001$) with biochemical, hematological, and ultrasonic parameters that define PE onset and severity.

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Furthermore, VUS discriminated PE cases at a cut-off value of < 66 unit^3, associated with 93.3%,92%, and P-value<0.001 sensitivity and specificity, respectively.
VUS's strong relations and high discrimination power regarding PE onset and severity make it a recommendable parameter. It is simple and has an easy technique, without extra charge. We recommend incorporating it into anti-natal care services. More studies are warranted to unveil prognostic and other diagnostic applications in practice.

Key words:
Volume under the surface; Doppler, 3-dimensional re-modeling; preeclampsia; screening; severity.

INTRODUCTION

Adverse pregnancy outcomes are becoming a major public health concern. Every day, over 800 women die due to pregnancy-related complications, particularly in high-risk pregnancies like preeclampsia (PE) [1]. Added to the higher maternal-perinatal morbidity and mortality seen in PE women, there is an added long-term health consequence [2].
Preeclampsia is a serious pregnancy-related condition. A consensus among researchers exists about a two-stage developmental model. The first stage ensues subsequent to the faulty implantation of trophoblasts. Abnormal vascular development of the placenta means that the blood flow pattern in those vessels will differ from that in normal normotensive women, thereby inducing a state of hypoxia. In this context, the presence of diminished uterine artery blood flow can be detected using Doppler ultrasound [3]. The onset of symptoms and clinical indicators marks the start of the second stage, which predominantly occurs after the 20th week of gestation. This stage is primarily associated with the release of placental factors into the maternal bloodstream. As a result, the occurrence of systemic inflammation leads to endothelial damage in many organs, which is accompanied by the typical symptoms of PE [4].
Many researchers seek early and accurate screening for PE since there is no current treatment but to end the pregnancy. Biochemical screening has the advantage of being rapid and non-invasive, yet it has low accuracy [5]. For example, soluble fms-like tyrosine kinase-1 [4]
In contrast, ultrasonic screening, 2-dimensional (2D) Doppler indices (including pulsatility index PI, resistance index RI), and flow-mediated dilatation were heavily examined and investigated [6].

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They need repeated follow-up and can have false-positive predictive power, which raises the problem of overdiagnosis of fetal compromise and increases operative intervention [7]. Although there is no consensus on which method is best, the current screening for PE, and in particular that based on maternal history, uterine artery Doppler, and biomarkers, is effective in predicting PE [8].

Briefly, placental blood flow in PE is significantly reduced in the uterine and umbilical arteries, which can be screened and recorded by Doppler studies of those blood vessels. Assessment of this alteration is important in choosing the type of care and the obstetrical decision regarding pregnancy [9].

Doppler waves are primarily two-dimensional plots of blood speed vs. time, and one heartbeat typically has two waves. The first wave represents systolic blood velocity, whereas the smaller second wave represents blood vessel changes during diastole [10].

Many parameters can be determined from peak systolic and diastolic blood velocity changes to assess screening and preeclampsia severity. However, with the advancement of current digital computers and the introduction of new, highly efficient modeling software, new perspectives for more effective screening and assessing preeclampsia severity are emerging [6, 10].

This paper adopted a newer approach by converting the traditional 2-dimensional Doppler strip into a 3-dimensional surface by creating replicas of the original wave projecting along the y-axis, creating a surface on the z-axis; see Fig. 1. Measuring volume under the surface, or (VUS) for this 3-dimensionally modeled Doppler plane corresponding to one heartbeat may result in obtaining a highly useful parameter for better predicting and assessing preeclampsia-associated complications. We believe that VUS may be much more predictive for screening as well as assessment of preeclampsia severity since it has a wider range, or variance, in statistical terms [11].Measuring this volume is simply conducted nowadays by the available online free version of MATLAB software and OCTAVE software [12].

This study aims to verify whether volume under the surface of three-dimensionally modeled Doppler waves (VUS) can be a reliable new novel marker that may be useful in the screening and assessment of preeclampsia severity.

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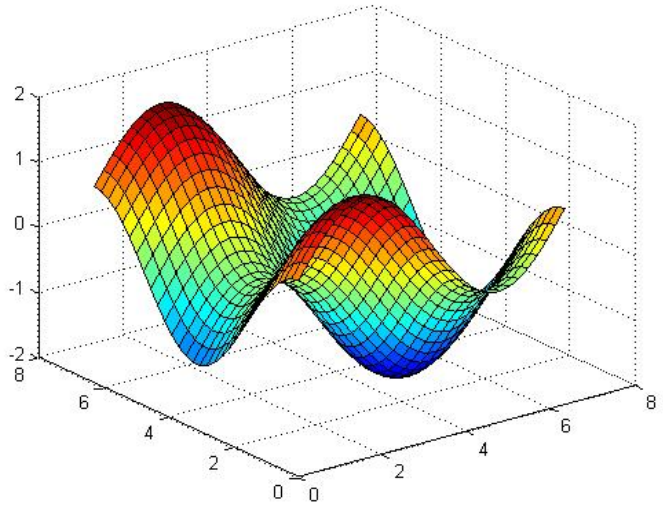

Figure 1. Example showing how the 3 dimensionally modeled Doppler wave looks like.

PATIENTS AND METHODS

An observational case-control study was conducted in Al-Yarmouk Teaching Hospital and took about 14 months to be completed, starting in early January 2021 and ending in March 2022.

Inclusion and exclusion criteria

All women included in this study were singleton primigravida, matched at their age and body mass index (BMI). They had an age range of 18–35 years, and their body mass index was less than 29.9 kg/m2. They should have confirmed dating based on LMP and early dating ultrasonic reports. Participants were sequentially recruited while attending the maternity clinics for routine visits. They were informed about the research plan and aims. The study workflow was conducted in accordance with the Helsinki Declaration.

Pregnant women who agreed to participate were screened and followed for 20 weeks of gestation during the reference period. Starting at 30 weeks of gestation, women were re-grouped into two major study groups: healthy control (45/90) women and study group (PE cases) (45/90).

Both groups were given special preprinted forms and contact information and instructed to consult the hospital at exactly 34 weeks of pregnancy for Doppler assessment as well as laboratory investigations.

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The study group were newly diagnosed PE cases based on the NICE guidelines [13] and had not started any treatment.

Risk group cases, including twins' pregnancy, diabetes, placenta previa, uterine fibroids, chronic inflammatory diseases, asthma, and cases of impending eclampsia or those who needed urgent termination, were all omitted. Those suffering from blood dyscrasia, smokers, those on drugs affecting blood coagulation or vascular resistance like aspirin and corticosteroids, and those with incomplete data were excluded, too.

Study methodological standards: the workflow at 34 weeks of gestation

All eligible pregnant women came at 34 weeks of gestation, where a formal general examination (blood pressure, height, and weight) and an obstetrical examination (uterine fundus height) were done.

To start with, they were all sent for lab investigation after a one-night fast; tests included urinary protein over creatinine ratio, blood urea, serum creatinine, serum fibrinogen level, platelet count, and serum glutamic-oxaloacetic transaminase (SGOT) and glutamic pyruvic transaminase levels (SGPT).

When lab tests were completed, participants were scheduled for ultrasound examination for fetal parameters [amniotic fluid index (AFI) and estimated fetal weight (EFW)]. Additionally, a Doppler study of the umbilical artery was conducted using the transabdominal sector probe 3.5 - 5 MHZ, performed (EDAN Acclarix LX8). Umbilical flow measurements were quantified by measuring at least three consecutive Doppler waveforms. The Doppler angle is aligned with the vessel axis at less than 60°. Subsequently, the resistance and pulsatility index (RI and PI) were recorded by automated machine measurements.

After that, the Doppler operator took a clear 2D strip, which was isolated and frozen. Then one heartbeat is chosen where the speed of blood in Doppler strips is measured at five regions; those are:

The start of systole, peak systolic velocity, end-systolic velocity, peak diastolic velocity, and finally, end-diastolic velocity (see Figs. 2b, 3a) These five measurements were taken for every patient and sent back to be used for the measurement of the volume under the surface (VUS) of a 3-dimensionally modeled Doppler wave.

We feed those 5 readings into a square matrix whose dimension is the same number of readings as shown in (Fig. 2c, Fig. 3b). This matrix can be easily used to create a surface projecting into the z-axis over the x- y plane by interpolating the data in its elements by any mathematical software (MATLAB or OCTAVE) capable of drawing 3-dimensional surfaces from its raw

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elements, with only 3 steps as shown in (Fig.2d and Fig.3c). The concept will be explained in detail in the next sections.
(SGPT).

Patient and public involvement

Iraqi pregnant females at Al-Yarmouk Teaching Hospital / Baghdad; Iraq.

The concept of creating a 3D surface from 2D Doppler strips and measuring VUS

Preliminary concepts

Any 3-dimensional surface function has the following format:
z=f (x,y) by drawing a surface projecting into the z-axis over the x-y plane [14].The type of function applied to the independent variables x and y may be trigonometric, exponential, power, or logarithmic manipulations. Irrespective of the initial type of function, the volume under this surface may be calculated by the general formula given below, which involves complex double integrations. [15];

$$\text{volume}(z,y) := \int_a^b \int_c^d f(x,y)\, dy\, dx$$

Where c and d are the limits of integration with regard to the y-axis, while a and b are the limits of integration with regard to the x-axis. Unfortunately, this method cannot be applied to Doppler strip waves since those waves have no defined equation, nor can they be built. Doppler waves in the umbilical artery change daily from the start of pregnancy till delivery, even in normal pregnancy, making formula building for them virtually impossible. Instead, we will use the matrix-building format described in detail below.

Matrix representation of 3-dimensional surfaces

Matrix is simply a set of numbers arranged in a certain number of rows and columns. The product of the matrix number of rows by columns is called the matrix dimension. In the 3-dimensional surface representation of the Doppler wave, the first row contains the different speeds recorded along one heartbeat calculated from the Doppler strip. Since they are 5 recordings, then there ex

ist 5 columns. While the 2nd,3rd,$4^{th,}$ and 5th rows are the replicas of the recording in the first row(see Fig. 2c and Fig.3b). Accordingly, the matrix dimension is 5 by 5. Fortunately, this matrix form can

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be drawn in 3-D formats by feeding them into MATLAB or OCTAVE. In addition, they can be double integrated to calculate the volume under their surface as shortly as described below in further detail.

Mathematical modulation of the 2-dimensional Doppler strips into the 3-dimensional surface

Creating a surface replicating the Doppler strip's wave is easy to understand. Ordinary Doppler waves are projected into 2-axes: the x-axis represents the time while the y-axis measures the blood speed. The basic idea is to take serial measurements of Doppler height covering one heartbeat plotted on the x-axis and create replicas of those reading along the y-axis, creating a surface on the z-axis. From those readings covering the x and y axis on the surface, a matrix can be built easily and double-integrated with MATLAB or OCTAVE software, as shown in (Fig. 2c and Fig.3b).

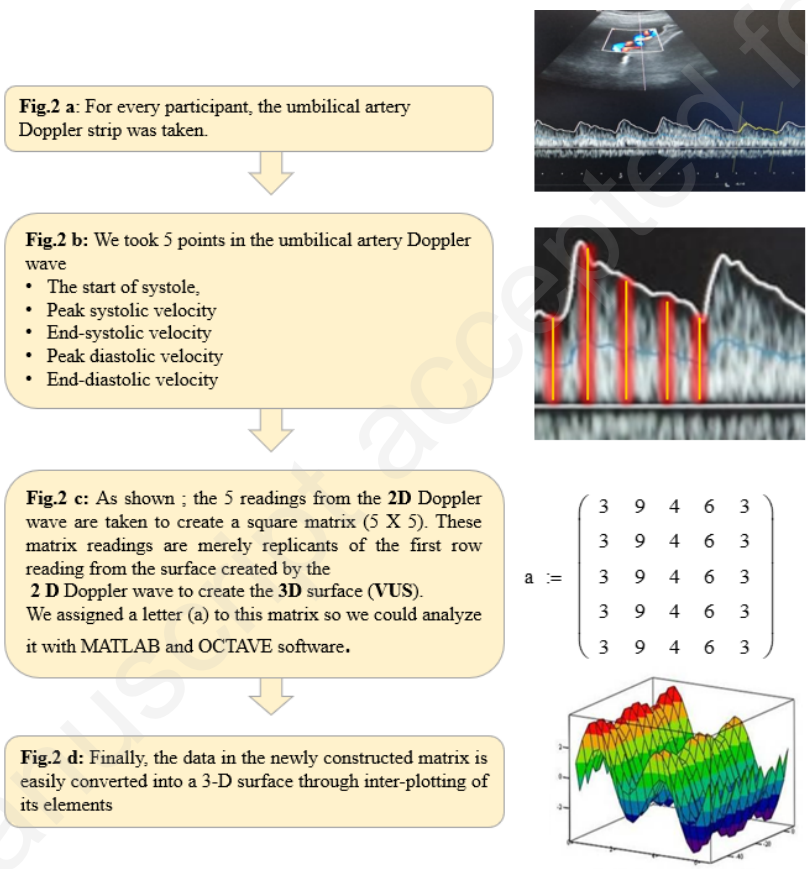

Figure 2. Shows the algorithm for building a matrix and 3-dimensional plot from 5 readings taken from the Doppler strip through the construction of the matrix.

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Calculation of volume under the surface from the matrix by double integration

The obtained 5 readings are first arranged in a square matrix. Since they are 5 readings, the number of rows in the matrix will be 5 or simply 5 replicas. Each number in this matrix corresponding to a certain row or column number is the same reading or value of Doppler height obtained by the sonographer. Then we write the following script directly into the workspace of either MATLAB or OCTAVE software workspace(see Fig.3c), remembering the original data were 3, 9, 6, 4 and 3 successively;

Scriptwriting in MATLAB or OCTAVE software

- a=[3 9 6 4 3 ; 3 9 6 4 3 ; 3 9 6 4 3 ; 3 9 6 4 3 ; 3 9 6 4 3]; ……..…1 enter the matrix into MATLAB first single row
- b=trapz (a) ……..…2 perform the 1st integration
- VUS= trapz (b) ……3 perform the 2nd integration to calculate VUS

The script to measure VUS is simple; although it involves double integrations, it is calculated through 3 simple steps.

1- We enter the readings of the matrix obtained in the previous step in a single line. Two square brackets are used to define the whole matrix, while a semicolon or (;) is inserted between readings in each row, as shown above. Finally, this matrix is randomly assigned to a letter like (a), as shown above.
2- Second, we take the first integral by the built-in function TRAPZ of the above-mentioned matrix, as shown in the script above, and assign to the letter b.
3- Finally, the volume under the surface is measured by the built-in function TRAPZ applied to the result of the previous step, as shown in the third line. In this line, we assigned the output of the function to the letters VUS short of volume under the surface.

This approach is a huge simplification of one of the most complicated concepts in the field of calculus mathematics. With the availability of modern software, we can do it through three steps.

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The screenshot taken for the same steps listed in (Fig.3c) is exactly how they are written in MATLAB software. The volume under the surface is 88 units [3].

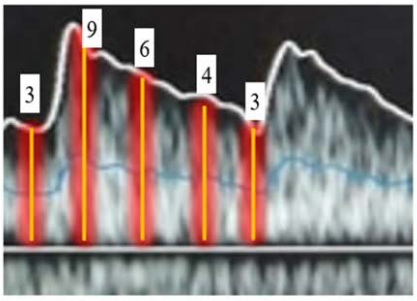

Figure 3a

$$a := \begin{pmatrix} 3 & 9 & 6 & 4 & 3 \\ 3 & 9 & 6 & 4 & 3 \\ 3 & 9 & 6 & 4 & 3 \\ 3 & 9 & 6 & 4 & 3 \\ 3 & 9 & 6 & 4 & 3 \end{pmatrix}$$

Figure 3b

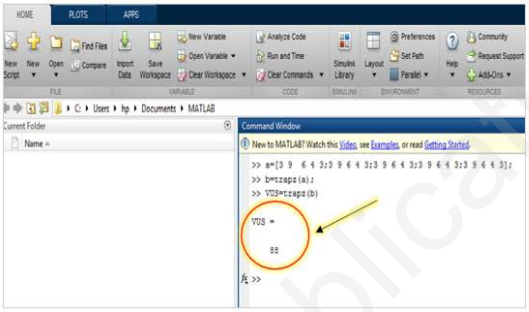

Figure 3c

Figure 3. Shows how the readings made at the ultrasound clinic are converted into the matrix and entered into MATLAB or OCTAVE software to measure volume under the surface or VUS. **3a.** Shows how 5 readings are taken for blood speed height in the strip by the ultrasonographic; **3b:**Demonstrates the 5 X 5 square matrix whose dimensions are the same number of readings. From them, the 3-dimensional created Doppler waves are generated; **3c**: The MATLAB software workspace is shown where measuring the volume under this newly created surface is made via the double integral of the readings in the feed matrix through its built-in function TRAPZ as shown in the red highlighted circle = 88.

The use of the online version of MATLAB and OCTAVE software to VUS

MATLAB software is expensive software widely used in virtually every science branch for conducting highly professional calculations, including biological and pharmaceutical types. The website provides a free basic online version highly compatible with the script mentioned in the current paper. It is available at the following website after registration with an e-mail: https://matlab.mathworks.com/ [16]

On the other hand, another free software is available to conduct the same script used, called OCTAVE software, available in online and downloadable versions. It is completely free of charge and compatible with all MATLAB files. It is available at the following website, which requires a simple registration with an e-mail at the following website;

https://octave-online.net/ [17]

The sample size calculation

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On the basis of the prevalence rate of PE, that is, 7%; which corresponds to a 95% confidence level and a 5% deviation from the general population, it has been calculated that a case group consisting of 45 patients with adequate controls would be sufficient [18].

Statistical analysis

Data normality was checked by the Shapiro-Wilk test. Continuous data were expressed as mean and standard deviation and compared with unpaired t-student tests among the 2 study groups. A series of linear regressions were conducted between VUS, and various variables are taken into account in this study with the measurement of the correlation coefficient and associated P-values. ROC curve was constructed to measure the best cut-off value for VUS between normal pregnant women and preeclamptic women. Medclac software was used to conduct the statistical analyses. On the other hand, the VUS of the Doppler wave was calculated by the online version of MATLAB software and further checked by OCTAVE software, which is freely downloadable from the internet. A P-value of <0.05 was set as significant for all tests.

RESULTS

Ninety participants were sub-grouped into two major groups (controls and PE cases) at 34 weeks of gestation. **Table 1** shows the main demographic criteria of the two study groups with their statistical comparisons.

Table 1. Shows the main demographic characteristics of the two study groups.

variable	Normal Pregnancy (N=45)	Pre-eclampsia (N=45)	P-value
Age(years)	24.89±3.07	25.45±3.50	P = 0.52
BMI (Kg/m2)	28.2 ± 0.37	29.04 ± 0.82	P = 0.94
Systolic BP mm Hg	126.10±7.79	135.87±26.73	P < 0.001
Diastolic BP mm Hg	72.28±7.32	103.87±11.71	P < 0.0001
UPCR mg/mg	0.17±0.04	1.68±0.83	P < 0.001
Serum uric acid mg/dl	4.55±0.51	6.45±1.8	P < 0.001
Blood urea mg/dl	14.35±3.08	19.87±3.03	P < 0.0001
Platelet count/mm^3	274.31±29.04	209.87±30.86	P < 0.0001
Serum Fibrinogen mg/dl	212.71±25.47	193.45±108.66	P < 0.0001

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SGOT IU/L	22.79±8.47	50.82±9.19	P < 0.0001
SGPT IU/L	21.51±5.89	51.32±7.24	P<0.0001
AFI cm	16.37±2.73	7±2.22	P<0.0001
Fetal weight (gm)	2481.89±221.1	1654.94±288.79	P < 0.0001
PI Umbilical Artery	1.00±0.15	1.39±0.12	P < 0.0001
RI Umbilical Artery	0.52±0.014	0.66±0.07	P < 0.0001
VUS Unit^3	77.42±8.64	45.10±8.63	P < 0.0001

BP: blood pressure; UPCR: urinary protein over creatinine ratio; SGOT: serum glutamic-oxaloacetic transaminase; SGPT Serum glutamic pyruvic transaminase; AFI: amniotic fluid index; PI: pulsatility index; RI: resistance index; VUS: volume under the surface.

Table 2. Shows the coefficient of correlation of volume under the surface VUS versus the demographic criteria taken in the study with the associated P-value.

Correlation variables	Correlation Coefficient	P- value
VUS vs Systolic BP	-0.95	P<0.001
VUS vs Diastolic BP	-0.98	P<0.001
VUS vs UPCR	-0.84	P<0.001
VUS vs serum uric acid	-0.82	P<0.001
VUS vs blood urea	-0.86	P<0.001
VUS vs platelet count	0.73	P<0.001
VUS vs serum fibrinogen	0.94	P<0.001
VUS vs SGOT	-0.89	P<0.001
VUS vs SGPT	-0.82	P<0.001
VUS vs AFI	0.79	P<0.001
VUS vs fetal weight (34 weeks)	0.88	P<0.001
VUS vs PI (Umbilical artery)	-0.87	P<0.001
VUS vs RI (Umbilical artery)	-0.93	P<0.001

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VUS: volume under the surface; BP: blood pressure; UPCR: urinary protein over creatinine ratio, SGOT: serum glutamic-oxaloacetic transaminase; SGPT Serum glutamic pyruvic transaminase; AFI: amniotic fluid index; PI: pulsatility index, RI: resistance index.

The blood pressure, protein over creatinine ratio, liver enzymes, and hematological parameters significantly differed among the two study groups. At the end of the **Table**, VUS was significantly lower among PE cases compared to healthy controls. To have better insight regarding VUS's role in assessing preeclampsia, a series of linear regressions in **Table 2** showed the coefficient correlation and associated P-value between VUS as the primary independent variable and various demographic criteria taken in this study used to assess women with preeclampsia. VUS had a strong inverse correlation with systolic and diastolic blood pressure, urinary protein over creatinine ratio (UPCR), serum uric acid, blood urea, and liver enzymes SGOT and SGPT. All the above correlations were statistically significant, with a P-value of <0.001. On the other hand, VUS has a strong direct correlation with platelet counts and serum fibrinogen. In addition, VUS has a strong inverse correlation with resistance and pulsatility indices in the fetal umbilical artery (r = (-0.93, -0.87), P<0.001. Lastly, VUS correlates significantly with amniotic fluid index and fetal weight; r = (0.79, 0.88), P<0.001.

Finally, to assess the predictive capability of VUS in screening for preeclampsia-associated variables, a ROC curve was conducted with an assessment of the associated cut-off value and associated sensitivity and specificity. The VUS equivalent to (<66) unit3 is associated with preeclampsia onset among 93.3% of women within this value range, with an associated specificity of 92%, P-value<0.001. While women whose VUS > 66 units^3 may be more likely to have a normal, uncomplicated pregnancy with well-fetal being, see **Fig. 4.**

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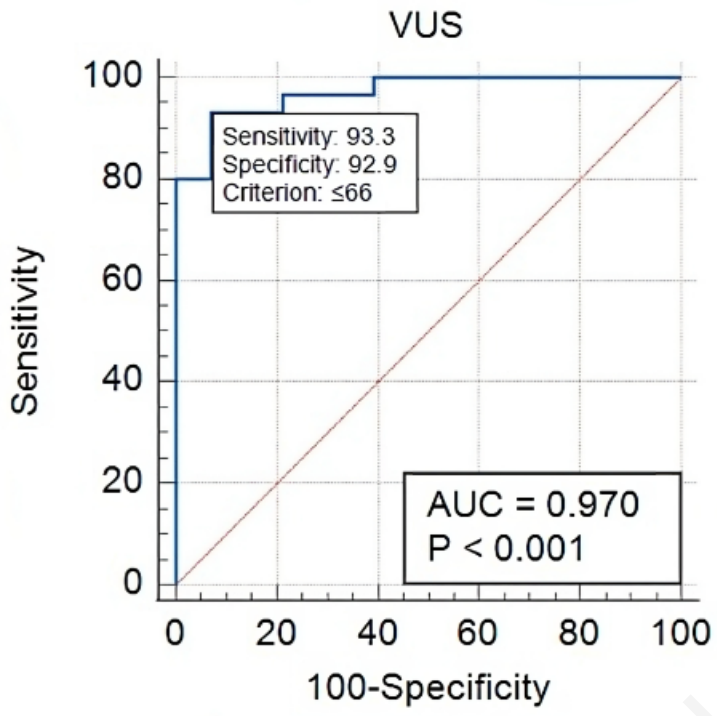

Figure 4: ROC curve showing the cut-off value < 66 unit3 is associated with a sensitivity of 93.3% and specificity of 92.9 %; P value < 0.001.

DISCUSSION

The current study examined the value of 3-dimensional modeling of the umbilical artery Doppler strips, VUS, in preeclampsia. The volume under the surface was found to be significantly lower in PE cases vs. controls. Furthermore, it showed strong and meaningful correlations to all demographic, biochemical, and ultrasonic parameters that define PE onset and severity. The main findings are summarized in **Table 3**.

Preeclampsia is a serious pregnancy condition. Scientists agree on a two-stage theory. Stage I occurs due to faulty trophoblast implantation, which causes placental hypoxia with increased placental resistance to the blood flow coming from the fetal umbilical arteries [19]. To combat the high resistance in PE cases, the placenta secretes many biomarkers to re-direct the blood to the placenta and fetus in stage II of PE [20].

Analysis showed that PE cases had significantly high blood pressure and renal and liver biomarkers. In contrast, platelets, AFI, and EFW were significantly low in PE mothers, in accordance with published literature [21].

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The 3D marker, VUS, had strong and meaningful correlations with all parameters that define PE onset and severity. It was strongly correlated with blood pressure, renal parameters, liver enzymes, and platelet counts. The reason is that the placenta in PE contradicts reduced flow by re-directing the blood to the fetus at the expense of maternal circulation [22]. This caused a systemic inflammatory response(causing decreased platelets) and reduced blood supply to the pregnant main organ, manifested by the classic PE symptoms. Maternal vascular tone will be increased, and renal and liver biomarkers will rise too [23].

In contrast, the AFI and EFW will be reduced due to lower placental perfusion, while RI and PI will increase in response to higher placental resistance, in line with earlier works. Doppler's indices showed a strong correlation to VUS. This suggests that VUS may be a strong predictor of PE-associated complications [24].

The Doppler wave mirrors increased resistance from umbilical arteries by reducing the diastolic and systolic blood speeds in Doppler strip [6].

By re-modeling Doppler wave from the 2D curve to the 3D surface format, naturally, the volume under this created surface will be smaller among PE women compared to normal pregnant women. Accordingly, any maternal or fetal variable linked with PE should have an inverse correlation with VUS of the three modeled Doppler waves, and vice versa is also true.

This was the rationale of this study: creating a new variable with a greater statistical variance or range [25]. Thus, VUS may serve better in screening and assessing PE and its associated complications than the currently used 2D Doppler indices. Indeed, the results obtained in this study support this. The Doppler study has limitations in screening for placental insufficiency, especially in fetal growth restriction [26].

Table 3. Summary of the main study finding regarding VUS and its correlation with the study parameters.

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Parameters	Groups	t-test	P-value	Pearson Correlation	P-value	ROC
Volume under the surface (VUS)	Healthy group(45/90)	77.42±8.64	< 0.0001	VUS was strongly correlated to: Systolic and diastolic BP, UPCR, serum uric acid, blood urea, platelet count, serum fibrinogen, SGOT, SGPT, AFI, fetal weight, PI, and RI	<0.001	At a cut-off value < 66 unit3 VUS was linked with 93.3% sensitivity and 92.9 %; P-value < 0.001 in discriminating PE cases
	Preeclampsia cases(45/90)	45.10±8.63				

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Limitations and Strengths

As with any ultrasonic parameter, it depends on the operator's experience added to his own fetal echocardiography training [27], so intra-observer differences must be acknowledged [28].

Another limitation is that it is a single-center study, in addition to the study design. A longitudinal study would better assess the fluctuations of VUS in accordance with PE severity. Finally, we collected most of our data during COVID-19, which implicated more than one aspect of medical research [29, 30].

The 3D re-modeling of the Doppler wave (VUS was easy to measure by the sonographer, the technique is easily reproducible, and it can be integrated into routine antenatal visits of pregnant moms at no extra charge. VUS showed a significant correlation to maternal and fetal indicators in PE with good discrimination power. The software used was downloadable and free of charge. Moreover, Doppler studies are non-invasive and highly acceptable to pregnant mothers.

In view of the current results, we recommend further studies to explore the association of VUS not only in prediction and evaluation but also in the prognosis of PE, response to treatment, and possibly the implication on the neonatal and maternal outcomes.

Interpretation and comparison with other literature

In fact, there is no consensus regarding the prediction power of umbilical artery PI, and there are demands for standardization of its value. Currently, routine screening of low-risk pregnancies by Doppler is not advisable. It was found that Doppler did not improve the neonatal outcome or prevent fetal demise [31].

As for high-risk pregnancies such as PE and abnormalities in placentation, Doppler was found to have good predictive power. However, its role in diabetic cases and post-term pregnancies is unconfirmed [32].

Studies have discussed that it is the uterine artery PI rather than the umbilical artery PI that could screen for PE and predict its adverse outcome [33, 34, 35].

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Others proposed that PI prediction power should be interpreted with caution. Owing to the high false positive rate, which ranged from 10-70%, especially for late-onset PE [34,36,37].

Malhotra et al . have invented a modified biophysical profile to be added to umbilical artery Doppler indices to improve its prediction ability. They recommended their approach to screen all higher-risk pregnancies even in the presence of normal Doppler studies aiming for better perinatal outcomes [38].

Zarean et al. [39] stressed taking the ratio of middle cerebral artery parameters to the umbilical artery to gain better results. However, Akolekar et al. [40] disagree with their result. Additionally, they discussed how maternal factors like ethnicity, parity, BMI, and gestational age affected the values of PI obtained through Doppler studies.

In fact, the screening of the umbilical artery has not reached the agreed level of prediction ability among all women.

Our study has adopted a completely new approach, which may be more straight forward with a better cost-benefit analysis via the introduction of VUS. We can understand that most physicians are not familiar with using MATLAB. However, the approach adopted, as explained in the method section, is practically easy, reproducible, and accurate.

Since preeclampsia imposes severe complications for the mother and her unborn fetus, appropriate screening and risk assessment are indispensable [32][41,42].

This study has examined and validated VUS's role in PE cases. VUS was reliable in distinguishing pregnant women with PE with 93.3% and 92.9% specificity, a P value < 0.001, and a significant AUC of 0.97. It may guide the clinician in managing PE mothers for more vigorous follow-up and earlier termination of pregnancy. It may affect the mode of termination, whether by labor induction or having a lower threshold for C-section [43].

Being simple, safe, and precise are the main criteria for a screening test in practice. Some may argue that the feasibility of this study may be limited in practice, yet we need only 3 simple steps to measure this volume, which can be done by any doctor on any internet-connected device like mobile, tablet, or computer, as explained in the method section.

In view of the current results, we recommend further studies to explore the association of VUS not only in prediction and evaluation but also in the prognosis of PE, response to treatment, and possibly the implications for neonatal and maternal outcomes.

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CONCLUSIONS

The efficacy of the 3-D VUS as a diagnostic tool in PE cases was evaluated, revealing a statistically significant correlation with biochemical, hematological, and ultrasonic parameters associated with PE. Furthermore, a significant correlation was observed between VUS and 2-D Doppler indices that predicted fetal growth restriction in PE mothers. The high discriminatory efficacy of VUS concerning the onset and severity of PE renders it a valuable parameter. The method is simple, features a user-friendly approach, and does not entail any additional cost. It is recommended that VUS be integrated into the anti-natal care services. Further research is necessary to reveal potential prognostic and diagnostic applications in medical practice.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

WA 1: validation, visualization, statistical analysis, and writing the original draft

W N 2: conceptualization, methodology, project administration, software, supervision, validation, visualization, writing review, and final draft editing.

MAZ 3: data curation, investigations, writing, and literature review.

Funding: Nil.

Study registration: N/A

Disclosure of Interests: None

Ethical Approval: The protocol was approved by the Mustansiriyah ethics committee of Obstetrics and Gynaecology/Iraq on January 9 th /2021, IRB(208).

Informed consent: Written informed consent was provided by all pregnant enrolled following the Declaration of Helsinki and local guidelines.

Data sharing: No.

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REFERENCES

1.Tadese M, Dagne K, Wubetu AD, Abeway S, Bekele A, Misganaw Kebede W, et al. Assessment of the adverse pregnancy outcomes and its associated factors among deliveries at Debre Berhan Comprehensive Specialized Hospital, Northeast Ethiopia. PLoS One. 2022 ;17(7):e0271287. doi: 10.1371/journal.pone.0271287.

2. Roberti R, Rocca M, Iannone LF, Gasparini S, Pascarella A, Neri S, Cianci V, Bilo L, Russo E, Quaresima P, Aguglia U, Di Carlo C, Ferlazzo E. Status epilepticus in pregnancy: a literature review and a protocol proposal. Expert Rev Neurother. 2022;22(4):301-312. doi: 10.1080/14737175.2022.2057224.

3.Nori W, Shallal F, Zghair MAG. Aspirin effect on Mid luteal Phase Doppler Indices in Patients with Recurrent Pregnancy Loss. Int J Pharm Res 2020;12:2929-34. DOI: 10.31838/ijpr/2020.12.03.413

4. Laganà AS, Favilli A, Triolo O, Granese R, Gerli S. Early serum markers of preeclampsia: are we stepping forward? J Matern Fetal Neonatal Med. 2016;29(18):3019-23. doi: 10.3109/14767058.2015.1113522.

5. Huang T, Bedford HM, Rashid S, Rasasakaram E, Priston M, Mak-Tam E, et al . Modified multiple marker aneuploidy screening as a primary screening test for preeclampsia. BMC Pregnancy Childbirth. 2022;22(1):190. doi: 10.1186/s12884-022-04514-4.

6.Farid Fahim Hassan S, Zakaria AE, Saeed Faraj S. Value of 3-d USS of placental volume, uterine and umbilical artery Doppler in prediction of preeclampsia. Al Azhar Med J.2021;50(3):1945-58.

7.Gana N, Sarno M, Vieira N, Wright A, Charakida M, Nicolaides KH. Ophthalmic artery Doppler at 11–13 weeks' gestation in prediction of preeclampsia. Ultrasound Obstet Gynecol.2022;59(6):731-6.

Manuscript accepted for publication

8. O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, Nicolaides KH. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. Am J Obstet Gynecol. 2016;214(1):103.e1-103.e12. doi: 10.1016/j.ajog.2015.08.034.

9.de Freitas Leite J, Lobo GA, Nowak PM, Antunes IR, Júnior EA, da Silva Pares DB. Prediction of preeclampsia in the first trimester of pregnancy using maternal characteristics, mean arterial pressure, and uterine artery Doppler data in a Brazilian population. Obstet Gynecol Sci. 2019 ;62(6):391-6.

10.Wu C, Huang C. Blood flow imaging of high frame rate two-dimensional vector in cardiovascular ultrasound detection. IET Image Processing. 2020;14(13):3014-20.

11. Chen L, Pi Y, Chang K, Luo S, Peng Z, Chen M, et al. Screening models combining maternal characteristics and multiple markers for the early prediction of preeclampsia in pregnancy: a nested case-control study. J Obstet Gynaecol. 2022 ; 42(6):1889-1896.
doi: 10.1080/01443615.2022.2054675.

12. Ren R, Sun XE, Hu L. A new method for hosting and sharing MATLAB Web App. Sci Rep. 2022 ;12(1):21645. doi: 10.1038/s41598-022-26165-3.

13.Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. Bmj. 2019;366.

14.Corke P, Jachimczyk W, Pillat R. Image formation. InRobotics, Vision and Control: Fundamental Algorithms in MATLAB® 2023 (pp. 543-591). Cham: Springer International Publishing.

15.Thomas GB. Thomas's Calculus, Multivariable, 12th ed. Pearson Education; 2009.

16. https://matlab.mathworks.com/ accessed on 20/4/2023
17. https://octave-online.net/ accessed on 20/4/2023.

18. Wang X, Ji X. Sample Size Estimation in Clinical Research: From Randomized Controlled Trials to Observational Studies. Chest. 2020;158(1S):S12-S20. doi: 10.1016/j.chest.2020.03.010.

Manuscript accepted for publication

19. Staff AC. The two-stage placental model of preeclampsia: An update. J Reprod Immunol. 2019 ;134-135:1-10. doi: 10.1016/j.jri.2019.07.004.
20.Harmon AC, Cornelius DC, Amaral LM, Faulkner JL, Cunningham MW Jr, Wallace K, et al. The role of inflammation in the pathology of preeclampsia. Clin Sci (Lond). 2016;130(6):409-19. doi: 10.1042/CS20150702.

21.Tomimatsu T, Mimura K, Matsuzaki S, Endo M, Kumasawa K, Kimura T. Preeclampsia: Maternal Systemic Vascular Disorder Caused by Generalized Endothelial Dysfunction Due to Placental Antiangiogenic Factors. Int J Mol Sci. 2019;20(17):4246. doi: 10.3390/ijms20174246

22. Ives CW, Sinkey R, Rajapreyar I, Tita ATN, Oparil S. Preeclampsia-Pathophysiology and Clinical Presentations: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020 ;76(14):1690-1702. doi: 10.1016/j.jacc.2020.08.014.

23. Tian Y, Yang X. A Review of Roles of Uterine Artery Doppler in Pregnancy Complications. Front Med (Lausanne). 2022;9:813343. doi: 10.3389/fmed.2022.813343.

24.Nori W, Hamed RM, Roomi AB, Akram W. Alpha-1antitrypsin in preeclampsia; from a clinical perspective. J Pak Med Assoc. 2021;71(Suppl 8)(12):S53-S56.

25.Bhorat I. Preeclampsia and the foetus: a cardiovascular perspective. Cardiovasc J Afr. 2018;29(6):387-393. doi: 10.5830/CVJA-2017-039.

26.Broady A, Zalud I. Guidelines for the Doppler Assessment of the Umbilical and Middle Cerebral Arteries in Obstetrics. Donald School J Ultrasound Obstet Gynecol 2016;10(4):418-421.
27.Quaresima P, Fesslova V, Farina A, Kagan KO, Candiani M, Morelli M, Crispi F, Cavoretto PI. How to do a fetal cardiac scan. Arch Gynecol Obstet. 2023;307(4):1269-1276. doi: 10.1007/s00404-023-06951-8.
28. Lyu S, Zhang Y, Zhang M, Jiang M, Yu J, Zhu J, et al . Ultrasound-based radiomics in the diagnosis of carpal tunnel syndrome: The influence of regions of interest delineation method on mode. J Clin Ultrasound. 2023;51(3):498-506. doi: 10.1002/jcu.23387.

Manuscript accepted for publication

29. Nori W, Ghani Zghair MA. Omicron targets upper airways in pediatrics, elderly and unvaccinated population. World J Clin Cases. 2022 ;10(32):12062-12065.
doi: 10.12998/wjcc.v10.i32.12062.

30. Dellino M, Vimercati A, D'Amato A, Damiani GR, Laganà AS, Cicinelli E, et al. "GONE WITH THE WIND": The Transitory Effects of COVID-19 on the Gynecological System. J Pers Med. 2023;13(2):312. doi: 10.3390/jpm13020312.

31. Figueira CO, Surita FG, Dertkigil MS, Pereira SL, Bennini JR Jr, Morais SS, et al . Fetal Hemodynamic Parameters in Low Risk Pregnancies: Doppler Velocimetry of Uterine, Umbilical, and Middle Cerebral Artery. ScientificWorldJournal. 2016;2016:1693704. doi: 10.1155/2016/1693704.

32. Alfirevic Z, Stampalija T, Dowswell T. Fetal and umbilical Doppler ultrasound in high-risk pregnancies. Cochrane Database Syst Rev. 2017;6(6):CD007529. doi: 10.1002/14651858.CD007529.pub4.

33. Adekanmi AJ, Roberts A, Akinmoladun JA, Adeyinka AO. Uterine and umbilical artery doppler in women with preeclampsia and their pregnancy outcomes. Niger Postgrad Med J. 2019 ;26(2):106-112. doi: 10.4103/npmj.npmj_161_18.

34. Shen G, Huang Y, Jiang L, Gu J, Wang Y, Hu B. Ultrasound prediction of abnormal infant development in hypertensive pregnant women in the second and third trimester. Sci Rep. 2017 ;7:40429. doi: 10.1038/srep40429.

35.Adekanmi A, Adeyinka A, Roberts A. Comparative Study of Uterine and Umbilical Artery Doppler and Pregnancy Risk Status in Predicting Adverse Pregnancy Outcome. Trop J Obstet Gynaecol. 2021;38(1):61-71.

36. Llurba E, Carreras E, Gratacós E, Juan M, Astor J, Vives A, *et al* . Maternal history and uterine artery Doppler in the assessment of risk for development of early- and late-onset preeclampsia and intrauterine growth restriction. Obstet Gynecol Int. 2009;2009:275613. doi: 10.1155/2009/275613.

Manuscript accepted for publication

37. Papageorghiou AT, Yu CK, Erasmus IE, Cuckle HS, Nicolaides KH. Assessment of risk for the development of preeclampsia by maternal characteristics and uterine artery Doppler. BJOG. 2005;112(6):703-9. doi: 10.1111/j.1471-0528.2005.00519.x.

38.Malhotra K, Kumari A, Anand HP. Comparison of modified biophysical profile and Doppler ultrasound in prediction of perinatal outcome in high-risk pregnancies. Int J Reprod Contracept Obstet Gynecol. 2020;9(7):2808-13.

39. Zarean E, Azami N, Shahshahan Z. Predictive Value of Middle Cerebral Artery to Umbilical Artery Pulsatility Index Ratio for Neonatal Outcomes in Hypertensive Disorders of Pregnancy. Adv Biomed Res. 2022 ;11:46. doi: 10.4103/abr.abr_93_20.

40.Yousefi M, Khedmat L, Akbari N, Kashanian M, Moradi Lakeh M. The adherence adequacy to antenatal care in alleviating the adverse maternal and neonatal outcomes of iranian pregnant women: A retrospective-prospective study. Ital J Gynaecol Obstet. 2020;32(2):107-18. doi: 10.36129/jog.32.02.03.

41.Nori W, Hussein ZA, Salman AF, H. Hameed B. The capacity of RDW and platelet indices in defining pre-eclampsia severity: a case-control study. Ital J Gynaecol Obstet. 2023;35(2): 229-237. DOI: 10.36129/jog.2022.73

42. Akolekar R, Sarno L, Wright A, Wright D, Nicolaides KH. Fetal middle cerebral artery and umbilical artery pulsatility index: effects of maternal characteristics and medical history. Ultrasound Obstet Gynecol. 2015;45(4):402-8. doi: 10.1002/uog.14824.

43. Roberts JM, King TL, Barton JR, Beck S, Bernstein IM, Buck TE, *et al* . Care plan for individuals at risk for preeclampsia: shared approach to education, strategies for prevention, surveillance, and follow-up. Am J Obstet Gynecol. 2023:S0002-9378(23)00260-0. doi: 10.1016/j.ajog.2023.04.023.

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