Doppler Changes in Pre-Eclampsia

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Abstract

Background: Preeclampsia is a multisystem disorder of pregnancy defined by the combination of new-onset hypertension and proteinuria that contribute substantially to perinatal morbidity and mortality worldwide.

Aim of Study: This study was sought to use Doppler ultrasound to assess the hemodynamic changes in the uterine, umbilical, and middle cerebral arteries, among pregnant women with and without Preeclampsia.

Patients and Methods: A prospective Observational study of pregnant women who recruited from Department of Obstetrics and Gynecology, Aswan University Hospitals during September 2019 until March 2020, and may be extended if needed.

Results: There is statistically significant difference between groups as regard to umbilical artery (RI and abnormality), middle cerebral artery (PI, RI and abnormality) and uterine artery (PI, RI, abnormality and notch) but there is no statistically significant difference between groups as regard to umbilical artery PI (*p*-value=0.117).

Conclusion: This study demonstrated that Doppler US can reveal the underlying hemodynamic repercussion in the maternal-fetal circulation and thus can be used to determine the proper level of antenatal care in pregnant women. Umbilical artery and Middle cerebral arteries indices were more altered in Preeclampsia.

Key Words: Doppler ultrasound – Maternal – Fetal circulation – Mortality – Preeclampsia – Pregnancy.

Introduction

PREECLAMPSIA is a multisystem disorder of pregnancy defined by the combination of newonset hypertension and proteinuria that contribute substantially to perinatal morbidity and mortality worldwide. Pre-eclampsia complicates 2 to 8% of all pregnancies in the world. The prevalence of hypertensive diseases of pregnancy in Egypt (4.2%) had pregnancy induced hypertension, (3.8%) had preeclampsia and eclampsia was (0.3%) [1]. It is associated with hypertension and proteinuria existing after the 20th week of pregnancy. Many risk factors such as primigravida, younger age and twin pregnancy have been identified. The main consequence of placental ischemia is the generalized endothelial dysfunction, which is responsible for clinical symptoms and complications (e.g. eclampsia, placental abruption and hemolysis, elevated liver enzymes, and low platelets syndrome) [2].

Mild preeclampsia is defined as the presence of hypertension (BP >140/90mm Hg) on 2 occasions, at least 6 hours apart. Proteinuria is defined as the presence of greater than or equal to 1+protein on random dipstick or at least 300mg of protein in a 24-hour urine collection. Some investigators and clinicians have accepted a urine protein-creatinine ratio of at least 0.3 as a criterion for proteinuria, but the American College of Obstetricians and Gynecologists (ACOG) has not yet incorporated this in their definition [3].

The use of Doppler ultrasound in pregnancy to evaluate the uterine, middle cerebral and umbilical arteries is an important clinical tool in detecting obstetric complications resulting from uteroplacental insufficiency, which may increase the risk of an adverse effect on both the mother and the fetus during pregnancy, labor, and delivery [4].

Disease entities related to uteroplacental deficiency, majorly from hemorrhage (39%) and maternal hypertensive (9.1%) disorders, have been observed to account for the largest proportion of maternal death in developing countries [4].

During pregnancy, there is modification of the vascular structure within the uterus leading to the development of neovascularization within the placenta and the fetus including redistribution of blood

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flow and alteration in circulating blood volume [5]. Hypertensive disorders in pregnancy lead to impairment of this normal physiological vascular modification resulting in abnormal hemodynamics and obstetric complications of impaired placentation. These complications are fetal growth restriction [intrauterine growth restriction (IUGR)], preeclampsia, intrauterine death, and placental abruption [5].

The correlation between elevated uterine artery impedance assessed by uterine artery Doppler (UAD) velocimetry and a high risk of pregnancyinduced-hypertension/preeclampsia and/or fetal growth restriction (FGR) first demonstrated in clinical studies at mid-second trimester when the placentation process has ended [6].

By using Doppler in the early detection of preeclampsia and its fetal complication namely growth restriction we can arrange the management decisions and monitoring strategy for preeclampsia [⁷].

Patients and Methods

A prospective Observational study of pregnant women who recruited from Department of Obstetrics and Gynecology, Aswan University Hospitals during September 2019 until March 2020, and may be extended if needed. The hospital operates Antenatal clinics six hours every day except Friday.

Aswan University Hospitals is the only hospital in Aswan which receives patients from all over the governorate and the surrounding governorates, since its transformation to a university hospital.

Inclusion criteria: Pregnant women with; BP >140/90mm Hg, Singleton pregnancy, and who will accept the study protocol.

Exclusion criteria: Discrepancy with any of the inclusion criteria and tructural anomaly of the baby.

Sample size: Sample size was 90 patients in the 3rd trimester. Cases divided into 3 groups as follow: Group A: 30 matched non-preeclampsia (non-PE) pregnant women will act as control. 60 confirmed diagnosis of PE according to the guidelines of the International Society for the Study of Hypertension in Pregnancy divided into: (Brown et al., 2001; Azad Saleem Hassan, 2018). Group B: 30 cases with mild PE. Group C: 30 cases with sever PE. Study Instruments:

- All patients in this study subjected to the following:
 - I- History taking:
- a- Personal (age, duration of marriage, special habits).
- b- Menstrual: LMP, Regularity of the cycle (had three regular periods before the last one), length of the cycle and amount of flow (LMP) normal in duration and amount of flow, breast feeding at the time of conception and had not used oral contraceptive pills in the three months proceeded the pregnancy or depot injectable contraception for 6-8 months before the LMP.
- c- Obstetric (parity, mode of delivery, fetal outcome).
- d- Presenthistory of any medical or obstetric problems.
- e- Past history.
- f- Contraceptive history.
- g- Familyhistory.
- II- *Clinical examination:* General and obstetric examination.

III- Investigational studies: Laboratory investigation: Urine analysis by dipstick and blood sample taken from the patient for laboratory investigations in the form of CBC, coagulation profile, liver function tests and kidney function tests.

IV- Ultrasound study: Ultrasound done for all cases including fetal biometry, placental morphology assessment and 2D Doppler ultrasound for umbilical artery (RI&PI). Ultrasound scheduled and undertaken between 11 0/7 and 13 6/7 weeks by measuring crown-lump length (CRL) and 3D sweeps of the entire placenta acquired by ultrasound equipment equipped with a 4 to 8 MHz transducer. Identical pre-established instrument power settings used in all cases.

Doppler study:

Uterine artery: Afterward, ultrasound Doppler examination performed for all cases for the uterine arteries.

Color Doppler used to identify the uterine artery at the level of the cervicocorporeal junction. Measurements taken at the point before the uterine artery branches into the accurate arteries. Once it had been ensured that the angle of insonation less than 30°, the pulsed Doppler gate placed over the whole width of the vessel. The pulsatility index PI of the right and left uterine arteries measured and the mean PI calculated by this equation:

Mean PI = Right PI + Left PI

Moreover, the presence or absence of a bilateral early diastolic notch also noted. All these data introduced into a computer database.

Umbilical artery (UA): The patients placed in a semi recumbent position with left lateral tilt, and then the uterine contents quickly scanned with real time ultrasound in order to select an area of the amniotic cavity with several loops of umbilical cord. Using pulsed wave Doppler, the characteristic sound and shape of the umbilical artery waveform demonstrated and identified. When the screen showed several waveforms of similar height, the image frozen and the peak systolic frequency, end diastolic frequency, resistance index estimated.

Middle cerebral artery (MCA): The standard plane for measuring the biparietal diameter is visualized. This plane includes the thalamus and the cavum septi pellucidi, the color flow mapping function then superimposed and the middle cerebral artery can be seen pulsating at the level of the insula.

Follow-up of the cases: Monthly visit till the end of the second trimester. Then, fortnightly till the end of the 36th week, then, weekly until delivery.

Ethical consideration: Agreement for this study will obtain from the hospital's ethical committee; in addition, informed consent will obtain from pregnant women after adequate provision of information regarding the study requirements, purpose and risks.

Statistical analysis: Statistical correlation between the introduced database in the first visit (blood pressure values, platelets count, urea, creatinine, body weight, body height and body mass index), and the development of pre-eclampsia during the follow-up visits.

Results

A prospective observational study of pregnant women who recruited from Department of Obstetrics and Gynecology, Aswan University Hospitals included 90 patients in the 3rd trimester. Cases divided into 3 groups as follow: Group A: 30 matched non-preec lamp sia (non-PE) pregnant women as a control. Group B: 30 cases with mild PE. Group C: 30 cases with sever PE. There is no statistically significant difference between groups as regard to maternal age, gestational age and parity Table (1).

There is no statistically significant difference between groups as regard to placental site, thickness and maturation but there is statistically significant difference between groups as regard to complication (p-value=0.032) Table (2).

There is statistically significant difference between groups as regard to umbilical artery (RI and abnormality), middle cerebral artery (PI, RI and abnormality) and uterine artery (PI, RI, abnormality and notch) but there is no statistically significant difference between groups as regard to umbilical artery PI (*p*-value=0.117) Table (3).

Receiver operating curve (ROC) was used to determine the cutoff values of Umbilical Artery RI, Uterine RI, and Middle cerebral RI as predictors of PE. Our ROC results revealed that Umbilical Artery RI, and Uterine RI, cutoff values are higher than 61 and 53 and Middle cerebral RI cutoff value is lower than 86 and the area under the ROC curve is equal to 0.669, 0.840, and 0.863 which indicating that they are fair predictors for PE. The sensitivity values of Umbilical Artery RI, Uterine RI, and Middle cerebral RI were 81.0, 80.6, and 87.5 respectively and the specificity values were 73.3, 60.0, and 73.3 respectively Table (4), Figs. (1,2).

Table (1): Comparison between groups according to demographic data.

	Control (N=30)	Mild (N=30)	Sever PE (N=30)	<i>p</i> -value
Maternal age (years): - Mean ± SD - (Range)	25.40±4.88 (18-39)	26.63±4.85 (20-41)	28.23±3.83 (18-37)	Fp=0.059
Gestational age (weeks): - Mean ± SD - (Range)	32.10±3.20 (25-37)	33.87±2.86 (27-38)	33.07±3.05 (26-38)	Fp=0.085
Parity: - Primigravida N (%) - Multigravida N (%)	14 (46.7) 16 (53.3)	20 (66.7) 10 (33.3)	18 (60) 12 (30)	X2p=0.279

 χ^2 : Chi square test.

F : ANOVA test.

p: p-value for comparing between the studied groups.

*: Statistically significant at p0.05.

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	Control (N=30)	Mild (N=30)	Sever PE (N=30)	<i>p</i> -value	Post Hoc Test
Site:					
FundalN (%)	28 (93.3)	29 (96.7)	28 (93.3)	$\xi^2 p = 0.809$	
PreviaN (%)	2 (6.7)	1 (3.3)	2 (6.7)	5 4	
Maturation:					
Grade 0 N (%)	6 (20)	4 (13.3)	4 (13.3)	$\xi^2 p = 0.836$	
Grade 1N (%)	11 (36.7)	7 (23.3)	9 (30)	5 I	
Grade 2N (%)	11(36.7)	15 (50)	14 (46.7)		
Grade 3N (%)	2 (6.7)	4 (13.3)	3 (10)		
Complication:					<i>p</i> 1=1.00
Yes N (%)	1 (3.3)	1 (3.3)	6 (20)	$\xi^2 p = 0.032^*$	$p_{2=0.044*}$
No N (%)	29 (96.7)	29 (96.7)	24 (80)	5 P	p3=0.044*
Placental thickness	33.50±3.45	.35.23±2.64	34.38±2.81	Fp=0.087	

Table (2): Co	mparison of	placenta	characteristics	between	groups.
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 ξ^2 : Chi square test. F : F for ANOVA test, pairwise comparison bet. each 2 groups was done using Post Hoc Test, (Tukey).

p : p-value for comparing between the studied groups. p_1 : p-value for comparing between control and mild. p_2 : p-value for comparing between control and severe.

 p_{3} : *p*-value for comparing between mild and severe. : Statistically significant at *p*0.05.

Table (3):	Comparison	of Dopple	er data	between	groups.
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	Control (N=30)	Mild PE (N=30)	Sever PE (N=30)	<i>p</i> -value	Post Hoc Test
Umbilical Artery: - PI Mean ± SD - RI Mean ± SD	0.91±0.10 0.58±0.47	0.97±0.21 0.60±0.84	1.07±0.27 0.68±0.12	$F_{p=0.117}$ $F_{p=0.002*}$	p 1=0.25 p 2=0.001 * p 3=0.096
- Abnormality N (%)	2 (6.7)	5 (16.7)	11 (36.7)	ξ ² p=0.013*	p 1=0.228 p 2=0.005* p 3=0.080
- PI Mean ± SD	1.41±0.25	1.28±0.14	1.24±0.15	Fp=0.031 *	p 1=0.023* p2=0.339 p3=0.414
- RI Mean \pm SD	0.88±0.16	0.79±0.82	0.72±0.88	Fp=0.001 *	p 1=0.005* p 2=0.001 * p 3=0.048*
- Abnormality N (%)	1 (3.3)	3 (10)	9 (30)	ξ2 <i>p</i> =0.009*	p 1=0.301 p 2=0.006* p 3=0.053
PI Mean ± SD	0.76±0.11	1.45±0.26	1.58±0.27	Fp=0.001 *	p 1=0.001 * p 2=0.001 * p 3=0.083
RI Mean ± SD	0.50±0.57	0.57±0.65	0.63±0.94	Fp=0.001 *	p 1=0.002* p 2=0.001 * p 3=0.007*
Abnormality N (%)	1 (3.3)	5 (16.7)	15 (50)	ξ ² p=0.001 *	p 1=0.085 p 2=0.001 * p 3=0.006*
Notch N (%)	0 (0)	3 (10)	14 (46.7)	$\xi^2 p=0.001 *$	p 1=0.020* p 2=0.001 * p 3=0.012*

p: p-value for comparing between the studied groups. p_1 : p-value for comparing between control and mild. p_2 : p-value for comparing between control and severe. p_3 : p-value for comparing between mild and severe. : Statistically significant at p0.05.

 $[\]xi^2$: Chi square test. F : F for ANOVA test, pairwise comparison bet. each 2 groups was done using Post Hoc Test, (Tukey).

Table (4): Umbilical Artery RI, Uterine RI, and Middle cerebral RI as predictors of PE.

Test Result Variable (s)	Cut off*	AUC	<i>p</i> -value	95%	C.I	Sensitivity	Specificity
Umbilical Artery RI	6	0.669	0.009*	0.557	0.780	81.0	73.3
Uterine RI	53	0.840	0.000*	0.756	0.924	80.6	60.0
Middle cerebral RI	86	0.836	0.000*	0.732	0.940	87.5	73.3

AUC : Area Under a Curve.

CI

p-value : Probability value. : Confidence Intervals. * : Statistically significant at p0.05.

#: Cut off was choose according to Youden index.



Fig. (1): ROC curve of Umbilical Artery RI, and Uterine RI.



Fig. (3): Persistent end diastolic notch in uterin artery in late 2nd

Discussion

Preeclampsia is a multisystem disorder of pregnancy defined by the combination of new-onset hypertension and proteinuria that contribute substantially to perinatal morbidity and mortality worldwide. Pre-eclampsia complicates 2 to 8% of all pregnancies in the world. The prevalence of hypertensive diseases of pregnancy in Egypt (4.2%)had pregnancy induced hypertension, (3.8%) had preeclampsia and eclampsia was (0.3%) [1].



Fig. (2): ROC curve of Middle cerebral RI.



Fig. (4): Indices of Middles cerebral artery in third trimester Impaired.

The current study shows statistically significant difference between groups according to blood pressure and headache but there is no statistically significant difference between groups as regard to blurring of vision (*p*-value=0.053).

Our study showed no statistically significant difference between groups as regard to placental site, thickness and maturation but there is statistically significant difference between groups as regard to complication (*p*-value=0.032).

In match with our finidings Thompson et al., [8] found no correlation between a thick placenta and poor obstetrical outcome, apart from a mild association with severe preeclampsia.

Vachon-Marceau et al., [9] carried out a study aimed to estimate the association between firsttrimester maximum placental thickness and the subsequent risk of preeclampsia and/or the delivery of small-for-gestational-age (SGA) neonate.

They found that pregnancies developed preeclampsia (n=20) tended to have greater placental thickness (median: 1.10 MoM; IQ: 0.93-1.25 vs 0.97 MoM; IQ: 0.84-1.14; p=0.06) with values >1.2 MoM significantly increasing the risk for preeclampsia (relative risk: 3.6; 95% CI: 1.5-8.6, p<0.01). Pregnancies complicated by both SGA and preeclampsia (n=5) had similar placental thickness in the first-trimester in comparison with uncomplicated pregnancies (median: 1.03 MoM; IQ: 0.89-1.42 vs 0.98 MoM; IQ: 0.84-1.14; p=0.33).

This study concluded that First-trimester placental thickness diverges in pregnancies at risk of preeclampsia (increased) or SGA (decreased), but remains within normal values in pregnancies at risk of both conditions, suggesting that the underlying pathologies have some opposing effects on early placental growth. The current findings should be validated in a larger cohort.

Krielessi et al., [10] carried out a study on 55 singleton pregnancies complicated by mild hypertension and compared to 55 pregnancies complicated by severe hypertension. The aim of this study was to investigate the extent of placental lesions associated with blood pressure (BP) levels in pregnancies complicated by hypertension.

Our data analysis revealed a statistically significant difference between groups as regard to umbilical artery (RI and abnormality), middle cerebral artery (PI, RI and abnormality) and uterine artery (PI, RI, abnormality and notch) but there is no statistically significant difference between groups as regard to umbilical artery PI (*p*-value=0.117).

Hassan and Saeed, [11] conducted a study to assess the hemodynamic changes in pregnant women with and without PE, using Doppler ultrasound of the uterine, the umbilical, and the middle cerebral arteries. Forty pregnant women aged 19-40 years old, diagnosed with PE, were recruited from the outpatient gynecology clinic into a case-control study. Their Doppler ultrasound hemodynamic assessment of the uterine artery and its early diastolic notching, the middle cerebral artery, and the umbilical artery was compared to that of 60 matched control non-preeclampsia (non-PE) pregnant women aged 19-40 years old.

In agreement with our results, The principal features of PE diagnosis (arterial blood pressure) were significantly different for patients with PE, compared to non-PE women.

The authors reported a statistically significant difference between groups as regard to the overall abnormalities found by Doppler US in PE patients compared to non-PE women.

The proportions of patients with uterine artery, umbilical artery, and middle cerebral artery Doppler ultrasound abnormalities were 77.5%, 62.5%, and 37.5% in the PE group, compared to nil, 8.3%, and 11.7% in the non-PE women, respectively. Similarly, mean resistance index of each artery and proportions of notch parameters of the uterine artery showed significant differences between PE and non-PE patients (p<0.001).

Hassan and Saeed, [11] stated that Doppler ultrasound assessment in pregnant women of the uterine, the umbilical, and the middle cerebral arteries can be used to determine hemodynamic dysfunction associated with PE.

Fetal Doppler Ultrasound findings in Preeclamptic Women attending Antenatal Services at Muhimbili National Hospital by Mussa Ally, [12]. A Cross sectional hospital based study was conducted from July 2016 to December 2016 involving 143 pregnant women at MNH.

Ally, 2017 shows that there were significant abnormal resistive and pulsatility indices in Umbilical artery PI 8 (36.4%), *p*-value 0.000 1, RI 7 (31.8%) p-value 0.0001, Middle cerebral artery RI 12 (54.5%) *p*-value 0.036 and Middle cerebral and umbilical arteries PI 6 (27.3%) *p*-value 0.0001. Middle cerebral and umbilical arteries RI 7 (31.8%), *p*-value 0.0001 [12].

Mallikarjunappa et al., [13] reported a significant association of preeclampsia and abnormalities of Doppler velocity waveforms in the umbilical, the uterine, and the middle cerebral arteries.

In Lopez-Mendez et al., [14] study, as individual measurements, abnormal RI from umbilical artery, and altered PI from umbilical and middle cerebral arteries, were associated to PE; however, considering all the parameters reviewed in these arteries, the general results for each vessel did not show a difference between groups, suggesting that these individual parameters, but not the general Doppler US for these arteries, could be considered as indicators to evaluate the specific PE vascular alterations.

In contrast, Lopez-Mendez et al., [14] did not find differences in these parameters among the study groups. they observed no significant difference in the uterine arteries' PI and RI, but reported a significant difference in the umbilical artery PI and RI between HRP women with PE and those without PE.

It could be because the reference values considered in previous studies consisted of standardized measures for each population, and the abnormality limits of these values may differ between populations.

In a longitudinal cohort study by Adekanmi et al., [15] a high-risk singleton pregnant women enroled and had uterine and umbilical artery Doppler sonography at 22-24 weeks and 32-34 weeks gestation and had their delivery outcomes documented by the obstetrician and gynaecologist.

They reported that the uterine artery PI was significantly associated with PE. A unit increase in uterine PI in high-risk pregnancies, increases the odd of PE by 37.37 times (95% confidence interval; odds ratio=6.09, 241.9; *p*<0.001). The combination of the uterine and umbilical PSV predicted 80.3% of severe PE. All three spontaneous abortions were in women who developed PE, more caesarean section (48.4%) and 69.2% of 45 preterm deliveries occurred in women with severe PE.

The findings from this study show significantly lower uterine and umbilical arteries PSV and EDV but higher RI, PI and S/D in cases that developed PE. The uterine artery PI is the best predictor of PE, whereas the combinations of uterine and umbilical arteries PSV best predict severity of PE among high-risk pregnant Nigeria women [15].

Comparison between this study and other similar studies may be difficult due to different methodologies, screening time, sampling site, and abnormal waveform definitions.

Our ROC results revealed that Umbilical Artery RI, and Uterine RI, cutoff values are higher than 61 and 53 and Middle cerebral RI cutoff value is lower than 86 and the area under the ROC curve is equal to 0.669, 0.840, and 0.863 which indicating that they are fair predictors for PE. The sensitivity values of Umbilical Artery RI, Uterine RI, and Middle cerebral RI were 81.0, 80.6, and 87.5

respectively and the specificity values were 73.3, 60.0, and 73.3 respectively.

This is almost similar to a study conducted in France, on Hypertensive pregnancies using internal carotid and umbilical artery indices which demonstrated a sensitivity and specificity of 86% and 98% respectively.

Lopez-Mendez et al., [14] reported that the Doppler US parameters ability to classify the study groups. The general Doppler result had the most representative values with specificity and PPV of 75.7% and 78.6%, respectively. The sensitivity and the NPV for the general US examination were calculated in 50.8% and 46.7%, respectively.

The difference between result in this current study and the studies above could be because of differences in population dynamics and the abnormality limits of obstetric Doppler parameters which may differ between populations.

Conclusion:

This study demonstrated that Doppler US can reveal the underlying hemodynamic repercussion in the maternal-fetal circulation and thus can be used to determine the proper level of antenatal care in pregnant women. Umbilical artery and Middle cerebral arteries indices were more altered in Preeclampsia.

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تغيرات الدوبلر في حالات مقدمات الارتعاج

مقدمة: يعد تسمم الحمل (الارتعاج) من أخطر الأمراض التى تحدث بنسبة ٢-٨٪ فى العالم. من أهم الأعراض المصاحبة له ارتفاع ضغط الدم والزلال وذلك بعد ٢٠ أسبوع من بداية الحمل. ومن العوامل المساعدة على حدوثه هو الحمل بسن مبكر الحمل لأول مرة والحمل التوأمى. ومن النتائج المصاحب له (تكسير كرات الدم الحمراء والرتفاع بانزيمات الكبد وتشنجات).

وتعتبر موجات الدوبلر ثلاثية الأبعاد من أحدث الوسائل المستخدمة فى الكشف عن التغيرات الغير طبيعية التى تحدث بالاوعية الدموية المشيمية داخل الرحم وذلك لما لها من خصائص ومعايير خاصة تساعد على تقييم التغيرات التى تحدث بالأوعية الدموية المشيمية فى حالات الارتعاج والمخاطرالناتجة عنها للأم والجنين على حد سواء.

إن قياس التغيرات الغير طبيعية التى بالأوعية الدموية المشيمية داخل الرحم فى الربع الاخير من الحمل باستخدام موجات الدوبلر. سيكون مهما فى متابعة السيدات الاتى تعانين من تسمم الحمل ومؤشرات أفضل لتنمؤ حدوث مضاعفات تسمم الحمل. حيث أن مرض ما قبل تسمم الحمل من أهم وأخطر المضاعفات التى تحدث للمرأة الحمل وتؤثر سلبياً عليها وعلى الجنين داخل الرحم.

الهدف من البحث: كان الهدف من الدراسة الحالية هو استخدام الموجات فوق الصوتية دوبلر لتقييم التغيرات في الدورة الدموية في الشرايين الرحميين والشريان المخي الاوسط والشريان السري، وبين النساء الحوامل.