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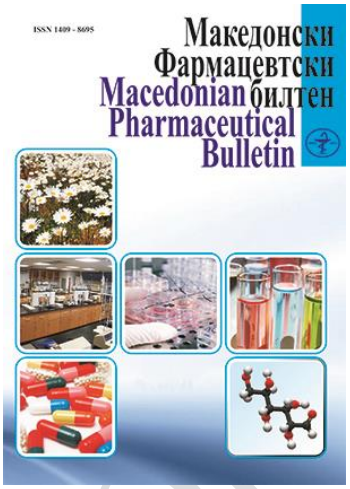

Title: Uterine artery pulsatility index as a relevant parameter in the prediction of preeclampsia

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Uterine artery pulsatility index as a relevant parameter in the prediction of preeclampsia

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Abstract

Preeclampsia is a clinical syndrome that occurs in 5-10% of pregnancies with increased perinatal morbidity and mortality. According to ISUOG (International Society of Ultrasound in Obstetrics & Gynecology), the use of the uterine artery pulsatility index (PI) is an important sensitive method in predicting the risk of preeclampsia.

This study is to emphasize the value of PI as a more relevant predictive parameter in the detection of preeclampsia in the second trimester compared to the presence of isolated uterine artery notch.

For the above purpose, 96 patients were examined at the University Clinic of Gynecology and Obstetrics in Skopje, divided into 2 groups: study and control group. The study group consisted of 48 patients from 14 to 20 gestational weeks with present uterine artery notch, being the main inclusion criterion. The control group consisted of 48 pregnant patients at the same gestational age with absence of uterine artery notch.

In the study group, 43.7% developed clinical syndrome of preeclampsia. The resistance index (RI) value was up to 0.73 and the predictive value of the RI was 57.1%. In patients who developed preeclampsia syndrome, the value of the PI above 1.75 was of much greater predictive value, with value of 71.4%. The sensitivity of these values was 88%, which is a reliable parameter.

PI is a reliable parameter in detecting the risk of developing preeclampsia and an indicator of great clinical significance in the daily practice in perinatology.

Keywords: preeclampsia; prediction; pulsatility index

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Introduction

Hypertensive disorders in pregnancy represent a serious health problem at a global level. The most common reason for maternal and fetal morbidity and mortality derives from them. According to the International Society for the study of Hypertension in Pregnancy (ISSHP, 2018) they are divided into 5 major groups: (1) Gestational hypertension, i.e., hypertension ≥140/90 mmHg developed after 20 weeks of gestation in previously normotensive patients in the absence of proteinuria; (2) Preeclampsia and/or eclampsia; (3) Chronic hypertension superimposed with preeclampsia; (4) Chronic hypertension with the presence of hypertension before the 20th gestational week persisting 6 weeks postpartum (Poon and Nicolaides, 2014) and (5) White-coat hypertension. According to the American Association of Obstetricians and Gynecologists (ACOG, 2013), preeclampsia is the presence of systolic blood pressure higher than or equal to 140 mmHg, and/or diastolic blood pressure higher or equal to 90 mmHg, after 20th gestational week, with present proteinuria greater than or equal to 300 mg/dL (or a minimum protein/creatinine ratio of 0.3 mg/dL or proteinuria ≥1+). If proteinuria is absent, at patients with hypertension, severe degree of clinical manifestations is present after 20 weeks of gestation. With these parameters preeclampsia can be diagnosed. They have manifestations of some of the following pathological conditions: thrombocytopenia below 100,000/μL, serum creatinine concentration greater than 1.1 mg/dL, or duplication of serum creatinine concentration in the absence of another renal disease, leading to renal insufficiency. Then the presence of elevated hepatic transaminases up to double the normal concentration leads to hepatic impairment, as well as the presence of cerebral and visual symptoms and pulmonary edema. In relation to the fetus, complications develop as a result of premature birth, placental abruption, and intrauterine growth restriction up to fetal death (Goel and Rana, 2014; Johns, 2014).

The etiopathogenesis of preeclampsia has not yet been fully defined and is therefore of significant interest. It is multifactorial, that is, it includes genetic, immunological, hematological and environmental factors, followed by angiogenic circulating factors, oxidative stress, inflammation, impaired hemostasis, protein lipid imbalance. The consequence is inadequate trophoblast remodeling of the spiral arteries,

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dysfunction of the mothers' endothel, inadequate placental implantation, and insufficient placental perfusion. It is divided into two stages, the first one, where endovascular invasion of the cytotrophoblast is reduced. The cytotrophoblast is not capable of changing from epithelial to endothelial phenotype, it cannot reduce the expression of adhesion molecules of the epithelium and accept the adhesion of the endothelium (which is, in fact, the pseudovasculogenesis), thus making the angiogenesis of the placenta inadequate (Cerdeira and Karumanchi, 2012).

Subsequently, inappropriate trophoblast remodeling of the spiral arteries occurs. The second stage contains the clinical expression of preeclampsia resulting from placental ischemia due to hypoperfusion and hypoxia. There is a varying degree of systemic inflammatory response, a widespread organic damage, explained by one theory - endothelial cell dysfunction. Glomeruloendotheliosis occurs in the kidneys, Kupffer cells accumulate in the hepatic sinusoids (HELLP syndrome) and endothelial cells involved in the blood-brain barrier (seizures at eclampsia).

The growth and development of uterine blood vessels is causing angiogenesis, which is the result of properly sent signals from proangiogenic and anti-angiogenic factors. The same blood vessels grow simultaneously, hypertrophy occurs (resistance decreases), then elongate (resistance increases), and after angiogenesis (decreased resistance) a total result of decreased vascular resistance to tissues for sufficient nutrition of the fetus (Nevers et al., 2011). Angiogenesis takes place in the early stages of pregnancy, but furthermore in the third trimester blood vessels have already developed, and any increase in the blood flow cannot be sufficiently compensated by vasodilatation.

Feto-placental markers important in prognosis are divided into (1) trophoblast invasion markers (PLGF, IGFBP-1, PAPP-A, Doppler ultrasound and HLA-G), (2) placental hypoxia (sFlt-1, VEGF, PLGF), (3) reactive oxygen species (lipid peroxide), and (4) placental function (activin/inhibin, CRH/CRHBP, and PAI-2). Maternal markers are also classified as: (1) metabolic syndrome BMI, leptin, insulin and glucose, (2) endothelial function (PAI-1, fibronectin, VCAM/ICAM), (3) prooxidants (PGF2a), (4) antioxidant reserve (Vit C and E) and (5) immunological function (AT-R autoantibodies). Despite advances in prediction, complete recognition is still lacking,

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with earlier stages of the condition designed to intervene well before the clinical symptomatology develops (Michita et al., 2018; Srinivas et al., 2009).

The early preeclampsia, is also called placental preeclampsia, due to a disruption of the trophoblast invasion at the level of the spiral arteries that, causing ischemia, leads to intrauterine growth restriction. Late preeclampsia, or maternal preeclampsia, is thought to occur secondary, as a consequence of maternal cardiovascular and metabolic predisposition to endothelial dysfunction due to the presence of the same risk factors as pre-existent hypertension, obesity, disorders in glucose tolerance and also dyslipidemia.

A significant contributor to the predictive value is the use of the uterine artery velocity. Increased flow resistance results in abnormal wavelengths and waveforms, resulting in increased pulsatility index (PI) or the presence of early diastolic notch. The value of the notch, as isolated screening, is of low sensitivity as a predictive parameter. The sensitivity of the present abnormal result for predicting preeclampsia is in the range of 20 to 60 percent. The notch of the uterine artery is considered a non rare occurrence, and can even be considered a normal finding in the first trimester in 46 to 64% of the pregnancies. After the twentieth week, the notch is defined as a fall of at least 50 cm/s from maximal diastolic velocity. The prevalence of the notch decreases as gestational age passes and stabilizes by the 25th gestational week (Barati et al., 2014).

According to ISUOG (ISUOG Guidelines, 2018), the use of the PI is an important sensitive method in predicting the risk of preeclampsia, with specific cut-off values in each trimester. Specifically, in the first trimester between 11 and 13.6 gestational weeks, the 95th percentile for PI noted a cut-off value of 2.35 measured transabdominally. In the second trimester, between 20 and 24 gestational weeks the cut-off value of PI is 1.44 (95th percentile measured transabdominally). In the third trimester, the 95th percentile for PI, noted a cut-off value of 1.17 measured transabdominally between 30 and 34 gestational weeks. Early preeclampsia is expected to have a disturbance of the flow through the uterine artery to be evident, while at late developed, the occurrence may be minimally present or close to the normal values.

Velauthar et al. (2014) performed a meta-analysis where they monitored the values of PI and resistance index (RI) indexes as well as the presence or absence of the notch.

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Therefore, this study was conducted to highlight the value of the uterine artery PI as a more relevant predictive parameter in the detection of preeclampsia in relation to isolated arterial notch. Patients examined were in their second trimester of pregnancy, from 14 to 20 weeks of gestation. The purpose was to assess the patient's risk of developing preeclampsia, and follow-up until clinical symptomatology and delivery.

Material and methods

For the realization of the set goals, the examinations were performed within the PHI University Clinic of Gynecology and Obstetrics in Skopje in outpatient conditions. The study is a cohort prospective one. Patients signed an informed consent to participate in the study. A total of 96 patients were examined and divided into 2 groups: study and control group. Detailed anamnesis data on pregnancy were taken before and during the examination. The study group, consisted of 48 patients from 14 to 20 gestational weeks. In addition to the routine ultrasound examination required to monitor fetal growth and development, a Doppler on the uterine artery was performed. The presence of uterine artery notch was the main inclusion criterion of the study group. The control group consisted of 48 pregnant patients at the same gestational age in the absence of uterine artery notch. Inclusion criteria for the control group included patients with normal pregnancy, with a single viable fetus and without hypertension.

Exclusion criteria of the study and control group included patients over 20 weeks gestation, multiple gestation, chromosomopathies, ultrasound verified fetal malformations or previous lethal fetuses.

After detailed ultrasound examination of the fetus, meticulous attention was conducted to the flow of the uterine artery. The examination was performed on ultrasound scanners Mindray DC-7 and Voluson 8 (General electric) with transabdominal probe 3-5 MHz. The Doppler examination was performed by standard technique. The abdominal probe was placed in the lower quadrant of the abdomen under a medial angular, the patient was in a supine position, and then a color Doppler was inserted to identify both uterine arteries bilaterally approximately, 1 cm distally from the point where it intersected with the external iliac artery. This point is the most accessible for proper examination in patients.

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The flow was shown until at least three consecutive waves were obtained (the intonation angle being less than 600). Parameters that were used, besides the notch, were RI, PI, Systolic Diastolic Ratio (S/D) as more specific and sensitive and are measured using autotrace. The presence or absence of uterine notch has been reported. Although it was important where the placenta was inserted, the measurement was made mutually.

The results were subjected to statistical analysis and processing with computer programs: STATISTICA 12 and SPSS 21.0 for Windows. On this basis, tests for significance between the comparison groups of all the parameters analyzed were performed.

Patients were monitored until the end of pregnancy in order to follow the development of clinical manifestations of preeclampsia.

Results

The results were analyzed by comparison between the two groups of patients, 48 in the study group (with presence of notch in the uterine artery) and 48 in the control group (in the absence of notch). Their anamnestic data showed a statistically significant result in terms of preeclampsia data in previous pregnancy with $p<0.05$, but without statistically significant result $p>0.05$ in relations to the body max index, gestational week and previous comorbidities.

The assesment of the blood flow and abnormal uterine artery Doppler was visualized and interpreted for every patient. The abdnormal uterine artery Doppler is described in Fig. 1.

Fig. 1

In those patients with present notch (48), it was noted as more often unilateral (30 (62.5%)), less frequently bilateral (18 (37.5%)) and in this case more frequent on the right side. The one-sided versus two-sided curve is statistically significant calculated with p value, i.e. $p<0.05$, $p=0.014$, which can be seen in Table 1.

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Table 1

Auto trace values of the resistance RI and PI were obtained. The value of RI obtained for the upper limit is 0.68. In the control group i.e. patients with normal pregnancy the value is 0.50±0.08 with 95% RI to 0.68 (95^{th} percentile = mean RI ± 0.038 standard deviation).

The median RI value is higher in patients who are later at risk of developing hypertension. PI parameters have the same tendency for growth. The values obtained were tabulated and their correlation coefficient where the significance obtained for the different values was marked, which can be seen in Table 2.

Table 2

The present notch of the uterine artery and the increased RI of over 0.68 on the uterine artery above 0.38 in the utero-placental arteries was defined as abnormal flow.

In the studied patients with notch present value reaches up to 0.73, compared with those without notch where RI is up to 0.58.

The PI in the control group ranges from 1.1 to 1.75 with a mean of 1.43, while in the study group it reaches to 2.2, meaning that these values increase in patients at risk for developing hypertension. An increase in flow resistance with measured PI and RI values above 1.75 and respectively 0.68 or the presence of unilateral and bilateral diastolic notch is considered as abnormal results for the uterine artery.

The comparison of the values between the study and control groups and the significance calculation using the T test and the p test between both groups are shown in Table 3.

Table 3

Statistical significance was recorded in the values of PI and RI in patients shown by T-test for significance of differences, T-test for PI of 11.96 and T-test for RI of 8.65 indicating a significance level $p<0.01$.

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Following the already elaborated results from the flow indexes, patients were examined in the third trimester of pregnancy, where they initially developed the first clinical manifestation of preeclampsia at 31th gestational weeks in the study group. The mean value for systolic blood pressure in the manifestation of preeclampsia was 171 mm Hg, measured with the lowest value of 150 mm Hg to the highest value of 178 mm Hg. In patients without preeclampsia in the study group the mean systolic pressure was 163 and in the control group 117 mm Hg. Diastolic pressure measured at baseline showed a mean of 101 mm Hg in those with preeclampsia, 82 mm Hg in the second, and 73 mm Hg in the control group with $p<0.01$. There were statistically significant differences in the laboratory analyzes (CRP, LDH, acidum uricum, proteinuria and 24 hour proteinuria ($p<0.01$) between groups.

Of the 48 patients with arterial notch present, 21 developed preeclampsia syndrome, which means, isolated, the notch had a positive predictive value of 43.7%. Of these 21 patients, 15, had PI above 1.75 which is of much greater predictive value and accounted for 71.4%. Using a calculator, we obtained a sensitivity of these values of 88% (63.56-98.54%, 95% CI), specificity of 16%, which is a reliable result with high predictive value by analyzing the patients. The test had a positive predictive value of 41.67% and a negative predictive value of 66.67%. With respect to the RI, 12 patients reported a deviation above the normal value, above 0.68 with a predictive value of 57.1%, which is more but insufficient prognostic parameter. The calculated values for RI sensitivity are 85.71% and for specificity 25%, with positive predictive value 36.36% and negative predictive value 77.78%.

Discussion

Thadhani et al. (2011) reported significantly higher values of vascular indexes measured over a 7 to 15 gestational weeks in patients who subsequently developed preeclampsia later in pregnancy. Increased blood vessel turbulence, increased resistance to flow, and the presence of notch are also associated with a subsequent increase in arterial tension, which is also consistent with the results of our study.

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Plasencia et al. (2008) concluded that the PI decreased in normotensive patients and increased in preeclampsia, analyzing patients between 11 and 13.6 gestational weeks and between 21 and 24.6 gestational weeks.

In our study, in patients where the notch of the uterine artery was primarily verified, isolation itself did not have a very high predictive value. Its value was complemented by values from the PI that shows a tendency to rise above the normal values in patients who later develop preeclampsia. In our study, the upper limit of the PI was up to 1.75 and of the RI to 0.68, which is close to the values accepted broadly by the cited authors as postulates for further research. The increase in their values in patients from the study group up to 2.2 for PI and 0.73 for RI was respectively statistically significant $p<0.01$.

Martin et al. (2001) found that preeclampsia screening in the first trimester of 11 to 14 weeks of gestation using the uterine artery Doppler, allows identification of the severe form of preeclampsia and the presence of intrauterine growth restriction. In contrast, Sciscione and Hayes (2009) did not recommend ultrasound or uterine artery Doppler in either low or high risk pregnancies, for its low predictive value.

Park et al. (2015) according to a meta-analysis of 79,547 single pregnancies demonstrate that Doppler of the uterine artery has better features in the second trimester than in the first trimester and is useful for the detection of severe preeclampsia or early-onset preeclampsia. In low-risk patients, elevated PI in the second trimester has a sensitivity of 78% and a specificity of 95% for the diagnosis of severe preeclampsia. Overall, increased PI and notch emergence in the second trimester is the best predictive marker for low risk and high risk for preeclampsia.

It is very important to have a certain cut-off value of the PI, the RI for each population. It could be expected a variability across the investigating region and diferences according to the socio-demographic factors. Also, it is important that the Doppler is available and not an expensive method and it is necessary to be carried out by professionally educated medical staff following the latest guidelines.

Our aim was several additional factors (maternal factors and bioactive factors in circulation) to be taken in account in the detection of preeclampsia. With their inclusion the new method scoring system for predicting of the development of preeclampsia could be implemented.

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Uterine artery PI according to Plasencia et al. (2008) in the first trimester of patients, was detected in over 90 percentiles in 77% in early preeclampsia and 27% in late preeclampsia. With a predictive test model, including maternal factors, PI and then changes in PI in the second trimester early detection of preeclampsia is provided with a value up to 90.9% with a false positive score of 5%. He concluded that by including screening in the second trimester, high-risk patient groups receive a better degree of detection.

Similarly, Gomez et al. (2006) confirmed that subsequent measurement of uterine artery Doppler between 11 and 14 weeks of gestation and 19-22 weeks of gestation was important.

Specifically, he collected results from PI values and the presence of early diastolic notch. A value above 95 percentiles for PI is associated with a risk of more serious complications, which, if normalized to the second trimester and beyond, those pregnancies have a verifiable potential risk of pregnancy complications.

For the diagnostic value of the above-mentioned parameters in twin pregnancy, a correlation was made by Svirsky et al. (2014), who compared the values of mean arterial pressure and PI of the uterine artery Doppler and found that in twin pregnancies complicated with preeclampsia the mean arterial pressure was higher, but the values of PI were lower, compared to single pregnancies as a consequence of the greater compensatory activity of blood flow to the placenta.

Conclusion

In pregnant patients between 14 and 20 weeks of gestation, the presence of uterine artery notch, RI, PI values above 0.68 and 1.75 respectively, as an abnormal result, are an important predictive indicator of statistical significance.

Predictive value of the PI in patients with present uterine artery notch was 71.4%, with sensitivity of 88% (63.56-98.54%, 95% CI). This is a reliable predictive parameter in patients at risk of developing preeclampsia. It is a significant result worth implementing in the guidelines for every day clinical practise in the field of perinatology.

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Early detection of the risk of developing preeclampsia enables timely prevention, aware follow-up, on time diagnosis and appropriate treatment for a better perinatal outcome, for both the mother and the baby.

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Резиме

Пулсатилниот индекс на утеринатa артерија како релевантен параметар во предвидувањето на прееклампсијата

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Клучни зборови: прееклампсија, предвидување, пулсатилен индекс

Прееклампсијата е клинички синдром што се јавува кај 5-10% од бременостите со зголемен перинатален морбидитет и морталитет. Според ISUOG (Меѓународно здружение за ултразвук во акушерството и гинекологијата), Употребата на пулсатилниот индекс на утеринатa артерија е важен сензитивен метод во предвидување на ризикот од прееклампсија.

Целта на оваа студија беше да се потенцира вредноста на пулсатилниот индекс (PI) како порелевантен предиктивен параметар при откривање на прееклампсијата во вториот трисеместар во споредба со присуството на notch (забец) на утеринатa артерија, изолирано.

За горенаведената цел, на Универзитетската клинивка за гинекологија и акушерство во Скопје беа прегледани 96 пациентки, поделени во 2 групи: испитувана и контролна група. Испитуваната група се состоеше од 48 пациентки од 14 до 20 гестациска недела со присутен notch на утеринатa артерија, што всушност беше главниот инклузионен критериум. Контролната група се состоеше од 48 бремени пациентки на истата гестациска возраст во отсуство на артериски notch.

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Од испитуваната група, 43,7% од пациентките развија клинички синдром на преeклампсија. Вредноста на индексот на резистенција (RI) беше во пораст до 0,73, а неговата предиктивна вредност беше 57,1%. Кај пациентките кои го развија синдромот на преeклампсија, вредноста на PI над 1,75 беше со многу голема предиктивна вредност и изнесуваше 71,4%. Сензитивноста на овие вредности беше 88%, што е веродостоен параметар.

PI е значаен параметар при откривање на ризикот за развој на преeклампсијата и индикатор од големо клиничко значење во секојдневната пракса во перинатологијата.

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Table 1. Detected notch in patients

Total patients with measured notch of the uterine artery (96)	
Patients with absent notch (48)	0
Patients with notch (48) P=0.01428*	unilateral (30 (62,5%))
	bilateral (18 (37,5%))

*The result is significant with p<0.05

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Table 2. Statistical analysis of the values of PI and RI indices

Presence of notch		Number of patients	Mean value	Standard Deviation (SD)	Std. Error Mean
PI	Examined group	48	1.9585	0.15269	0.02204
	Control group	48	1.4327	0.26359	0.03805
RI	Examined group	48	0.6498	0.10558	0.01524
	Control group	48	0.5094	0.03878	0.00560

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Table 3. T-test for significance of differences and P-test for significance between test and control group

Indexes	T	Df	p-Significant (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
						Lower	Upper
PI	11.959	94	0.004 *	0.52583	0.04397	0.43853	0.61313
	11.959	75.351	0.005 *	0.52583	0.04397	0.43825	0.61342
RI	8.649	94	0.011 *	0.14042	0.01623	0.10818	0.17265
	8.649	59.455	0.007 *	0.14042	0.01623	0.10794	0.17290

* The result is significant at p <0.05

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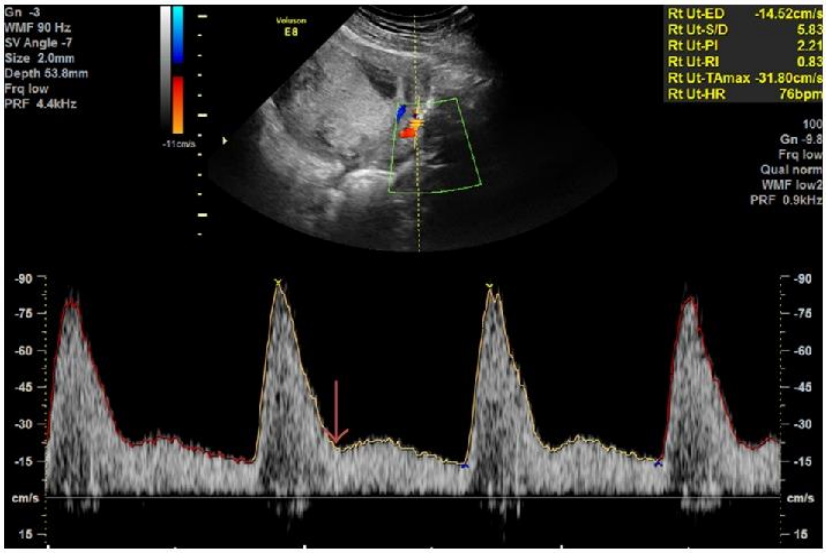

Fig. 1. Abnormal uterine artery Doppler.

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