The Egyptian Journal of Hospital Medicine (July 2017) Vol.68 (3), Page 1442-1451

Role of The First Trimester Maternal Serum High Sensitivity C–Reactive Protein and Second Trimester Placental Volume Measurement by 3d Doppler Ultrasound in Early Detection of Pre-Eclampsia

Osama Saleh Elkady, Osama Ismail Kamel, Wesam Abd Elmohsen Mohammed Badawy
Department of Obstetrics and Gynecology, Faculty of Medicine,
Ain Shams University

ABSTRACT

Background: Pre-eclampsia (PE) is a disorder of pregnancy characterized by the onset of high blood pressure and a significant amount of protein in the urine. It affects 2–8% of pregnancies worldwide. Complications include impaired liver function, kidney dysfunction, visual disturbances and red blood cell Breakdown. PE continues to be a major cause of maternal and fetal mortality. Thus, efforts at discovering reliable prediction models to identify those at risk at an early stage are critical. And since Placental maldevelopment plays a pivotal role in the pathogenesis of PE, therefore, evaluation of the placental volume and vascular flow indices using different techniques can contribute in the prediction of adverse pregnancy outcomes.

Aim of the Work: to assess the ability of high sensitivity c reactive protein (Hs CRP) and 3D power Doppler of placental volume and vascular flow indices to predict Preeclampsia.

Patients and methods: This is a prospective cohort study by multi operators conducted on 200 women with singleton pregnancy who underwent screening for eligibility and eventually included with respect to the inclusion criteria. The study has been done during the period from October 2015 till December 2016. 1st trimesteric serum level of HsCRP detection tests, 1st trimesteric abdominal ultrasonographic examination and 2nd trimesteric color-Doppler techniques were done and placental volume was measured and Follow up at delivery to confirm Pre-eclampsia has followed. Study Outcomes included the development of hypertention, limb edema or other of pre-eclampsia complication. Data were statistically analyzed using IBM© SPSS© Statistics version 23.

Results: HsCRP was significantly (P≤ 0.05 and 0.01) high in Pre-eclampsia group compared to the normal pregnancy group. Moreover, Placental volume (PV), Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI) were significantly (P≤ 0.05 and 0.01) lower in Pre-eclampsia group than the normal pregnancy group.**Conclusion:** there was a statistically significant correlation between first-trimester HsCRP and the 2nd trimester placental volume and its vascular indices in the prediction of complications of uteroplacental insufficiency. Further studies with large number of patients have to be carried out to reach conclusive evidence of the significance Doppler in prediction of pre-eclampsi, .and HsCRP.

Keywords: Preeclampsia, C –Reactive Protein, 3d Doppler Ultrasound, Placental Volume Measurement.

INTRODUCTION

Pre-eclampsia is defined as new onset of hypertension and either proteinuria or end organ dysfunction after 20 weeks of gestation in previously normotensive woman , Severe hypertension and signs/symptoms of end organ injury are considered the severe spectrum of the disease [(1)].

Pre-eclampsia is one of the most serious complications during pregnancy and is a major cause of maternal mortality and morbidity.

It is also one of the complications during pregnancy. It is seen in about 5-10% of all pregnancies [(2)].

Associated symptoms with severe pre-eclampsia are systolic blood pressure ≥160mmHg or diastolic pressure ≥110mmHg on two occasions at least 4 hours apart, persistent headache, visual disturbances, persistent epigastric or upper abdominal pain, nausea, vomiting ,mental changes, elevated serum creatinine (more than1.2mg/dL), thrombocytopenia (platelet count <100000/L), elevated serum transaminases twice upper limit of normal level, heamolytic anaemia, and dypnea, retrosternal chest pain[(1)].

Despite many studies on its pathogenesis, there are still many unanswered questions. Abnormal trophoblastic invasion, immunologic mal-adaptation between fetal, maternal paternal tissue, and also genetic factors, all have been reported as causative factors [(3)].

Human placenta produces Hs-CRP and releases it predominantly into the maternal blood. Hs-CRP is a systemic inflammatory marker and it has been shown that it can be found in amniotic fluid and fetal urine. Its increased amount directly relates to poor pregnancy outcome[(4)]. Previous studies have reported that maternal Hs-CRP level increases during pre-eclampsia. At the same time it has been shown that

Received: 6 / 6 /2017
Accepted:15 /6 /2017
DOI: 10.12816/0039687

not only had it higher level in pre-eclamptic woman, but also higher levels related to clinical parameters of pre- eclampsia[5]. The test of serum Hs-CRP is fast and inexpensive and used as a screening method of prediction of pre-eclampsia in the first trimester[3].

Also depending on several theories for pathogenesis of pre-eclampsia including abnormal placentation, novel assessment of placental volume by 3D Doppler Ultrasound is more available including surface-rendering imaging and volume measurement, with the recent advances in 3D power Doppler more powerful evaluation of vascularization and blood flow of placenta is available [6].

PATIENTS AND METHODS

This is a prospective cohort study which was conducted at Ain Shams maternity university hospital laboratory and special fetal care unit by multi operators on 200 women with singleton pregnancy. The study has been done during the period from October 2015 till December 2016. The study protocol was approved by the Ethical Committee of faculty of medicine, Ain Shams University.

We aimed at studying the ability of high sensitivity c reactive protein (Hs CRP) and 3D power Doppler of placental volume and vascular flow indices to predict Preeclampsia .We started with 230 pregnant women and they were subjected to the following inclusion and exclusion criteria:

Inclusion criteria

1) Singleton pregnancy
2) Visualization of the entire placenta
3) Woman in child bearing period between 23-40 years.
4) The gestational age of 8-13 weeks at study enrollment.
5) Placentae fundal anterior and can be visualized to be estimated.

Exclusion criteria

1) Any maternal systemic disorder eg:chronic hypertension, diabetes mellitus, collagen vascular disease, renal disorder, malignancies, any recent or present fever ,or infectious disease, multiple pregnancies, auto immune disease.
2) Drug use (except usual supplement including vitamins and iron),Smoking or Drug, alcohol, nicotine abuse.
3) Any vaginal bleeding.

After exclusion of pregnant women not fulfilling inclusion criteria we had 222 women and 7 of them had aborted by end of first trimester lastly 15 pregnant women underwent drop out phenomena so we resumed study having 200 pregnant women.

All females in the study were subjected to:

1. Written informed consent concerning tests were obtained from each patient.
2. Full history taking in terms of (Age, Duration of marriage, Parity, Occupation, Residence, Mode of delivery, History of abortion, Medical and Surgical history).
3. General Examination including: (Pulse, Blood Pressure, Temperature ,Chest and cardiac examination) and Abdominal examination.
5. Investigations: obstetric ultrasonography and Laboratory investigation: (Complete blood picture,), Coagulation profile: (PT and PTT), Liver function: (ALT, AST and Billirubin), Renal function: (Urea, Createnine and Urine analysis), and one hour postprandial blood sugar.

1st trimesteric serum level of HsCRP detection

Venous blood sample each of about 3 ml was shared from the samples obtained for routine antenatal checkups. Blood samples were collected in plain bulbs. Sera were separated out by centrifuging at 3000 rpm for 10 min and stored separately at - 2C to 8C for up to 48 hours untill used for estimating HsCRP. It was estimated in serum samples by Enzyme-Linked Immunosorbent Assay (ELISA) Kit for the quantitative measurement of CRP in human serum, proprietry name :hs-CRP ELISA DSL-10-42100 ,manufactured by Diagnostic system Laboratories Incorporate Headquarter,445 Medical Center Blvd.Webster,Texas 77598-4217 USA. Kits were brought from Omega company and this work was done in Ain Shams University Maternity Hospital Lab.

.***Ultrasonography assessment***

•Women underwent 1st trimesteric abdominal ultrasonographic examination and 2nd trimesteric color-Doppler techniques at special fetal care unit of Ain Shams Maternity Hospital by multioperators using Voluson E6 GE Healthcare with transabdominal transducer probe frequency of 7 MHz. to assess the following data:

• In first trimester gestational age was determined from the onset of -the last normal menstrual period; measurement of fetal crown-rump length (CRL)was done to confirm the fetal gestational age. The fetal viability and careful search for any fetal abnormalities present.

• In 2nd trimester measurement of the pulsatility index (PI), the resistance index (RI) in the uterine arteries both on the left and right side, detection for

the presence of notch and determine whether it is unilateral or bilateral. Trans-abdominal ultrasound examination was performed with the woman placed in a recumbent or semi recumbent position & carried out for measurement of uterine artery pulsatility index (UtA-PI) & uterine artery resistance index (UtA-RI). For the Doppler studies a sagittal section of the uterus was obtained, and the cervical canal and internal cervical os were identified. Subsequently, the transducer was gently tilted from side to side and color flow mapping was used to identify each UtA along the side of the cervix and uterus at the level of the internal os . Pulsed wave Doppler imaging was used with the sampling gate set at 2mm to cover the whole vessel and care was taken to ensure that the angle of insonation was less than 50◦. When three similar consecutive waveforms had been obtained the UtA-PI and UtA-RI were measured, and the mean UtA-PI and UtA-RI of the left and right arteries were calculated.

Measurement and interpretation of placental volume

The volume of the placenta was measured with a 3D transabdominal ultrasound transducer with a full bladder and the transducer placed perpendicular to the placenta to see the entire placenta. The adjustments to 3D placental scan were an angle of 70° and a maximum region of interest that allowed the full placental surface. The external limits of the placenta were defined by the basal plate and the chorionic plate excluding the myometrium. The image was recorded in 3 orthogonal planes and stored for subsequent calculation of the placental volume, the placental volume was calculated with 4D View software Voluson E6 (GE Healthcare) by multioperators . The calculation was done twice using the same image, and the time spent was recorded. The VOCAL mode with an angle of rotation of 30° was chosen; the axial plane was the reference; and the calipers were placed on either side of the placenta. With 6 planes, it was possible to reconstruct the volume measured in cubic centimeters. If the quality criteria were not attained, another acquisition was done. If it was not possible to calculate the volume, the patients were excluded from the study. To get better resolution and therefore define the contours of the placenta, we used optimal harmonic and focal settings. Volumes were then stored in View Point software Voluson E6 (GE Healthcare).

Follow up at delivery to confirm Pre-eclampsia

Pregnancy related hypertensive diseases in this study were defined according to the guidelines of the International Society for the Study of hypertension in Pregnancy (ISSHIP). Gestational hypertension was defined as a blood pressure of at least 140/90 mmHg taken on two occasions more than 4 h apart after the 20th week of pregnancy. Pre-eclampsia was defined as a blood pressure 140/90 mmHg and proteinuria of 300 mg in 24 hours, or two readings of at least 2+ on dipstick analysis of midstream urine specimens if no 24-hour urine collection was available in absence of urinary tract infection.

Pregnant women were under close follow up by attendance at antenatal care clinics as they told to do antenatal care every 2 weeks :

1- obstetric U/S.

2- Measure blood pressure.

3- Urine analysis for early detection of albumin in urine

4-They are informed about dangerous symptoms for early detection of PE occurance .

Outcomes considered include:

A) During pregnancy:

•The development of hypertention and/or lower limb oedema.

•The development of any of pre-eclampsia complication.

The study was done after approval of ethical board of Ain Shams university and an informed written consent was taken from each participant in the study.

Statistical analysis

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 15 (MedCalc© Software bvba, Ostend, Belgium). Normally distributed numerical variables were presented as mean and SD and inter-group differences were compared using the independent samples t test [(7)].

Categorical variables were presented as number and percentage and differences were compared using Fisher's exact test (for nominal data) or the chi-squared test for trend (for ordinal data).

Correlations were tested using Pearson correlation analysis. The Pearson correlation coefficient (r) is interpreted as follows [(8)] :

Significance level was considered at $p < 0.05$ & highly significant was considered at $p < 0.01$.

Graphical presentation for relevant variables was done using box plot & bar charts.

The ROC curve analysis & graph was used to measure the sensitivity & specificity of ultrasound parameters[(9)].

RESULTS

Data were analyzed using IBM© SPSS© Statistics version 23 (IBM© Corp., Armonk, NY, USA) and MedCalc© version 15 (MedCalc© Software bvba, Ostend, Belgium).

Normally distributed numerical variables were presented as mean and SD and inter-group differences were compared using the independent samples t test.

Table 1. Demographic characteristics of the study population

Variable	Mean ± SD / n (%)
Maternal age (years)	27.7 ± 4.2 (range, 23 – 40)
BMI (kg/m^2)	24 ± 4
Parity	
P0	101 (50.5%)
P1	45 (22.5%)
P2	30 (15.0%)
P3	20 (10.0%)
P4	3 (1.5%)
P5	1 (0.5%)
Gestational age at hsCRP assay (weeks)	10.8 ± 1.5 (range, 8 – 13)
Gestational age at placental volume measurement (weeks)	17.7 ± 1.8 (range, 14 – 20)

Table 2. Blood pressure and albuminuria at 1st trimestert

Variable	Mean ± SD / n (%)
SBP at 1st trimester (mmHg)	105 ± 15
DBP at 1st trimester (mmHg)	69 ± 11
MAP at 1st trimester (mmHg)	81 ± 10
Albuminuria at 1st trimester	
Negative	200 (100.0%)
Positive	0 (0.0%)

Table 3. HsCRP, placental volume, and placental VI

Variable	Mean ± SD
HsCRP (mg/l)	3.33 ± 1.33
Placental volume (cm^3)	168 ± 49
Placental VI	18 ± 8

Table 4. Blood pressure, albuminuria, and incidence of PE at term

Variable	Mean ± SD / n (%)
SBP at term (mmHg)	112 ± 22
DBP at term (mmHg)	72 ± 13
MAP at term (mmHg)	85 ± 15
Albuminuria at term	
Negative	176 (88.0%)
Positive	24 (12.0%)
Hypertensive disorders at term	
No hypertensive disorders	169 (84.5%)
PE	24 (12.0%)
Pregnancy-induced hypertension	7 (3.5%)

Table 5. Correlation between HsCRP and other quantitative variables

	HsCRP	
Variable	**Pearson r**	**p-value**
Placental volume	-.465**	<.001
Placental VI	-.210**	.003
SBP at 1st trimester	.186**	.008
DBP at 1st trimester	.196**	.005
MAP at 1st trimester	.233**	.001
SBP at term	.691**	<.001
DBP at term	.603**	<.001
MAP at term	.676**	<.001

**. Correlation is significant at the 0.01 level (2-tailed)

Table 6: Characteristics of patients with or without PE at term

Variable	No PE (n=176)	PE (24)	t / χ^2	df	p-value
Maternal age (years)	27.7 ± 4.2	27.6 ± 4.0	.089	198	.929¶
BMI (kg/m^2)	24 ± 5	21 ± 2	6.754	83.332	**<.001**¶
Parity			1.747	1	.186§
P0	84 (47.7%)	17 (70.8%)			
P1	42 (23.9%)	3 (12.5%)			
P2	29 (16.5%)	1 (4.2%)			
P3	18 (10.2%)	2 (8.3%)			
P4	2 (1.1%)	1 (4.2%)			
P5	1 (0.6%)	0 (0.0%)			

Data are mean ± SD or number (%), *t*, t statistic; χ^2, chi-squared statistic; *df*, degree of freedom.
¶Unpaired t test, §Chi-squared test for trend.

Table 7. 1st HsCRP, placental volume, and placental VI in patients with or without PE at term

Variable	No PE (n=176)	PE (24)	t	df	p-value¶
HsCRP (mg/l)	2.71 ± 1.69	7.86 ± .99	-14.584	198	**<.001**
Placental volume (cm^3)	176 ± 45	106 ± 28	10.660	42.431	**<.001**
Placental VI	18 ± 8	14 ± 4	4.167	57.358	**<.001**

Data are mean ± SD. *t*, t statistic; *df*, degree of freedom. ¶Unpaired t test.

Table 8. Receiver-operating characteristic (ROC) curve analysis for prediction of PE at term using hsCRP

Sample size	**200**			
Positive group (PE at term)	24 (12%)			
Negative group (No PE at term)	176 (88%)			
Disease prevalence (%)	12			
ROC curve analysis				
Index	**Statistic**	**95% CI**	**z statistic**	**p-value¶**
Area under the ROC curve (AUC)	0.972	0.938 to 0.990	44.899	**<.0001**
Youden index (J)	0.94			
Associated criterion	>5.07 mg/l			
Sensitivity (%)	100	85.8 to 100.0		
Specificity (%)	93.8	89.1 to 96.8		
Positive likelihood ratio (LR+)	16	9.0 to 28.4		
Negative likelihood ratio (LR-)	0	to		
Positive predictive value (PV+) (%)	68.6	50.7 to 83.1		
Negative predictive value (PV+) (%)	100	97.8 to 100.0		

¶DeLong method.

Table 8 HsCRP had excellent predictive value with an area under the ROC curve (AUC) of 0.972 (95% CI, 0.938 to 0.990; p-value, <.0001).
The best cut-off criterion was an hsCRP level >5.07 mg/l which had a sensitivity of 100% (95% CI, 85.8% to 100.0%) and specificity of 93.8% (95% CI, 89.1% to 96.8%).

Table 9. Receiver-operating characteristic (ROC) curve analysis for prediction of PE at term using placental volume

Sample size	**200**			
Positive group (PE at term)	24 (12%)			
Negative group (No PE at term)	176 (88%)			
Disease prevalence (%)	12			
ROC curve analysis				
Index	**Statistic**	**95% CI**	**z statistic**	**p-value¶**
Area under the ROC curve (AUC)	0.906	0.857 to 0.943	13.257	<.0001
Youden index (J)	0.75			
Associated criterion	≤139 cm^3			
Sensitivity (%)	91.7	73.0 to 99.0		
Specificity (%)	83.5	77.2 to 88.7		
Positive likelihood ratio (LR+)	5.6	3.9 to 7.9		
Negative likelihood ratio (LR-)	0.1	0.03 to 0.4		
Positive predictive value (PV+) (%)	43.1	29.3 to 57.8		
Negative predictive value (PV+) (%)	98.7	95.2 to 99.8		

¶DeLong method.

Table 9 The placental volume had excellent predictive value with an area under the ROC curve (AUC) of 0.906 (95% CI, 0.857 to 0.943; p-value, <.0001).
The best cut-off criterion was a placental volume ≤139 cm^3 which had a sensitivity of 91.7% (95% CI, 73.0% to 99.0%) and specificity of 83.5% (95% CI, 77.2% to 88.7%).

Table 10. Multivariable binary logistic regression analysis for prediction of PE at term

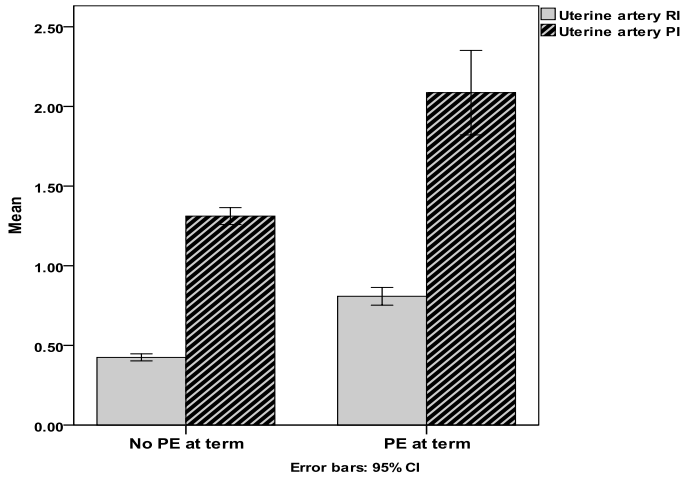
Variable	**Regression coefficient**	**SE**	**Wald**	**p-value**	**Odds ratio**	**95% CI**
hsCRP (mg/l)	0.90	0.22	16.75	**<.0001**	2.45	1.60 to 3.76
Placental volume (cm3)	-0.01	0.01	1.30	.255	0.99	0.97 to 1.01
Placental VI	-0.02	0.10	0.04	.849	0.98	0.81 to 1.19
BMI (kg/m^2)	-0.28	0.13	4.31	**.038**	0.76	0.59 to 0.98
Gestational age at assay of hsCRP (weeks)	0.36	0.25	2.14	.144	1.43	0.88 to 2.32
Constant	-5.38					

SE, standard error; 95% CI, 95% confidence interval.
Table 10 shows the results of multivariable binary logistic regression analysis for prediction of PE at term. After adjustment for the effect of other variables, HsCRP (odds ratio, 2.45; 95% CI, 1.60 to 3.76; p-value, <.0001) and the BMI (odds ratio, 0.76; 95% CI, 0.59 to 0.98; p-value, .038) were independent predictor for the occurrence of PE at term.

Table 11. Uterine artery Doppler indices at 2nd trimester in patients with or without PE at term

Variable	***No PE (n=176)***	***PE (24)***	***t***	***df***	***p-value¶***
Uterine artery RI	0.42 ± 0.15	0.81 ± 0.13	-12.014	197	**<.001**
Uterine artery PI	1.31 ± 0.36	2.09 ± 0.63	-5.908	25.058	**<.001**

Data are mean ± SD.
t, t statistic; *df*, degree of freedom.



¶Unpaired t test.

Figure 1. Uterine artery RI and PI in patients with or without PE at term.

Table 12. Receiver-operating characteristic (ROC) curve analysis for prediction of PE at term using uterine artery RI at 2nd trimester

Sample size	**200**			
Positive group (PE at term)	24 (12%)			
Negative group (No PE at term)	176 (88%)			
Disease prevalence (%)	12			
ROC curve analysis				
Index	**Statistic**	**95% CI**	**z statistic**	**p-value¶**
Area under the ROC curve (AUC)	0.935	0.892 to 0.965	17.976	**<.0001**
Youden index (J)	0.8481			
Associated criterion	>0.6			
Sensitivity (%)	91.7	73.0 - 99.0		
Specificity (%)	93.1	88.3 - 96.4		
Positive likelihood ratio (LR+)	13.4	7.6 - 23.4		
Negative likelihood ratio (LR-)	0.09	0.02 - 0.3		
Positive predictive value (PV+) (%)	64.7	46.5 - 80.3		
Negative predictive value (PV+) (%)	98.8	95.7 - 99.9		

¶DeLong method.

Table 12 Uterine artery RI had excellent predictive value with an area under the ROC curve (AUC) of 0.935 (95% CI, 0.892 to 0.965; p-value, <.0001).

The best cut-off criterion was an RI >0.6 which had a sensitivity of 91.7% (95% CI, 73.0% to 99.0%) and specificity of 93.1% (95% CI, 88.3% to 96.4%).

DISCUSSION

Pre-eclampsia is one of the most serious complications during pregnancy and is a major cause of maternal mortality and morbidity. It is also one of the complications during pregnancy that we know little about causative factors [(2)].

Pre-eclampsia is defined as new onset of hypertention and either proteinuria or end organ dysfunction after 20 weeks of gestation in previously normotensive woman. Severe hypertention and signs/symptoms of end organ injury are considered the severe spectrum of the disease [(1)].

Preeclampsia affects 2–8% of pregnancies worldwide. Hypertensive disorders of pregnancy (which include preeclampsia) are one of the most common causes of death due to pregnancy [(10)].

Despite many studies on its pathogenesis, there are still many unknown answers. It is abnormal trophoblastic invasion, immunologic mal-adaptation between fetal, maternal and paternal tissue, and also genetic factors and all have been reported as causative factors [(3)].

Due to the importance of pre-eclampsia during pregnancy, many studies have been performed on the different methods of predicting its occurrence. In a systematic review, a diagnostic value of 27 different tests (including alpha-fetoprotein, uterine artery Doppler, body mass index of more than 34, etc.) have been evaluated. Some of these methods have high sensitive but low specificity or they are very expensive. This study has concluded that these tests were not completely accurate. Therefore, it seems necessary to identify the accurate, inexpensive as well as most applicable tests. Then the optimal cut-off points have to be determined in order to perform them in practice [(11)].

We evaluated the role of first trimester maternal serum HSCRP and second trimester placental volume measurement by 3 D Doppler ultrasound in early detection of per eclampsia **.**

Human placenta produces Hs-CRP and releases it predominantly into the maternal blood. Hs-CRP is a systemic inflammatory marker and it has been shown that it can be found in amniotic fluid and fetal urine. Its increased amount directly relates to poor pregnancy outcome [(4)].

Neverthless, a study carried by ***Ertas et al.*** [(12)] Using cross-sectional study design, CRP was measured by a high sensitive immunoturbidimetric method in ***2010*** , between 24 and 40 weeks of gestation in normotensive controls (n = 115), in mild (n = 63) and severe (n = 34) pre-eclamptic patients. The receiver operating characteristic analysis was used to estimate the optimal threshold score of hs-CRP.

For disease severity evaluation, Hs-CRP concentration of 9.66 mg/L was determined as cut-off point with 88% sensitivity, 81% specificity, 71% positive predictive value and 92% negative predictive value. When all three groups of patients were adjusted for gestational age [24°/7–27,6/7 28°/7–33,6/7 34°/7–406/7] and BMI, hs-CRP levels of severe pre-eclamptic patients were significantly higher than mild ones and controls in the study group with BMI < 25 kg/m2 (P < 0.001). In the study group with BMI _ 25 kg/m2, only severe preeclamptic patients between 28°/7 and 336/7 weeks of gestation had significantly higher hs-CRP levels when compared with control and mild pre-eclamptic group (P < 0.001).When the patients were subgrouped as high (_9.66 mg/L) and low hs-CRP group (<9.66 mg/L), adverse outcomes for hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome and intrauterine growth-restricted baby were statistically significant higher in high hs-CRP group (P = 0.004 and P < 0.001, respectively).

In the present study, HsCRP was evaluated using prospective cohort study for better follow up of pregnant women at earlier stage of pregnancy between (8-13 weeks) ,we found mean in case of no PE is 2.71 ± 1.69 while in patient who developed PE at term was 7.86 ± o.99 (table 7).

Table 8 showed that there is a strong relation between level of HsCRP at 1st trimester and development of PE as the results of receiver-operating characteristic (ROC) curve analysis for prediction of PE at term using HsCRP at 1st trimester, HsCRP had excellent predictive value with an area under the ROC curve (AUC) of 0.972 (95% CI, 0.938 to 0.990; p-value, <.0001The best cut-off criterion was an HsCRP level >5.07 mg/l which had a sensitivity of 100% (95% CI, 85.8% to 100.0%) and specificity of 93.8% (95% CI, 89.1%to96).

Table 10 demonstrated the results of multivariable binary logistic regression analysis for prediction of PE at term. After adjustment for the effect of other variables, HsCRP was the only independent predictor for the occurrence of PE at term (odds ratio, 2.45; 95% CI, 1.60 to 3.76).

Our results seem to agree with those of ***Maryam et al*** **.** [(13)] who carried out a prospective cohort study was performed on 394 pregnant women in ***2013*** who were at the gestational age of 8–13 weeks. In all women, serum hs-CRP was measured by latex agglutination test. The women were then monitored to delivery. Hs-CRP of the two groups,was compared those with and without pre-eclampsia. Receiver–operator curve was used for finding the optimum cut-off points.

Out of 394 women, 42 cases (10.7%) were complicated by pre-eclampsia, of whom 23 women (56.1%) had severe pre-eclampsia. Mean serum Hs-CRP of the pre-eclamptic group was higher than that of the normotensive group (7.06 _ 2.6 mg/L vs 3.6 _ 2.3 mg/L, P = 0.001). The receiver–operator curve showed a significant difference between the under-curve zone for the hs-CRP level with the reference line. Serum Hs-CRP of 4 mg/L showed sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy as 78.1%, 72.1%, 25%, 96.5% and 72.8%, respectively. Hs-CRP of more than 7 mg/L was found in 26 (61.9%) cases of pre-eclampsia and 22 (6.25%) normotensive pregnancies, which showed a significant difference (P = 0.001, relative risk = 12.1, 95% confidence interval: 6.91–21.15). Hs-CRP of more than 7 mg/L was found in 17 (73.91%) cases of severe pre-

eclampsia and 22 (6.25%) normotensive pregnancies, which showed a significant difference (P = 0.001, relative risk = 9.35, 95% confidence interval: 4.48–19.52).

In a study conducted by ***Adali et al.*** [14] on pre-eclamptic women, the relation between maternal serum Hs-CRP level and uterine artery Doppler velocimetry was evaluated. This study showed that a serum level of Hs-CRP is higher in pre-eclamptic than normotensive women. Hs-CRP also related positively with the mean arterial pressure and its level was higher in pre-eclamptic women who had abnormal uterine artery Doppler velocimetry than preeclamptic women with normal Doppler

The study concluded that the Hs-CRP level of maternal serum has a correlation with severity of pre-eclampsia, which shows an endothelial dysfunction, and may be considered as a probable marker of pathologic uteroplacental perfusion.

This study has certain limitations due to its inability to justify whether elevation of CRP levels occurred after conception or whether the elevated levels existed at baseline. As a result, it is impossible to determine whether systemic inflammation was induced by specific pregnancy-related factors or by factors that predated pregnancy.

The placenta plays a central role in the pathogenesis of most adverse pregnancy outcomes. With improved 3-dimensional (3D) sonographic technology, it is now possible to evaluate the placental volume as well as vascularization status using power Doppler sonography [15].

Our study aimed at detecting the ability of 3D power doppler placental volume and vascular flow indices to predict preeclampsia as an additional tool for prediction of preeclampsia .

Obstetric Medicine Curriculum Bibliography, (2005) reported that laboratory manifestations of preeclampsia reflect that many systems involved in the disease. Proteinuria (> 300mg/dL per 24 hours) is one of the major manifestations of preeclampsia and is likely due to a lesion known as glomerular endotheliosis. This same lesion also is responsible for the elevated creatinine seen in many preeclamptic patients. Interpretation of creatinine, however, must be done with the knowledge that the average creatinine in pregnancy is 0.5 mg/dL. A creatinine of 0.9 mg/dL is abnormal.

A study conducted by ***Luo et al .*** [16] detailed the results of 26 studies that showed consistently but variably elevated risk of pre-eclampsia in primiparous vs. multiparous women in all studies in ***2007***. The crude ORs ranged from 1.44 to 5.48. There was significant heterogeneity in the magnitude of the association (heterogeneity chi-square test, P < 0.01), but the between-study variance was small (5.3%). The summary crude OR [95% CI] across all studies (based on a random-effects model) was 2.42 [95% CI 2.16, 2.71] for the risk of pre-eclampsia among primiparous vs. multiparous women No obvious publication biases . The summary OR was 2.26 [95% CI 2.22, 2.30] in cohort studies, slightly lower than that of 2.61 [95% CI 1.78, 3.82] in case–control studies. We also conducted a sensitivity analysis by restricting the analysis to studies that focused on the effects of primiparity (n = 13), and a similar summary crude OR of 2.34 [95% CI 1.82, 2.98] was obtained as compared with that of 2.42 in all studies. This came in concurrence with our study because women who developed PE (24) we find (17)women are primigravida (70.8) and (7)of them are multigravida (29.2%) as shown in table 6 . This observation being attributed to differences in immune response between primiparous and multiparous women, in angiogenic profile, or in insulin resistance reactivity pattern .

On the other hand we found that the mean of placental volume measured at the 2nd trimester in PE women was 106 ± 28 (cm3) which is more less than that of non PE women at same gestational age or near to it ,also in the same table we find that the mean Placental VI at 2 nd trimester in PE women was 14 ± 4 which is less than that of non PE women .The present results indicated that preeclamptic cases had significantly ($P \leq 0.0001$ and $P \leq 0.001$) lower placental volume (PV), Vascularization index (VI), Flow index (FI) and Vascularization flow index (VFI) than normal cases as shown in (table 7) .

In agreement with our findings, ***Costa et al.*** [17]. tested the hypothesis that parameters of vascularity and flow intensity of the placenta as determined by three-dimensional (3D) ultrasound, (1) are different in normal pregnancy compared to pre-eclampsia (2) decrease from the basal plate towards the chorionic plate. The results indicated that FI, VI and VFI were lower in pre-eclampsia compared to normal pregnancy in all regions of the placenta. This difference was statistically significant in most regions of the placenta after accounting for gestational age, body mass index and placental site. We were not able to demonstrate a decreasing gradient of these parameters from basal plate to chorionic plate. They concluded their results as 3D

ultrasound to assess placental vascularity and flow intensity appears to be an interesting research tool. However, other indices derived from Power Doppler may be more relevant to obstetric practice.

CONCLUSION

There was a statistically significant correlation between first-trimester HsCRP and the 2nd trimester placental volume and its vascular indices in the prediction of complications of uteroplacental insufficiency. Much more studies with large number of patients must be developed to reach conclusive evidence of the significance Doppler in prediction of pre-eclampsi, .and HsCRP.

REFERENCES

1. **Woelkers D, Barton J, von Dadelszen P, Sibai B (2015):** the revised 2013 ACOG definitions of hypertensive disorders of pregnancy significantly increase the diagnostic prevalence of preeclampsia. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health, 5(1):38.
2. **Cunningham FG "leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY (2010):** Abortion. Williams Obstetrics, 231-252.
3. **Jacquemyn Y, Zemtsova O (2010):** Risk factors and prediction of preeclampsia. Acta Clinica Belgica, 65(1):1-2.
4. **Malek A, Bersinger NA, Di Santo S, Mueller MD, Sager R, Schneider H, Ghezzi F, Karousou E, Passi A, De Luca G, Raio L (2006):** C-reactive protein production in term human placental tissue. Placenta., 27(6):619-25.
5. **Kumru S, Godekmerdan A, Kutlu S, Ozcan Z (2006):** Correlation of maternal serum high-sensitive C-reactive protein levels with biochemical and clinical parameters in preeclampsia. European Journal of Obstetrics & Gynecology and Reproductive Biology, 124(2):164-7.
6. **Hata T, Tanaka H, Noguchi J, Hata K (2011):** Three-dimensional ultrasound evaluation of the placenta. Placenta, 32(2):105-15.
7. **Sedgwick P(2010):** Independent samples t test. BMJ: British Medical Journal, 340:22-27.
8. **Ahlgren P, Jarneving B, Rousseau R (2003):** Requirements for a cocitation similarity measure, with special reference to Pearson's correlation coefficient. Journal of the Association for Information Science and Technology, 54(6):550-60.
9. **Hinkle DE, Wiersma W, Jurs SG (2013):** Applied statistics for the behavioral sciences, available at http://www.jstor.org/stable/pdf/1164825.pdf?seq=1#page_scan_tab_contents
10. **Arulkumaran N, Lightstone L (2013):** Severe pre-eclampsia and hypertensive crises. Best Practice & Research Clinical Obstetrics & Gynaecology, 27(6):877-84.
11. **Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, Ter Riet G, Duley L, Roberts TE, Mol BW, Van der Post JA, Leeflang MM, Barton PM (2008):** Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technology Assessment Journal, 12(6): 1-270
12. **Ertas IE, Kahyaoglu S, Yilmaz B, Ozel M, Sut N, Guven MA, Danisman N (2010):** Association of maternal serum high sensitive C-reactive protein level with body mass index and severity of pre-eclampsia at third trimester. Journal of Obstetrics and Gynaecology Research, 36(5):970-7.
13. **Kashanian M, Aghbali F, Mahali N (2013):** Evaluation of the diagnostic value of the first-trimester maternal serum high-sensitivity C-reactive protein level for prediction of pre-eclampsia. Journal of Obstetrics and Gynaecology Research, 39(12):1549-54.
14. **Adali E, Kurdoglu M, Adali F, Cim N, Yildizhan R, Kolusari A (2011):** The relationship between brachial artery flow-mediated dilatation, high sensitivity C-reactive protein, and uterine artery doppler velocimetry in women with pre-eclampsia. Journal of Clinical Ultrasound, 39(4):191-7.
15. **Guimarães Filho HA, da Costa LL, Júnior EA, Nardozza LM, Nowak PM, Moron AF, Mattar R, Pires CR (2008):** Placenta: angiogenesis and vascular assessment through three-dimensional power Doppler ultrasonography. Archives of gynecology and obstetrics, 277(3):195.
16. **Luo ZC, An N, Xu HR, Larante A, Audibert F, Fraser WD (2007):** The effects and mechanisms of primiparity on the risk of pre-eclampsia: a systematic review. Paediatric and perinatal epidemiology, 21(s1):36-45.
17. **Costa J, Rice H, Cardwell C, Hunter A, Ong S (2010):** An assessment of vascularity and flow intensity of the placenta in normal pregnancy and pre-eclampsia using three-dimensional ultrasound. The Journal of Maternal-Fetal & Neonatal Medicine, 23(8):894-9.