Severe Early– Onset Preeclampsia: Prognostic Role of Uterine Artery Doppler Examination

Lilyan W. Sersam*, Shamam Y. Mohammed**, Eftekhar Shmkhee Abood***

ABSTRACT:

BACKGROUND:
Preeclampsia is essentially an endothelial disease. Early- onset preeclampsia appears to be linked mainly to a failed placental vascular remodeling. Uterine artery Doppler is a validated noninvasive surrogate of trophoblastic invasion and placental perfusion.

OBJECTIVE:
To evaluate the predictive capacity of uterine artery Doppler investigation for maternal and neonatal complications in women with severe early- onset preeclampsia.

METHODS:
This prospective comparative study was carried out on sixty-five Iraqi pregnant women with severe early-onset preeclampsia. Their gestational age ranged from ۲۸-۳٤ weeks of gestation. A uterine artery Doppler examination was performed on admission to the participants. According to the result of Doppler ultrasound, they were arranged into two main groups: group one comprising twenty-nine patients with normal uterine artery Doppler results, and group two comprising thirty-six patients with abnormal uterine artery Doppler results. The maternal and neonatal outcome of women with abnormal uterine Doppler results was compared to those with normal Doppler results, and then results were analyzed accordingly.

RESULTS:
Sixty-five patients were enrolled in this study. In ٥۳٪ of them, uterine artery Doppler results were abnormal. This group showed statistically significant lower birth weight (p = ۰,۰۰۳), higher caesarean section rate (p= ۰,۰۱٤), abnormal umbilical artery Doppler examinations (p=۰,۰۰۰۱) and higher neonatal complications rate (P= ۰,۰۰٦). Regarding the maternal complications (HELLP syndrome, neurological manifestations, acute renal failure and pulmonary oedema), occurred at higher rate in the group with abnormal uterine artery Doppler compared with those having normal Doppler results (٥۸,۳٪ versus ۳۷,۹٪), but only acute renal failure reached the statistical level of significance (P=۰,۰۱۷).

CONCLUSION:
Women with severe early-onset preeclampsia are at higher risk of maternal and neonatal complications if abnormal uterine blood flow is present.
KEY WORDS: uterine artery doppler, early- onset preeclampsia.

INTRODUCTION:
Preeclampsia (PE) affects about ۲–۳٪ of pregnancies and is a major cause of maternal and perinatal morbidity and mortality [1–3]. Doppler studies were carried out in pregnancies presenting with preeclampsia or fetal growth restriction reported that the outcome was worse if there was increased, rather than normal, impedance to flow in the uterine arteries [4–6]. In recent years, it has been established that early- and late-onset preeclampsia are associated with different biochemical and clinical features: whereas the early-onset form is almost invariably associated with placental insufficiency and growth restriction, the late-onset form is more prevalent and, in general, placental involvement is minimally present [7]. Early-onset Preeclampsia and fetal growth restriction are placenta-mediated diseases that share important similarities as recently demonstrated by Crispi *et al.* [7,8]. Umbilical artery (UA) and middle cerebral artery (MCA) Doppler examinations are standard parameters used in the management of pregnancies at risk of placental insufficiency [9]. Uterine artery (UtA) Doppler has been widely studied for the prediction of preeclampsia and intrauterine growth

*Department of Obstetrics and Gynaecology, College of Medicine, Al-Mustansiriya University, Al-Yarmouk Teaching Hospital.
**Department of Radiology, Al-Yarmouk Teaching Hospital.
***Department of Obstetrics and Gynaecology, Al-Yarmouk Teaching Hospital.

restriction, reflecting a defective trophoblastic invasion. However, it has scarcely been evaluated as a prognostic tool at the onset of preeclampsia [5,6,10]. Early preeclampsia (before 34 weeks) is more often associated with altered uterine artery Doppler [11].

This study aimed to evaluate the predictive capacity of uterine artery Doppler examination for maternal and neonatal complications in women with severe early- onset preeclampsia.

MATERIALS AND METHODS:
This prospective comparative study was conducted at the department of Obstetrics and Gynecology at AL-Yarmouk Teaching Hospital for period extending from the first of November 2010 to the end of January 2012. The study comprised a total of 65 Iraqi pregnant women in their third trimester, their gestational age ranged from 28 to 34 weeks of gestation, with a diagnosis of severe preeclampsia. Severe preeclampsia was defined as preeclampsia with severe hypertention (diastolic blood pressure 110 mmHg or greater, systolic blood pressure 160mmHg or greater) and/or with symptoms, and/or biochemical and/or haematological impairment [12]; A uterine artery Doppler examination was performed on admission to the emergency ward to all participants. Exclusion criteria were: (1) undetermined gestational age; (2) Women in labor and/or with uterine activity; (3) twin pregnancies; (4) clinical urgency with maternal hemodynamic instability or an indication for immediate termination of pregnancy; (5) preexisting maternal chronic medical problems: chronic hypertension, diabetes mellitus, autoimmune disease, renal diseases, maternal heart disease, and thromboembolic disease ; (6) pregnancy with congenital fetal abnormalities; and (7) Dead fetus at admission to hospital. According to Doppler ultrasound results, our subjects were divided into 2 main groups:

Group 1: Normal uterine artery Doppler results (control group).
Group 2: Abnormal uterine artery Doppler results (case group).
The maternal and neonatal outcomes of women with abnormal uterine artery Doppler results (group2) were compared with those with normal Doppler results (group1). The women in both groups were matched for maternal age, body mass index (BMI) and gestational age. This study was approved by the Institutional Ethics Committee, and verbal informed consent was obtained from the

patients. In this study, National Institute for Health and Clinical Excellence Clinical Guideline definitions were used to define preeclampsia [12]. A detailed history was taken from all participants and complete examination (general and obstetric examination) was done and investigations were performed, all women were followed up till delivery to verify maternal and neonatal outcomes. All study subjects were submitted to an obstetrical Doppler scan standardized for the study, carried out by one single operator (the principal investigator), who was contacted at the time of inclusion of each woman in the study. The examinations were carried out using a color Doppler ultrasound scanner (Siemens, Acuson, Germany) with a 3,5 MHz transducer and with the filter adjusted to 100 Hz. Umbilical artery Doppler ultrasound examination was performed to the women in the left lateral recumbent position .The umbilical artery was identified and flow velocity waveforms were obtained from a free-floating loop of the cord during fetal quiescence. Flow velocity waveforms were considered abnormal when the mean PI was above the 95th centile for gestational age using published reference values [13]. Then the transducer was positioned on the lower right and left quadrant of the patient's abdomen, visualizing the external iliac artery and medially identifying the uterine arteries. Scans of each uterine artery were obtained at the point close to the external iliac artery prior to the division of the uterine artery into branches, following this, pulsatility index (PI) was measured, and the presence or absence of an early diastolic notch was noted. The process was then repeated for the contralateral uterine artery, and the mean PI (mPI) of the two vessels was calculated. Flow velocity waveforms were considered abnormal when the mean PI was above the 95th centile for gestational age using published reference values [14] or the presence of notching was noted. To evaluate maternal outcome, the following complications were considered: oliguria (defined as hourly diuresis <30 ml/h), acute pulmonary edema (presence of maternal respiratory distress with fine basal crepitiations detected at pulmonary auscultation requiring the use of diuretics), eclampsia and other neurological manifestations (visual disturbances or severe headache that persisted >24 hours); HELLP syndrome and acute renal failure Adverse neonatal outcome was defined by the presence of the following criteria: small-for-gestational age, fetal or neonatal death, 5-

minute Apgar score< ٧, or significant neonatal morbidity: (seizures, hypoxic ischemic encephalopathy, acute renal failure, or cardiac failure).

Statistical analysis:

Analysis of data was carried out using the available statistical package of SPSS-١٨ (Statistical Packages for Social Sciences- version ١٨ "PASW" Statistics). Data were presented in simple measures of percentage, mean, standard deviation and range (minimum-maximum values) The significance of difference of different means (quantitative data from different study groups and from comparison group) was tested using independent student-t-test for difference between two means, while different percentages (qualitative data from different study groups and from comparison group) were tested using Pearson Chi-square test (χ^2-test). Statistical significance was considered whenever the P value was less than ٠,٠٥.

RESULTS:

The study represents a case–control study on ٦٥ pregnant Iraqi women, in their third trimester, with a diagnosis of severe preeclampsia; In ٥٥,٣٪ of the cases (٣٦/٦٥), the uterine artery Doppler examination was abnormal, while it was normal in ٤٤,٦٪(٢٩/٦٥). Both groups were demographically comparable on bases of their maternal age (P=٠,٦٣٩), BMI (P=٠,٤٤٠), gestational age at admission (P=٠,٠٧١), and gestational age at delivery (P=٠,١٠٩). There was no statistically significant difference between both groups as the P value was more than ٠,٠٥. Table ١ shows the demographic characteristics for patients with normal and abnormal uterine artery Doppler findings. The mean maternal age (years) was ٢٥,٣٦±٥,٨١ for the abnormal uterine artery Doppler group (case group), with a range of (١٥-٤٠). For the normal uterine artery Doppler group (control group) the mean was (٢٤,٦٦±٦,٢٢), with a range of (١٦-٤١). Regarding the gestational age at admission, the mean gestational age (weeks) was (٣١,٠٠±١,٨٨) for the case group with a range of (٢٨-٣٤) while the mean was (٣١,٨٣±١,٧١) for the control group, with a range from (٢٨-٣٤).

Regarding gestational age (weeks) at delivery, mean was (٣١,٥٠±٢,٠٦) for the case group with a range of (٢٨-٣٦) while the mean was (٣٢,٣١±١,٩١) for the control group, with a range from (٢٨-٣٦). The mean maternal BMI (kg\m٢) was ٢٧,٣٠±٥,٥٦

for the case group with a range from (٢٠-٤٠) while the mean was ٢٨,٤٨±٦,٦٤ for the control group, with a range from ٢٠-٤٤. Among patients with abnormal uterine Doppler results, birth weights were significantly lower (p = ٠,٠٠٣) compared with the control group, with a mean of (١٦٢٥,٨±٤٢٤) gram in study group versus (٢٠٠٧,١±٥٦٩) gram in control group, as shown in table ٢. Table ٣ illustrates caesarean section distribution among both groups. In abnormal uterine artery Doppler group, caesarean section rate was significantly higher compared with controls, ٩٤,٤٪ (٣٤\٣٦) versus ٧٢,٤٪ (٢١/٢٩), (p= ٠,٠١٤), while only two patients (٥,٦٪) delivered by vaginal route in the study group versus eight patients (٢٧,٦٪) delivered by vaginal route in control group. In abnormal uterine artery Doppler group, abnormal umbilical artery Doppler examination rate was significantly higher compared with the control group, ٨٠,٦٪ (٢٩\٣٦) versus ٢٤,١% (٧\٢٩), (p= ٠,٠٠٠١), as shown in table ٤. Table ٥, summarized the maternal complications. Patients in the study group had higher rate of maternal complications than those in the control group (٥٨,٣٪ versus ٣٧,٩٪, P=٠,١٠٢) respectively although the difference between the two groups didn't reach the statistical level of significance. Further categorization of the results of maternal complications for the patients in the study and control groups, HELLP syndrome was seen in (١١,١٪ versus ٣,٤%), neurological manifestations occurred in (٥٠٪ versus ٣١٪), acute renal failure developed in (٢٥٪ versus ٣,٤٪) and pulmonary oedema complicated (٥,٦٪ versus ٣,٤٪) respectively, all these complications were seen at higher rate in study group compared with the control group, but only acute renal failure reached the statistical level of significance (P=٠,٠١٧). Table ٦ reveals the neonatal complications for both groups which were higher in patients with abnormal uterine artery Doppler (٧٢,٢٪) in comparison to that of controls (٣٧,٩٪).This difference in the neonatal complications was statistically highly significant (P=٠,٠٠٦). Regarding small-for-gestational age, study group developed higher rate of small-for-gestational age than control group (٢٢.٢٪ versus ١٣,٨٪), Apgar score at ٥ minute <٧ was seen in(٣٦,١٪ versus ٣٧,٩٪), significant neonatal morbidity developed in(١٩,٤٪ ersus ١٣,٨٪), and perinatal death complicated (٣٨,٩٪ versus ٦,٩٪) respectively which was statistically highly significant (p = ٠,٠٠٣).

Table ١: Demographic characteristics, for patients with normal and abnormal uterine artery Doppler.

Maternal characteristics	Cases (n= ٣٩		Control (n=٢٩)		P value
	Mean±SD	Range	Mean±SD	Range	
Maternal age (years)	٢٥,٣٦±٥,٨١	١٥-٤٠	٢٤,٦٦±٦,٢٢	١٦-٤١	٠,٦٣٩
Gestational age (weeks)	٣١,٠٠±١,٨٨	٢٨-٣٤	٣١,٨٣±١,٧١	٢٨-٣٤	٠,٠٧١
Gestational age at delivery (weeks)	٣١,٥٠±٢,٠٦	٢٨-٣٦	٣٢,٣١±١,٩١	٢٨-٣٦	٠,١٠٩
BMI (Kg/m²)	٢٧,٣٠±٥,٥٦	٢٠-٤٠	٢٨,٤٨±٦,٦٤	٢٠-٤٤	٠,٤٤٠
*Significant using Students-t-test for difference between two independent means at ٠,٠٥ level of significance					

Table ٢: Birth weight distribution among both groups.

Birth weight (Kg)	Cases (n=٣٦)		Control (n=٢٩)		P value
	No	%	No	%	
<١٢٥٠	٧	١٩,٤	٢	٦,٩	
١٢٥٠---	١١	٣٠,٦	٣	١٠,٣	
١٥٠٠---	٣	٨,٣	٣	١٠,٣	
١٧٥٠---	٦	١٦,٧	٧	٢٤,١	
٢٠٠٠---	٦	١٦,٧	٤	١٣,٨	
≥٢٢٥٠	٣	٨,٣	١٠	٣٤,٥	
(Range)Mean±SD	١٦٢٥,٨±٤٢٤	٩٠٠-٢٤٥٠	٢٠٠٧,١±٥٦٩	١١٠٠-٣٢٠٠	٠,٠٠٣*
*Significant using Pearson Chi-square test for difference between proportions and Students-t-test for difference between two independent means at ٠,٠٥ level of significance					

Table ٣: Caesarean section distribution among both groups.

Caesarean section	Cases (n=٣٦)		Control (n=٢٩)		P value
	No	%	No	%	
Yes	٣٤	٩٤,٤	٢١	٧٢,٤	٠,٠١٤*
No	٢	٥,٦	٨	٢٧,٦	
*Significant using Pearson Chi-square test for difference between proportions at ٠,٠٥ level of significance					

Table ٤: Rate of abnormal umbilical artery Doppler distribution among both groups

	Cases (n=٣٦)		Control (n=٢٩)		P value
	No	%	No	%	
Abnormal	٢٩	٨٠,٦	٧	٢٤,١	٠,٠٠٠١*
Normal	٧	١٩,٤	٢٢	٧٥,٩	
*Significant using Pearson Chi-square test for difference between proportions at ٠,٠٥ level of significance					

Table ٥: Maternal complications, for patients with normal and abnormal uterine artery Doppler

	Cases (n=٣٦)		Control (n=٢٩)		P value
	No	%	No	%	
Maternal complication	٢١	٥٨,٣	١١	٣٧,٩	٠,١٠٢
HELLP	٤	١١,١	١	٣,٤	٠,٢٤٩
Neurological manifestations	١٨	٥٠,٠	٩	٣١,٠	٠,١٢٣
Acute renal failure	٩	٢٥,٠	١	٣,٤	٠,٠١٧*
Pulmonary oedema	٢	٥,٦	١	٣,٤	٠,٦٨٧
*Significant using Pearson Chi-square test for difference between proportions at ٠,٠٥ level of significance					

Table ٦: Neonatal complications, for patient ٤٠ normal and abnormal uterine artery Doppler

	Cases (n=٣٦)		(Control (n=٢٩)		P value
	No	%	No	%	
Small-for-gestational age	٨	٢٢,٢	٤	١٣,٨	٠,٣٨٤
Neonatal complications	٢٦	٧٢,٢	١١	٣٧,٩	٠,٠٠٦*
Apgar score ٥ <٧	١٣	٣٦,١	١١	٣٧,٩	٠,٨٨٠
Neonatal morbidity	٧	١٩,٤	٤	١٣,٨	٠,٥٤٦
Perinatal death	١٤	٣٨,٩	٢	٦,٩	٠,٠٠٣*
*Significant using Pearson Chi-square test for difference between proportions at ٠,٠٥ level of significance					

DISCUSSION:

Preeclampsia remains an important cause of maternal and neonatal complications and death [١٥-١٧]. Doppler ultrasonography of the uterine arteries is becoming a routine part of pregnancy surveillance in high-risk pregnancies and is a promising technique for predicting these complications [١٨]. This study demonstrates that in severe early-onset preeclampsia there is higher rate of abnormal uterine artery Doppler examinations (٥٥,٣٪) compared to normal uterine artery Doppler (٤٤,٦٪) , this finding was in agreement with that reported by Meler et al. [١٩] who studied the predictive capacity of umbilical, cerebral and uterine artery Doppler in women with preeclampsia (PE) , and the associated complications and adverse perinatal outcome. In both early- and late-onset forms, uterine artery Doppler examinations showed a greater capacity than umbilical and middle cerebral artery Doppler examinations for predicting adverse perinatal outcome. Pulsatility index (PI) is a good predictor of adverse outcome of pregnancies. Ghosh et al. [٢٠] demonstrated that RI and PI as measures of third trimester utero-placental vascular impedance were the best predictors of adverse outcome in high risk pregnancy. In this study we depend on PI and /or notching as a predictor of adverse maternal and neonatal outcome. In their study, Cnossen, et al. [٢١] reported that pulsatility index alone or combined with notching, was the most predictive Doppler index in high risk pregnancy eg. preeclampsia. In the present study, abnormal uterine artery Doppler in the third trimester of pregnancy in women with severe early-onset preeclampsia was found to be predictive of a higher rate of maternal and neonatal complications. These findings were in agreement to those reported by Meler et al. in ٢٠١٠ [٢٢], While Ghi et al. in ٢٠٠٩ [٢٣] studied the usefulness of uterine artery Doppler in the prediction of outcome in patients with late-onset preeclampsia, They found that women with late-onset preeclampsia showed a higher risk of perinatal complications if uterine resistance was increased although maternal outcome does not seem to be related to Doppler findings. ٤١

With respect to the evaluation of the biological characteristics of the patients enrolled in the present study, there was no statistically significant difference between two groups with respect to maternal age, BMI, gestational age at admission, gestational age at delivery, with a tendency towards overweight found in the present study, this was similar to the profile observed in patients with a greater risk for preeclampsia in pregnancy and was in agreement with the results reported by de Melo et al. [٢٤]. With respect to gestational age at delivery, mean gestational age was lower in the group with a resistant uterine artery Doppler compared to the group with normal uterine artery Doppler, but the difference was not significant, this finding disagree with Meler et al. [٢٢], Ghi et al. [٢٣], de Melo et al. [٢٤] who found statistically significant difference in gestational age at delivery. This might be due to small sample size enrolled in this study. Among patients with abnormal uterine Doppler results, mean birth weight was significantly lower in study group compared with controls. A higher rate of small-for-gestational age was also found in study group compared to controls. These findings were in agreement to those reported by Ghi et al. [٢٥] Carbillon et al. [٢٦] and Yu et al. [٢٧].

In the current study, a significantly higher rate of cesarean delivery was found in group with increased uterine artery resistance in the third trimester. Our findings were in agreement to those reported by Vergani et al. [٢٨]. It might seem

reasonable to expect that in cases with high-resistance placental circulation there would be reduced fetal tolerance to the intermittent oxygen deprivation produced by labor contractions leading to higher rate of fetal distress.

In abnormal uterine artery Doppler group, abnormal umbilical artery Doppler examination was significantly higher compared to controls

(p=٠,٠٠٠١). This finding was consistent with that reported by Chosh and Gudmundsson [٢٩], they also reported that these two vessels were comparable in predicting adverse outcome.

This study shows that patients with severe preeclampsia with increased uterine artery resistance in their third trimester were at higher risk of obstetric and perinatal complications. As shown in table ٥, maternal complications rate was higher in study group compared with controls, although it didn't reach statistical level of significance. Nevertheless, the absolute frequency of all the complications was evaluated. These higher rates reported in our study did not reach statistical significant difference, except for acute renal failure in which the difference was statistically significant (p=٠,٠١٧). This partially agree with the results found by Meler *et al.* [٣٢], who reported a significantly higher rate of maternal complications in patients with severe early-onset preeclampsia with increased uterine artery resistance in their third trimester. Regarding the rate of neonatal complications, for both groups it was significantly higher in abnormal uterine artery Doppler group as compared with controls, (P=٠,٠٠٦). In the present study there was a statistically highly significant difference in perinatal death rate between cases and controls (P=٠,٠٠٣), this may be contributed to high number of small-for-gestational age and lower birth weight in study group compared with controls. These findings agree with majority of researchers who investigated uterine artery Doppler as predictive tool of adverse neonatal complications [٢٢-٢٧].

It is possible that future studies with larger sample size will show statistically significant differences with respect to the frequency of these outcomes.

CONCLUSION:
Women with severe early-onset preeclampsia are at higher risk of maternal and neonatal complications if abnormal uterine blood flow is present. Uterine artery Doppler examination is a good predictor for maternal and perinatal outcome in pregnancies complicated with preeclampsia and can be included as a primary surveillance test for high risk group.

REFERENCES:
١. World Health Organization (WHO): Make Every Mother and Child Count. WHO Report, ٢٠٠٥. Geneva, WHO, ٢٠٠٥.
٢. Confidential Enquiry into Maternal and Child Health (CEMACH) Perinatal Mortality ٢٠٠٦: England, Wales and Northern Ireland. London, CEMACH, ٢٠٠٨.
٣. Duley L: The global impact of pre-eclampsia and eclampsia. Semin Perinatol ٢٠٠٩; ٣٣: ١٣٠–١٣٧.
٤. Van Asselt K, Gudmundsson S, Lindqvist P, Marsal K: Uterine and umbilical artery velocimetry in pre-eclampsia. Acta Obstet Gynecol Scand ١٩٩٨; ٧٧: ٦١٤–١٩.
٥. Frusca T, Soregaroli M, Platto C, Enterri L, Lojacono A, Valcamonico A: Uterine artery velocimetry in patients with gestational hypertension. Obstet Gynecol ٢٠٠٣;١٠٢:١٣٦–٤٠.
٦. Li H, Gudnason H, Olofsson P, Dubiel M, Gudmundsson S: Increased uterine artery vascular impedance is related to adverse outcome of pregnancy but is present in only one third of late third trimester pre-eclamptic women. Ultrasound Obstet Gynecol ٢٠٠٥;٢٥: ٤٥٩–٦٣.
٧. Crispi F, Dominguez C, Llurba E, Martin-Gallan P, Cabero L, Gratacos E: Placental angiogenic growth factors and uterine artery Doppler findings for characterization of different subsets in preeclampsia and in isolated intrauterine growth restriction. Am J Obstet Gynecol ٢٠٠٦; ١٩٥:٢٠١– ٧.
٨. Crispi F, Llurba E, Dominguez C, Martín-Gallan P, Cabero L, Gratacos E. Predictive value of angiogenic factors and uterine artery Doppler for early- versus late-onset pre-eclampsia and intrauterine growth restriction. Ultrasound Obstet Gynecol. ٢٠٠٨; ٣١:٣٠٣–٩.
٩. Baschat AA: Integrated fetal testing in growth restriction: combining multivessel Doppler and biophysical parameters. Ultrasound Obstet Gynecol ٢٠٠٣; ٢١: ١–٨.
١٠. Hernandez-Andrade E, Brodszki J, Lingman G, Gudmundsson S, Molin J, Marsal K: Uterine artery score and perinatal outcome. Ultrasound Obstet Gynecol ٢٠٠٢;١٩:٤٣٨-٤٢.
١١. Huppertz B. Placental origins of preeclampsia: challenging the current hypothesis. Hypertension. ٢٠٠٨; ٥١: ٩٧٠ –٧٥.

٤٢

۱۲. National Institute for Health and Clinical Excellence. Hypertention in Pregnancy. The Management of Hypertensive Disorders during Pregnancy. NICE Clinical Guideline ۱۰۷, ۲۰۱۰. Available at: www.nice.org.uk/nicemedia/live/۱۳۰۹۸/۵۰٤۱۸/۵۰٤۱۸.pdf.

۱۳. Acharya G, Wilsgaard T, Berntsen GK, Maltau JM, Kiserud T. Reference ranges for serial measurements of umbilical artery Doppler indices in the second half of pregnancy. Am J Obstet Gynecol ۲۰۰۵;۱۹۲:۹۳۷-٤٤.

۱٤. Gómez O, Figueras F, Fernández S, Bennasar M, Martínez JM, Puerto B, Gratacós E. Reference ranges for uterine artery mean pulsatility index at ۱۱–٤۱ weeks of gestation. Ultrasound Obstet Gynecol ۲۰۰۸;۳۲:۱۲۸–۳۲.

۱۵. Sibai B, Dekker G, Kupferminc M. Pre-eclampsia. Lancet ۲۰۰۵; ۳۶۵:۷۸۵-۹۹.

۱٦. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. Lancet ۲۰۰٦; ۳٦۷:۱۰٦٦-۷٤.

۱۷. Walker JJ. Pre-eclampsia. Lancet ۲۰۰۰; ۳۵٦:۱۲٦۰-۵.

۱۸. McLeod L: How useful is uterine artery Doppler ultrasonography in predicting pre-eclampsia and intrauterine growth restriction? CMAJ ۲۰۰۸;۱۷۸:۷۲۷-۲۹.

۱۹. Meler E, Figueras F, Mula R, Crispi F, Benassar M, Gómez O, Gratacós E: Prognostic role of uterine artery Doppler in patients with preeclampsia. Fetal Diagn Ther ۲۰۱۰;۲۷: ۸-۱۳.

۲۰. Ghosh G, Breborowicz A, Brazert M, Maczkiewicz M, Kobelski M, Dubiel M, Gudmundsson S: Evaluation of third trimester uterine artery flow velocity indices in relationship to perinatal complications. J Matern Fetal Neonatal Med. ۲۰۰٦; ۱۹: ۵۵۱-۵۵.

۲۱. Cnossen JS, Morris RK, ter Riet G, Mol BW, van der Post JA, Coomarasamy A, Zwinderman AH: Use of uterine artery Doppler ultrasonography to predict pre-eclampsia and intrauterine growth restriction: a systematic review and bivariable meta-analysis. CMAJ. ۲۰۰۸;۱۷۸:۷۰۱–۱۱.

۲۲. Meler E, Figueras F, Bennasar M, Gomez O, Crispi F, Gratacos E. The prognostic role of uterine artery Doppler investigation in patients with severe early-onset preeclampsia. Am J Obstet Gynecol. ۲۰۱۰; ۲۰۲: ۵۵۹.e۱-٤.

۲۳. Ghi T, Youssef A, Piva M, Contro E, Segata M, Guasina F, Gabrielli S, et al. The prognostic role of uterine artery Doppler studies in patients with late-onset preeclampsia. Am J Obstet Gynecol. ۲۰۰۹; ۲۰۱: ۳٦.e۱-۵.

۲٤. de Melo BC, de Amorim MM, Katz L, Coutinho I, Veríssimo G: Uterine artery Doppler in the third trimester of pregnancy and postnatal outcome of patients with severe preeclampsia. Hypert in Preg ۲۰۱۰;۲۹:۱۳۵–٤۷.

۲۵. Ghi T, Contro E, Youssef A, Giorgetta F, Farina A, Pilu G, Pelusi G: Persistence of increased uterine artery resistance in the third trimester and pregnancy outcome. Ultrasound Obstet Gynecol. ۲۰۱۰;۳٦: ۵۷۷-۸۱.

۲٦. Carbillon L, Uzan M, Largillière C, Perrot N, Tigaizin A, Paries J, Pharizien I, Uzan S: Prospective evaluation of uterine artery flow velocity waveforms at ۱۲–۱٤ and ۲۲–۲٤ weeks of gestation in relation to pregnancy outcome and birth weight. Fetal Diagn Ther ۲۰۰٤;۱۹:۳۸۱-۸٤.

۲۷. Yu CK, Khouri O, Onwudiwe N, Spiliopoulos Y, Nicolaides KH: Prediction of pre-eclampsia by uterine artery Doppler imaging: relationship to gestational age at delivery and small-for-gestational age. Ultrasound Obstet Gynecol ۲۰۰۸; ۳۱: ۳۱۰–۱۳.

۲۸. Vergani P, Roncaglia N, Andreotti C, Arreghini A, Teruzzi M, Pezzullo JC, Ghidini A: Prognostic value of uterine artery Doppler velocimetry in growth-restricted fetuses delivered near term. Am J Obstet Gynecol ۲۰۰۲;۱۸۷:۹۳۲–۳٦.

۲۹. Ghosh GS, Gudmundsson S: Uterine and umbilical artery Doppler are comparable in predicting perinatal outcome of growth-restricted fetuses. BJOG ۲۰۰۹;۱۱٦:٤۲٤-۳۰.

۲۳