The Egyptian Journal of Hospital Medicine (July 2021) Vol. 84, Page 1852-1857

Screening of High-Risk Patient by Uterine Artery Doppler Analysis in The 1st Trimester to Predict Early Onset Pre-Eclampsia

Hasnaa Mohamed Elfouly Mohamed, Ahmed Mahmoud Moustafa Badawy, Ashraf Ghanem, Khaled Samir Ismail

Department of Obstetrics and Gynecology, Faculty of Medicine - Mansoura University, Egypt

***Corresponding Author:** Hasnaa Mohamed Elfouly Mohamed, **Mobile:** (+20)01068360579,

Email: elawadyabdalla88@gmail.com

ABSTRACT

Background: Preeclampsia (PE) is still a major obstetrical problem world-wide. First trimester prediction of PE is of great clinical importance, as it would allow clinicians to focus on high-risk groups and initiate prophylactic medical treatment. The first stage of pre-eclampsia begins in the first trimester by impaired placentation. High-resistant spiral arteries can be detected from the 11th week of gestation by uterine artery (UtA) Doppler examination.

Objective: To assess the relationship between 1st trimester uterine artery pulsatility index (UtA PI) and the development of early onset PE. **Patients and Methods:** Prospective observational study was performed at Mansoura University Hospital**.** This study was conducted on 109 pregnant women who attended their routine antenatal care visits at the Outpatient Obstetrics and Gynecology Clinic of Mansoura University Hospital.

Results: There were statistically high significant difference between both groups in the BMI ($p = 0.003$), and no statistically significant difference as regards the age, gravidity and gestational age ($p > 0.05$). Statistically significant difference was evident between two groups in the mean values of UtA PI ($p = 0.028$). The best cutoff value of UtA PI for the prediction of early onset preeclampsia was ≥ 2.03 with accuracy of 0.79, and that of BMI was ≥ 35 with accuracy of 0.93.

Conclusion: This study revealed that first trimester uterine artery Doppler can be used as a reliable screening test for prediction of preeclampsia in high risk women. It is a reliable, noninvasive method of examining uteroplacental perfusion. Abnormal UA Doppler ultrasonography (elevated PI) in 11–14 weeks' gestation can predict pre-eclampsia.

Keywords: Early onset pre-eclampsia, High risk patient, Screening, Uterine Artery Doppler.

INTRODUCTION

Preeclampsia (PE) is still a major obstetrical problem world-wide. It is one of three major factors causing maternal and fetal morbidity and mortality, and at the same time being one of the most important factors responsible for preterm birth [(1)].

Currently, there is no treatment for PE other than delivery. Furthermore, the lack of specific predictive and diagnostic tools makes clinical handling of the disease a global maternal health problem with many unmet clinical needs. PE is a syndrome of pregnancy defined by its clinical manifestations, proteinuria, and hypertension [(2)].

First trimester prediction of PE is of great clinical importance, as it would allow clinicians to focus on high-risk groups and initiate prophylactic medical treatment. Health economists have calculated that it would be economically beneficial to screen for PE as long as there is an effective intervention method available [(3)].

The first stage of pre-eclampsia begins in the first trimester by impaired placentation that leads to shallow trophoblast invasion of the maternal decidua and spiral arteries, resulting in insufficient remodeling of the smooth muscle wall of the arteries and consequently, inadequate perfusion of the placenta [(4)]. Impaired developments of the placenta translate into persistently elevated resistance to blood flow in the uteroplacental circulation. This is reflected in abnormal waveform patterns of the uterine arteries on sonograghic Doppler velocimetry evaluation with increase pulsatility and resistance indices seen [(5)].

High-resistant spiral arteries can be detected from the 11th week of gestation by uterine artery (UtA) Doppler examination [(6)]. Therefore, first trimester UtA Doppler examination may be a good noninvasive method for predicting PE that reflects abnormal trophoblast invasion [(7,8)].

The aim of this study was to assess the relationship between 1st trimester uterine artery pulsatility index (UtA PI) and the development of early onset PE through prospective observational study.

PATIENTS AND METHODS

Prospective observational study was conducted on 109 pregnant women who attended their routine antenatal care visits at the Outpatient Obstetrics and Gynecology Clinic of Mansoura University Hospital.

Ethical consent:

An approval of the study was obtained from Mansoura University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in this research.

Inclusion criteria: Nulliparous pregnant women, a singleton pregnancy, gestational age of 11 to 13 weeks,

Received: 21/ 01/2021
Accepted: 18/ 03/2021

age less than 17 and more than 35 years, and BMI > 25.
Exclusion criteria: Multipara pregnant women, multiple pregnancy, current or prior history of hypertension, the development of complications during pregnancy, cardiovascular disease, diabetes mellitus, hepatic or renal disease, and connective tissue diseases, metabolic diseases, immunological diseases e.g., systemic lupus erythematosus.

All patients were subjected to the following:
1-Full history taking: Personal history, obstetric history, history of present illness, and family history.
2-Clinical Examination: Full general and local examination, blood pressure measurement, and all subjects were refrained from caffeine and drugs that could alter the cardiovascular system function on the day before the tests.
3-Ultrasound examination:

- The ultrasound machine used for imaging was Voluson 530D® (Medison-Kretz, Zipf, Korea-Austria) with a 3.5- 5-MHz curvilinear probe for transabdominal ultrasound and TVS probe (6-9 MHz).
- The patients were evaluated trans-abdominally with full bladder to confirm a live fetus and to determine the gestational age. Uterine artery PI was then measured.
- All quantitative Doppler measurements were performed by a single examiner to obviate inter observer variability.
- Ultrasound assessment of uterine artery Doppler velocimetry was performed using color Doppler in the 2D mode, and flow velocity waveforms were obtained from the ascending main branch of the uterine artery on the right and left sides of the cervix in a longitudinal plane before they entered the uterus, or from the proximal part of the main UtA.
- The gate of the Doppler was positioned when the vessel with good color signals was identified on the screen.
- Pulsed-wave Doppler was applied to capture UtA Doppler flow velocity waveforms from which UtA PI measures were calculated automatically by the system.
- At the level of the internal os pulsed-wave Doppler was used with the angle of insonation <30 and the sampling gate set at 2 mm and with the appearance of three typical and identical consecutive waves, the PI of both uterine arteries was detected, and the mean PI of them was calculated.

4-Follow up:

- The included individuals were followed up and they were evaluated for arterial blood pressure measurements and laboratory urine protein findings. The results were correlated with the recorded Doppler measurements.
- The included individuals were followed up and they were evaluated for arterial blood pressure measurements and laboratory urine protein findings. The results were correlated with the recorded Doppler measurements.
- The primary outcome of the study was the development of early onset PE, which was defined as new onset hypertension (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) plus proteinuria (> 0.3 g/24 hours) after 20 weeks of gestation according to recommendations of The American College of Obstetricians and Gynaecologists [(10)].

Statistical analysis

Data were tabulated and introduced into a PC using MedCalc, version 17.9.7 (MedCalc Software bib, Ostend, Belgium). Data were represented as mean and standard deviation (SD) for numerical data and frequency and percentage for non-numerical data. Fisher exact test was used for comparison of categorical data. Student t-test was used for comparison between two samples' means. If the *P* value was less than 0.05 it was considered statistically significant and *P* value less than 0.01 was considered statistically highly significant. ROC curve analysis was performed to test the validity of screening tests including the sensitivity, specificity, and accuracy.

RESULTS

Table 1 shows that the mean age of the study participants was 36.33 years. 4.58% of them were ≤ 17 years and 95.42% were ≥ 35 years. The mean BMI was 29.43 Kg/m^2, 54.63% of them had a BMI value of 25 - < 30 and 45.37% had a value of ≥ 30 Kg/m^2. The mean gravidity was 1.81 times and few of the participants (7.34%) were having > 3 pregnancies. The mean GA was 12.11 weeks.

Table (1): Participants demographic and obstetric history

	Study patients (n = 109)	
	Mean	**SD**
Age (years)	36.33	5.03
BMI (Kg/m^2)	29.43	3.25
Gravidity	1.81	1.04
GA (weeks)	12.11	0.72
	Frequency	**Percentage**
Age (years)		
Age group ≤ 17	5	4.58%
Age group ≥ 35	104	95.42%
Gravidity		
Gravida 1-3	101	92.66%
Gravida > 3	8	7.34%
BMI (Kg/m^2)		
BMI: 25 – 30	59	54.63%
BMI: ≥ 30	50	45.37%

Table 2 shows that the mean UtA PI was 1.74, and

that 11% of the study participants developed early onset preeclampsia.

Table (2): UtA PI of the study participants and the percentage of patients diagnosed as early onset preeclampsia on the follow up (n = 109)

	Mean	SD
UtA PI	1.74	0.52
	Number	**Percentage %**
Early onset preeclampsia patients	12	11%

Table 3 shows the comparison between the normal participants and the patients developed early onset preeclampsia at the follow up. There was statistically high significant difference between both groups in the BMI, and no statistically significant difference as regards the age, gravidity and gestational age. Statistically significant difference was evident between two groups in the mean values of UtA PI.

Table (3): The Participants clinical data to the final diagnosis

	Normal participants N = 97	Early onset preeclampsia patients N = 12	P
Age (years)	36.25 ± 4.83	36.98 ± 6.63	0.637
BMI (Kg/m^2)	29.14 ± 2.94	31.79 ± 4.63	0.007**
Gravidity	1.78 ± 0.98	2 ± 1.48	0.24
GA (weeks)	12.09 ± 0.71	12.33 ±0.81	0.279
UtA PI	1.71 ± 0.49	2.01± 0.64	0.028*

*: significant, **: highly significant.

Table 4 **s**hows that there was statistically significant difference between the two groups in the distribution of BMI categories. While, no statistically significant differences were noted as regarding the age groups as well as the number of gravidity.

Table (4): Distribution of the participants' clinical data

	Normal participants N = 97	Early onset preeclampsia patients N = 12	P
Age			
Age group ≤ 17	4 (4.12%)	1 (8.33%)	1
Age group ≥ 35	93 (95.88%)	11 (91.67%)	
Gravidity			
Gravida 1-3	90 (92.78%)	11 (91.67%)	1
Gravida > 3	7 (7.22%)	1 (8.33%)	
BMI (Kg/m^2)			
BMI: 25 - 30	57 (58.76%)	2 (16.67%)	0.011*
BMI: ≥ 30	40 (41.24%)	10 (83.33%)	

*: significant

Table 5 shows that the best cutoff value of UtA PI for the prediction of early onset preeclampsia was ≥ 2.03 with accuracy of 0.79, and that of BMI was ≥ 35 with accuracy of 0.93.

Table (5): ROC curves evaluation for the use of UtA PI and BMI in the prediction of early onset preeclampsia

	UtA PI	BMI
Area under the curve (AUC)	0.76	0.6859
Sensitivity	0.75	0.3333
Specificity	0.79	1.0000
Cutoff value	≥ 2.03	≥ 35.00
Accuracy	0.79	0.93
P	0.0017	0.0221*

*: significant

DISCUSSION

In the present study, 11% of the study participants developed early onset preeclampsia and uterine artery PI was 1.74.

Further comparison between the normal participants and the patients developed early onset preeclampsia at the follow up revealed that there was statistically high significant difference between both groups in the BMI, and no statistically significant difference as regards the age, gravidity and gestational age. Statistically significant difference was evident between the two groups in the mean values of uterine artery PI.

In a recent Nigerian study of **Adekanmi *et al.* [(11)],** the authors evaluated the uterine arteries changes and pregnancy outcomes in cases that developed PE and those that did not among a cohort of high-risk pregnancy (HRP) women. They aimed at evaluation of the Doppler parameters that best predict PE in high-risk pregnant women. In agreement with our study results, they reported that there was no significant difference in the age between the women who developed PE and pregnant women who did not develop PE. The results of **Yıldırım *et al.* [(12)]** also revealed no significant difference between both groups as regards the age and gravidity.

As regards BMI, our results were in agreement with the study of **Demers *et al.* [(13)]**, as they reported significant difference between both groups in the BMI values. However, **Liu *et al.* [(14)]** reported that age showed significant difference among eclampsia cases and controls. This difference may be due to the patient selection criteria of eclampsia cases employed in their study compared with PE cases in this study.

Several studies have reported various proportions of occurrence of PE among high-risk pregnant women **[(14)]. Diguisto *et al.* [(15)]** conducted a study aiming at evaluation of the accuracy of uterine artery Doppler in the first trimester for preeclampsia screening. In accordance to this study, they prospectively enrolled women at high risk of preeclampsia. Out of 226 women

included in their study, 27 (11.9%) women developed preeclampsia. This is similar to our finding (11%). A recent Egyptian study was performed by **Sileem *et al.*** [16], at Al Azhar University Hospital. In consistency with the result of the present study, they reported that of the enrolled pregnant women, 20 (12%) developed preeclampsia during follow-up (preeclampsia group), whereas 150 (88%) remained normotensive (control group). Another Egyptian study performed at Zagazig University Hospitals by **Salem and Ammar** [17], to assess the reproducibility of uterine artery PI to predict preeclampsia, they reported that 10% of the study participants developed preeclampsia.

In contrast, **Adekanmi *et al.*** [11], among the Nigerian women studied, 62.2% of women with high risk pregnancy had preeclampsia with or without other complications. In the **Oancea *et al.*** [18] study, the investigators explored the hypothesis that a basic, routinely performed procedure, first-trimester ultrasound monitoring, may provide a window of opportunity for screening for preeclampsia using a standalone biomarker, in pregnant women with known risk factors for the disorder. Therefore, they studied the potential of first trimester uterine artery Doppler ultrasonography for the early prediction of PE, in at-risk pregnant women. They conducted a prospective longitudinal study, including Caucasian pregnant women with risk factors for PE. The potential of pulsatility indexes (PI) and notch was assessed as a tool for preeclampsia screening. They reported that 21.6% of their study participants developed preeclampsia during pregnancy. It should be noted that the presence of vascular pathology prior to pregnancy or obstetric accidents unexplained at the time of their occurrence increases the risk of PE. **Liu *et al.*** [14] described in their study findings that among 412 Taiwanese with gestational hypertensive disorders; preeclampsia was developed in 88.3% of the high risk women. In their study, **Adekanmi *et al.*** [11], **Liu *et al.*** [14] and **Oancea *et al.*** [18] did not exclude participants with hypertension or other comorbidities; and this might account for the observed high discrepancy in the proportion of women developed preeclampsia in their study relative to the low finding in the present study.

Our observation of increased mean uterine artery PI in women that developed PE compared with those that did not is in accordance with the findings of **Adekanmi *et al.*** [11], **Diguisto *et al.*** [15] and **Barati *et al.*** [19]**.** Uterine artery PI reflects total measurable distal vascular resistance and provides information about placental volume and the cross-section of placental vessels [20]. Multiple studies have evidenced that predisposing maternal factors may induce functional atherosclerotic and vasoactive changes in spiral arteries, which are more or less transformed into uteroplacental arteries, resulting in preeclamptic syndrome [21, 22].

Plasencia *et al.* [23] examined the uterine artery PI in 3107 pregnancies at 11 to 13 weeks and compared the measurements with those at a later gestation (21to 23 weeks). The uterine artery PI was above the 90th centile in 77% of cases of early preeclampsia and in 27% of the late preeclampsia cases. An elevated uterine artery PI above the 90th centile persisted at 21 to 24 weeks in 94% of the early preeclampsia cases, 74% of the late preeclampsia cases, and 37% of those who did not develop preeclampsia. A predictive testing model incorporating maternal factors, uterine artery PI in the first trimester, and the change in uterine artery PI between the first and second trimesters achieved a detection rate for early preeclampsia of 90.9% at a false positive rate of 5%.

A similar study was performed by **Gómez *et al.*** [7] where sequential uterine artery Doppler recordings were taken at 11–14 weeks and repeated at 19-22 weeks. The mean PI was calculated from bilateral uterine artery measurements. Women whose pregnancies went on to develop complications (preeclampsia, gestational hypertension, and FGR) demonstrated a higher mean PI. A persistently raised uterine artery PI > 95th centile was associated with the greatest risk of adverse outcome. Even when the uterine artery PI normalized between the first and second trimesters, women still had a substantially increased risk of pregnancy complications**.**

The data obtained in this study also showed that in PE screening, in patients at high risk, Doppler examination of the uterine artery performed early at 12–13 weeks allows the detection of pregnancies that will develop PE with a sensitivity of 75% and a specificity of 79% based on PI analysis. The results of our study are in agreement with other studies which, analyzing Doppler changes in the first trimester of pregnancy, reported similar detection rates of overall PE, with a higher prediction for early onset PE (<34 weeks) [18,24,25]**.**

The present study showed that the best cutoff value of uterine artery PI for the prediction of early onset preeclampsia was ≥ 2.03 with accuracy of 79% and AUC of 76%. These findings are in consistency with the findings of **Spencer *et al.*** [26] and **Plasencia *et al.*** [23], in which the uterine artery mean PI in the second trimester correctly predicts about 79% and 67% of all cases of PE. These values were slightly lower than what was documented by **Adekanmi *et al.*** [11], and higher than that documented by **Oancea *et al.*** [18], they reported AUC values of 86.2% and 62.12%, respectively. In the study of **Yıldırım *et al.*** [12], a comparable cutoff value was determined**.** They cited that in their study, when UtA PI cut-off value was taken as >2.23 in the prediction of PE cases, sensitivity was 42.31% and specificity was 82.10%. In our study we observed slightly lower specificity (79%), and considerably higher sensitivity (75%). **Velauthar *et al.*** [27] in their meta-analysis reviewed the accuracy of uterine artery Doppler analysis in first trimester and they found that the sensitivity of uterine artery PI for

detection of early onset PE is around 47%, and for any PE it is 26%. The Egyptian study of **El-hassab *et al.*** [28] found that uterine artery PI could predict PE at a sensitivity and specificity of 81.3 % and 72.2 % respectively. However, in the study of **Demers *et al.*** [13], first-trimester uterine artery PI was associated with preterm but not with term PE**.**

In a study by **Gomaa *et al.*** [29], they found that at 11–13 weeks of pregnancy the mean PI of uterine arteries was significantly higher in preeclamptic (2.46 ± 0.28) than in normal women (1.435 ± 0.45), and this is similar to our results. A value of PI ≥ 1.7 using the ROC curve gave sensitivity of 100%, specificity of 84.4%, PPV of 41.7%, NPV 100% and an accuracy of 94.3%. In **Salem and Ammar** [17] study, using a lower cutoff value for uterine artery Doppler study (PI > 1.69), they found higher sensitivity rates (100%). These findings confirmed the data previously mentioned in the review article of **Carbillon** [30] that showed high sensitivity of uterine artery PI in preeclampsia prediction**.**

Previous researchers have reported different findings on the Doppler parameter that best predict PE among high-risk patients. These include abnormal uterine artery PI values of >1.45 and/or the presence of bilateral diastolic notch [19]**. Adekanmi *et al.*** [11] evaluated various combinations of the uterine and umbilical arteries Doppler parameters that best predict PE, and they observed that the uterine artery PI alone best predict PE. They also observed that the uterine artery PI significantly predict about 86% of PE cases correctly in their study (AUC = 0.862). This is slightly higher than the figures reported by our study**.**

In line with our study, the significantly higher mean uterine artery PI among PE cases compared to women without PE, support the report by **Mallikarjunappa *et al.*** [31] that the uterine and umbilical artery Doppler study showed elevation of these three parameters among pregnant women with PE in the second and third trimester. This was also corroborated by **Li *et al.*** [32] report. However, most published data do not support the routine introduction of uterine artery PI alone as a sole predictive test, but it should be combined with serum biochemical markers to increase its predictive value [15-17, 30].

In contrast, **Lopez-Mendez *et al.*** [33] observed no significant difference in the uterine arteries' PI and resistance index (RI), but reported a significant difference in the umbilical artery PI and RI between high risk women with preeclampsia and those without. These differences could be because of differences in population dynamics and the abnormality limits of obstetric Doppler parameters which may differ between populations.

CONCLUSION

This study revealed that first trimester uterine artery Doppler can be used as a reliable screening test for prediction of preeclampsia in high risk women. It is a reliable, noninvasive method of examining uteroplacental perfusion. Abnormal UtA Doppler ultrasonography (elevated PI) in 11–14 weeks' gestation can predict pre-eclampsia. In cases where the test proves to be abnormal, increased surveillance and delivery in a well-equipped setup is necessary to reduce the maternal and fetal complications. However, this study was performed on a small group of women, and so further study in a large cohort is necessary to validate the results of this study.

REFERENCES

1. **Ghulmiyyah L and Sibai B (2012):** Maternal mortality from preeclampsia/eclampsia. Seminars in Perinatology, 36(1): 56–59.
2. **Brown M, Lindheimer M, De Swiet M *et al.* (2001):** The classification and diagnosis of the hypertensive disorders of pregnancy: statement from the international society for the study of hypertension in pregnancy (ISSHP). Hypertension in Pregnancy, 20(1): 9–11.
3. **Hadker N, Garg S, Costanzo C *et al.* (2010):** Financial impact of a novel pre-eclampsia diagnostic test versus standard practice: a decision-analytic modeling analysis from a UK healthcare payer perspective. Journal of Medical Economy, 13(4): 728–37.
4. **Roberts J and Hubel C (2009):** The two stage model of preeclampsia: variations on the theme. Placenta, 30: 32-37.
5. **Campbell S, Diaz-Recasens J, Griffin D (1983):** New Doppler technique for assessing uteroplacental blood flow. Lancet, 1(8326 Pt1): 675-677.
6. **Caniggia, I, Winter, J, Lye S *et al.* (2000):** Oxygen and placental development during the first trimester: implications for the pathophysiology of preeclampsia. Placenta, 21: 25-30.
7. **Gómez O, Figueras F, Martínez J *et al.* (2006):** Sequential changes in uterine artery blood flow pattern between the first and second trimesters of gestation in relation to pregnancy outcome. Ultrasound in Obstetrics and Gynecology, 28: 802-808.
8. **Akolekar R, Syngelaki A, Sarquis R *et al.* (2011):** Prediction of early, intermediate and late pre-eclampsia from maternal factors, biophysical and biochemical markers at 11-13 weeks. Prenatal Diagnnosis, 31: 66-74.
9. **Mayrink J, Souza R, Feitosa F *et al.* (2019):** Incidence and risk factors for preeclampsia in a cohort of healthy nulliparous pregnant women: a nested case-control study. Scientific Reports, 9: 1-9.
10. **Poon L and Nicolaides K (2014):** Early prediction of preeclampsia. Obstetrics and Gynecology International, 2014,:297397.
11. **Adekanmi A, Roberts A, Akinmoladun J *et al.* (2019):** Uterine and umbilical artery Doppler in women with pre- eclampsia and their pregnancy outcomes. Nigerian Postgraduate Medical Journal, 26: 106-12.
12. **Yildirim K, Çakiroğlu Y, Ceylan, Y *et al.* (2019):** Prediction of preeclampsia by uterine artery Doppler examination and placental growth factor, endoglin and pregnancy-associated plasma protein levels in maternal serum at 11- 13+6 pregnancy week. European Archives of Medical Research, 35(3): 137-42.

13. **Demers S, Boutin A, Gasse C *et al.* (2019):** First-trimester uterine artery Doppler for the prediction of preeclampsia in nulliparous women: the Great Obstetrical Syndrome study. American Journal of Perinatology, 36: 930-935.
14. **Liu C, Cheng P, Chang S (2008):** Maternal complications and perinatal outcomes associated with gestational hypertension and severe preeclampsia in Taiwanese women. Journal of the Formosan Medical Association, 107(2): 129–138.
15. **Diguisto C, Piver E, Gouge A *et al.* (2017):** First trimester uterine artery Doppler, sFlt-1 and PlGF to predict preeclampsia in a high-risk population. The Journal of Maternal-Fetal & Neonatal Medicine, 30(13): 1514–1519.
16. **Sileem S, El-Barody M, Okasha A *et al.* (2020):** The role of clinical and laboratory tests along with uterine artery Doppler indices in the prediction of pre-eclampsia and pregnancy outcome in Egypt. Al-Azhar Assiut Medical Journal, 18: 348-58.
17. **Salem M, Ammar I (2018):** First-trimester uterine artery pulsatility index and maternal serum PAPP-A and PlGF in prediction of preeclampsia in primigravida. Journal of Obstetrics and Gynaecology of India, 68(3): 192–196.
18. **Oancea M, Grigore M, Ciortea R *et al.* (2020):** Uterine artery Doppler ultrasonography for first trimester prediction of preeclampsia in individuals at risk from low-resource settings. Medicina (Kaunas, Lithuania), 56(9): 428-32.
19. **Barati M, Shahbazian N, Ahmadi L *et al.* (2014):** Diagnostic evaluation of uterine artery Doppler sonography for the prediction of adverse pregnancy outcomes. Journal of Research in Medicine and Science, 19: 515-9.
20. **Harrington K, Fayyad A, Thakur V *et al.* (2004):** The value of uterine artery Doppler in the prediction of uteroplacental complications in multiparous women. Ultrasound in Obstetrics & Gynecology, 23(1): 50–55.
21. **Aardema M, Saro M, Lander M *et al.* (2004):** Second trimester Doppler ultrasound screening of the uterine arteries differentiates between subsequent normal and poor outcomes of hypertensive pregnancy: two different pathophysiological entities?. Clinical science (London, England: 1979), 106(4): 377–382.
22. **Prefumo F, Sebire N, Thilaganathan B (2004):** Decreased endovascular trophoblast invasion in first trimester pregnancies with high-resistance uterine artery Doppler indices. Human Reproduction (Oxford, England), 19(1), 206–209.
23. **Plasencia W, Maiz N, Poon L *et al.* (2008):** Uterine artery Doppler at 11 + 0 to 13 + 6 weeks and 21 + 0 to 24 + 6 weeks in the prediction of pre-eclampsia. Ultrasound in Obsteterics and Gynecolology, 32: 138-146.
24. **Melchiorre K, Leslie K, Prefumo F *et al.* (2009):** First-trimester uterine artery Doppler indices in the prediction of small-for-gestational age pregnancy and intrauterine growth restriction. Ultrasound in Obstetrics and Gynecology, 33(5): 524–529.
25. **Pilalis A, Souka A, Antsaklis P *et al.* (2007):** Screening for pre-eclampsia and small for gestational age fetuses at the 11-14 weeks scan by uterine artery Dopplers. Acta obstetricia et gynecologica Scandinavica, 86(5): 530–534.
26. **Spencer K, Cowans N, Chefetz I *et al.* (2007):** First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound journal of Obstetrics and Gynecology, 29: 128-34.
27. **Velauthar L, Plana M, Kalidindi M *et al.* (2014):** First-trimester uterine artery Doppler and adverse pregnancy outcome: a meta-analysis involving 55 974 women. Ultrasound in Obstetrics and Gynecology, 43: 500-507.
28. **El-hassab M, Rashed M, Elghannam M *et al.* (2020):** Predictive value of both serum placental protein-13 level and uterine artery Doppler for prediction of pre-eclampsia. International Journal of Medical Arts, 2: 528-534.
29. **Gomaa M, Naguib A, Swedan K *et al.* (2015):** Serum tumor necrosis factor-α level and uterine artery Doppler indices at 11-13 weeks' gestation for preeclampsia screening in low-risk pregnancies: a prospective observational study. Journal of Reproductive Immunology, 109: 31–35.
30. **Carbillon L (2012):** First trimester uterine artery Doppler for the prediction of preeclampsia and foetal growth restriction. The Journal of Maternal-Fetal & Neonatal Medicine, 25(7): 877–883.
31. **Mallikarjunappa B, Harish H, Ashish S *et al.* (2013):** Doppler changes in Pre-42. Eclampsia. Journal of International Medicine and Science Academy, 26, 215-6.
32. **Li H, Gudnason H, Olofsson P *et al.* (2005):** 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 Journal of Obstetrics and Gynecology, 25: 459-63.
33. **Lopez-Mendez M, Martinez-Gaytan V, Cortes-Flores R *et al.* (2013):** Doppler ultrasound evaluation in preeclampsia. British Medical Collaboration Research Notes, 6: 477-80.