ON THE RELATIONSHIP OF VITAMIN D STATUS AND INDICATORS OF THE UTERINE ARTERIES PULSATION INDEX IN PREGNANT WOMEN AT RISK OF PREECLAMPSIA DEVELOPING: CROSS-SECTIONAL STUDY

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Abstract

Preeclampsia (PE) of pregnant women continues to be one of the leading causes of maternal and perinatal morbidity and mortality, and the existing theories about the pathogenetic mechanisms of its development are not absolutely convincing. To take into account the data on the pleiotropic effects of vitamin D (VD) and its effect on reproductive function, we set **a purpose** to study the relationship between hemodynamic parameters in the uterine arteries and the level of VD in the blood of women at risk of PE developing.

Materials and methods. From 2018 to 2021, 54 women with a risk of PE developing and VD insufficiency were under observation. A cross-sectional examination was carried out at the 1st trimester of pregnancy. Blood content of VD (25 (OH) D) was determined on an empty stomach by ELISA on a CobasIntegra 400 Plus analyzer (Roche Diagnostics, Switzerland). Measurement of the pulsation index in the uterine arteries (PI in UA) was done according to the recommendations of the Fetal Medicine Foundation (FMF) on an ultrasound apparatus "VOLUSON 730 EXPERT" (2008); volumetric convex intracavitary (RIC 5-9) and volumetric multifrequency convex probes (RAB 4-8P) were used.

Results and discussion. The mean age of the women under examination was 28.4 ± 4.9 y.o.; there were 64.8% of primiparas; 62.9% of women were 25 y. o. and over; 92.6% of pregnant women were overweight or had obesity of various degrees; 72.5% of them had various extragenital pathologies. (25 (OH) D) mean level was 25.8 ± 7.3 ng / ml; the mean PI in UA was 1.98 ± 0.504. There were 19 pregnant women with PI in UA ranging > 50 and <95 percentile (35.19%), in every fifth woman (11 patients or - 20.4%) resistance in MA exceeded 95 percentile. A significant negative statistical relationship was established between VD level in the blood and PI value in UA (r_s = -0.734; P <0.01).

Conclusions. Pregnant women with a high risk of PE development has pathologically increased resistance in the uterine vessels already in the first trimester of pregnancy. A strong inverse relationship was found between the level of vitamin D in the blood of high-risk pregnant women and indicator of impedance in the uterine arteries. Timely diagnosis and correction of vitamin D deficiency in women of reproductive age at the stage of preconception training can be a promising direction in the prediction and prevention of perinatal morbidity and mortality.

All human studies were conducted in compliance with the rules of the Helsinki Declaration of the World Medical Association "Ethical principles of medical research with human participation as an object of study". Informed consent was obtained from all participants.

Keywords: *vitamin D pleiotropic effect, pulsation index in the uterine arteries, risk of preeclampsia development.*

Introduction

Safe motherhood is medical and social task of high priority and the possibility of preclinical diagnostics, prevention of various complications of pregnancy plays a key role in this and ensures a "healthy start in life" for future generations. In the area of special attention of obstetricians and gynecologists, the problem of prevention of such complications of the gestational process as preeclampsia (PE), placental dysfunction, and intrauterine growth retardation, the frequency of which does not tend to decrease, still remains [1].

Hypertensive disorders complicate the course of 2 - 8% of all pregnancies and are one of the leading causes of maternal and perinatal mortality, and the prognosis of PE is based on anamnestic and obstetric risk factors. According to numerous studies, the pathogenesis of the disease is due to changes in hemodynamics from early pregnancy and is anatomically characterized by abnormal remodeling of the spiral arteries of the uterus [2].

The hemodynamic component of adaptive and compensatory changes in a woman's body during pregnancy is one of the basic in ensuring the normal intrauterine fetus' development and the failure of these compensatory mechanisms significantly increases the risk of a complicated pregnancy. In the last decade, the use of Doppler examination to assess hemodynamic parameters in the uteroplacental circulation has become a significant addition of PE prediction [3].

Various measurement methods and impedance indices are used to assess the relationship between uterine artery Doppler velocimetry and adverse pregnancy outcomes. In general, uterine artery Doppler examination made at the first trimester is considered to be better at predicting of PE early-onset, but as an isolated marker of PE and fetal growth retardation predicting in low-risk pregnant women, sensitivity of Doppler examination is 40–70%. It is likely that multiparametric prognostic models that combine the impedance of the uterine artery in the first trimester with other maternal characteristics and biochemical markers may provide a more sensitive rate of PE detection [3, 4].

Currently, Doppler examination the uteroplacental and fetal blood flow remains a priority method for diagnosing the functional state of the fetoplacental system up to 26 weeks of gestation, when the assessment of the biophysical profile of the fetus is not yet carried out, and the carditocographic study of the fetus is not informative [5].

According to recent literature data, vitamin D (VD) deficiency may be one of the possible risk factors for the formation of endothelial dysfunction and PE development [6, 7, 8, 9].

The participation of VD in the regulation of nitric oxide (NO) synthesis in endothelial cells by stimulating the activity of endothelial NO synthase (eNOS), in regulation of the activity of proinflammatory cytokines (tumor necrosis factor α (t TNF-α), interleukin-6 (IL -6)) and various atherosclerotic factors, as well as its participation in the regulation of the main target genes responsible for the processes of implantation and formation of the placenta [10, 11] may be an explanation of this.

The problem of PE and related perinatal complications, the search for possible predictors and issues of its preclinical prevention determine the relevance of further research in this direction.

Purpose: to study the relationship between hemodynamic parameters in the uterine arteries and the level of 25-hydroxy-cholecalciferol in the blood in the 1st trimester of pregnancy in women with risk of PE development.

Materials and methods

54 women in the 1st trimester of pregnancy underwent a cross-sectional examination (1 combined screening at 11-13 weeks) during 2018-2021. The examination was carried out at the clinical base of the Odessa National Medical University - Maternity Hospital No 5 of the Odessa City Council (Ukraine).

The study included women with insufficient or vitamin D deficient status and risk factors for PE development (history of preeclampsia, chronic hypertension, multiple pregnancy, diseases of the cardiovascular system, maternal age less than 18 and more than 35 y.o., kidney disease, use of assisted reproductive technologies, first birth).

To assess vitamin D status by enzyme-linked immunosorbent assay, the content of 25-hydroxy-vitamin D (25 (OH) D), which is a common circulating metabolite of vitamin D for chole- and ergocalciferol was determined. Cobas Integra 400 Plus analyzer

(Roche Diagnostics, Switzerland) was used. Blood for the study was collected on an empty stomach in the morning from a vein.

In addition to the generally accepted ultrasound parameters determined during the screening study of the uterine-placental-fetal complex in the 1st trimester, the pulsation index in the uterine arteries (PI in UA) was measured according to the recommendations of the International Fetal Medicine Foundation (FMF), herewith the VOLUSON 730 EXPERT (2008) was used. The volumetric convex intracavitary sensor RIC 5-9 and the volumetric multifrequency convex sensor RAB 4-8P were used. During abdominal ultrasound, a sagittal section of the uterus was obtained at the level of the internal os of the cervical canal, by changing the inclination of the sensor and using color Doppler mapping (CDM), each uterine artery was identified along the lateral surface of the cervix at the level of the internal os. Transvaginal examination was performed after preliminary emptying of the bladder in the patient's dorsal lithotomy position. To fix the uterine arteries, CDM at the level of os uteri internum, the sensor was sequentially turned in the direction of the left and right lateral vaults. After finding each uterine artery, the control window of the pulse-wave Doppler was set at the mark 2 mm to cover the entire vessel, taking into account the angle of insonation (less than 30˚). Differentiation of uterine arteries from arcuate ones was based on a systolic velocity of more than 60 cm / sec. After determining PI value in the right and left uterine arteries, its mean was calculated.

For the study, a positive decision of the Commission on Bioethics of the Odessa National Medical University was obtained. The basic moral and ethical principles of the Helsinki Declaration of the World Medical Association for Biomedical Research were observed, all women gave and signed informed consent to participate in the survey, they allowed to process their personal data.

Statistical processing of the results was carried out using Microsoft Excel and Statistica 7.0 software on a personal computer. The normality of distribution was determined using the Shapiro-Wilk criterion; to assess the relationship between the data, the Spearman's rank correlation coefficient (r_s) and the Student's t test were calculated.

Results

The mean age of women in the group was 28.4 ± 4.9 y.o.; 12.9% were over 35 y. o., every second (50%) woman was between 26 and 35 y. o. 94.4% (n =51) of women belonged to the European ethic group, 5.6% (n =3) to the Asian. 14.8% (n =8) of women because of infertility of various nature used ART (Table 1).

The tendency towards conscious motherhood at the older reproductive age is also reflected in the number of primiparous women in the group - 64.8%; 27.8% of the pregnant women were due to have their second births, the rest 7.3% had their third and fourth births.

When analyzing the body weight of pregnant women, it was revealed that only 7.4% of women have a normal body weight (BMI> = 18.5 and <25), the remaining 92.6% were overweight (44.4%) or obesity of varying degrees (47.9%).

The general somatic history of pregnant women was characterized by the presence of previous hypertensive disorders in every third woman - 33.4% (18 patients; in the population -14.10%; OR = 3.03; 95% CI 1.50-6.11); 9.3% of them had chronic arterial hypertension; 24.1% - vegetative-vascular dystonia (in the population - 7.2%; OR = 4.20; 95% CI 1.72-10.27). Chronic kidney disease was indicated by 9.3% (5 people; in the population - 8.5%; OR = 1; 95% CI 0.38-2.63), chronic venous insufficiency - 13% (7 people; in the population - 4.3%; OR = 3.57; 95% CI 113-11.41). In addition, 1 patient (1.9%) noted the presence of type 2 diabetes mellitus (medically compensated; in the population - 8.2%; OR = 4.26; 95% CI 0.88-20.59), 1 - bronchial asthma and 1 - cerebral angioedema; 3 women (5.6%) had autoimmune thyroiditis with hypofunction of the thyroid gland, medically compensated (in the population - 4.5%; OR = 0.989; 95% CI 0.28-3.56).

The average level of the total circulating metabolite of ergo- and cholecalciferol (25 (OH) D) in the blood of pregnant women was 25.8 ± 7.3 ng / ml, which reflects the presence of vitamin D insufficiency or deficiency; the minimum value is 7.1 ng / ml (Fig. 1).

The average value of the pulsation index in the uterine arteries was 1.98 ± 0.504; fluctuations were in the range of 0.64 - 3.44. According to the results of the distribution of PI indicators according to the

reference values, the following data were obtained (Table 2).

The number of pregnant women with PI in UA in the range> 50 and <95 percentile was 19 (35.19%), in every fifth woman (11 persons, 20.4%) resistance in the uterine arteries exceeded 95 percentile.

Calculation of the Spearman rank correlation coefficient made it possible to reveal the dependence of the echographic parameters of hemodynamics in the uterine arteries (PI) on the level of vitamin D in the blood of pregnant women: the lower is its value, the higher is the resistance of the uterine vessels (r_s = -0.734; P <0.01), i.e. there is a strong statistically significant inverse relationship (Fig. 7).

Evaluation of the correlation between the level of calciferol and the value of the pulsation index in the UA in the first trimester of pregnancy in women at risk for the development of preeclampsia allows to tell about high sensitivity (83.87%) and specificity (90.9%) of the method with its overall accuracy of 86.79 %.

Discussion

According to the literature, "delayed motherhood" is associated with a higher level of infertility in married couples, with an increase in the frequency of spontaneous abortions, ectopic pregnancy, congenital malformations (trisomy 21), premature birth, preeclampsia and other complications of pregnancy. The risk of these problems begins at about the age of 30, increases with age, and the most pronounced consequences are typical for the age over 40 [13, 14]. PE risk in primary pregnant women is three times higher than in re-pregnant women with uncomplicated previous pregnancies. In PE women during the first pregnancy the risk of recurrence of the problem is 14.7%, and in the case of PE during two previous pregnancies, it is 31.9%. According to Li X.L. et al. (2014), in women with early development of preeclampsia during the first pregnancy, the risk of early and severe PE in subsequent pregnancies increases [15, 16, 17]. According to our data, among pregnant women there is an increase in the number of primiparous (64.8%) women in the older age group (62.9%): i. e. there were both a risk factor associated with age and birth parity, which also emphasizes the importance and need to search for PE modifiable predictors.

It is known that the micronutrient status of a woman, a deficiency of calcium, protein, a number of vitamins and minerals, essential fatty acids, as well as overweight or pathological weight gain during pregnancy play a role in PE occurrence.

On the other hand, obesity with its characteristic hyperinsulinism, insulin resistance and systemic inflammatory process can act as an independent triggering mechanism of endothelial dysfunction [18]. The risk of PE developmment in obesity is also associated with impaired cytotrophoblast migration with subsequent placental ischemia, release of soluble placental factors into the mother's bloodstream, and vascular dysfunction [19]. According to a meta-analysis of literature data conducted by Schenkelaars N. et al. (2021), weight control and weight loss at the stage of preconception preparation, despite the complexity of the pathophysiological mechanisms of the development of hypertensive complications during pregnancy, can significantly reduce the risk of PE, arterial / chronic hypertension and HELLP syndrome [20] development.

Our results showed that only 7.4% of women had BMI corresponding to normal weight, the rest 92.6% of women were overweight or had obesity of varying degrees, which emphasizes the need and importance of pregravid weight correction, especially in the risk group.

As for the management of pregnancy in women with chronic general somatic diseases, thanks to the development of a multidisciplinary approach and joint efforts of obstetricians-gynecologists, therapists and doctors of other specialties, the tactics of managing pregnancy and childbirth in women at risk group have changed, the concept of "high-risk pregnancy" has been formed and the most optimal approaches to planning and management of pregnancy, as well as to delivery of such women [21] has been developed.

It is necessary to take into account all factors, including behavioral, dietary habits, etc., in order to minimize the adverse effects of pregnancy itself on the function of the mother's particular organ, the influence of the existing disease on the formation, development and subsequent functioning of the uteroplacental-fetal complex.

The chronic diseases of the cardiovascular system (in every third woman), kidney diseases (in every tenth woman), thyroid diseases, etc., which are available in the group under analysis, determined the selection of these women in the risk group for PE development of preeclampsia.

As the term increases in the physiological course of pregnancy, the Doppler spectrum of the uterine arteries (UA) is characterized by the presence of a shallow notch at the beginning of diastole, the magnitude of which increases as pregnancy progresses and subsequently completely disappears [22]. Photos 3, 4 (own data) show the results of echography of the UAs in the 1st trimester in women with the physiological course of pregnancy and without risk factors.

The completion of morphological changes in the spiral arteries and the final formation of low-resistance blood flow in the UA basin is characterized by a maximum decrease in resistance by 16 weeks of gestation. In the case of defective invasion of the spiral arteries and abnormal placentation, the resistance in the UA remains high, which causes a high impedance. The phenomenon of impedance increasing in UA is regarded as a predictor of PE development and its diagnosis is possible with the first ultrasound screening [23]. The results of our own research are presented in Fig. 5 and 6. The results of our own research are presented in Fig. 5 and 6.

Combined with maternal history, mean arterial pressure (MAP) and some biochemical markers (PAPP-A, placental growth factor or PlGF), uterine artery Doppler ultrasonography is now considered an important additional screening tool for predicting PE [22].

As for the possible influence of calciferol level on hemodynamic parameters in the uterine basin, there is literature data according to which with the optimal content of vitamin D in the blood (30-50 ng / ml), the course of pregnancy is much less often complicated by PE development, whereas under the conditions of calcitriol deficiency in the blood (<20 ng / ml) the risk of severe PE development increases 4 times, and less than 15 ng / ml - 5 times. Apparently, the participation of VD in angiogenesis, regulation of endothelial function, as well as its immunotropic effect in its insufficiency can contribute to a decrease in the rate of gestational transformations in the spiral vessels even at the stages of implantation and subsequent placentation. Insufficient morphological transformations of the spiral vessels of the uterus lead to a decrease in the total area of the intervillous space and hypoxia / ischemia of the placenta, which further leads to an increase in the total peripheral resistance in the microcirculatory bed, the development and progression of endothelial dysfunction [6, 24, 25, 26, 27]. We hypothesize that under the conditions of colecalciferol deficiency, one of the causes of endothelial dysfunction as the basis for the development of PE may be impaired expression of NO synthase followed by dysfunction of the bioregulatory system L-arginine - nitric oxide. Pathological angiogenesis and vasospasm in the uteroplacental bed, impaired blood coagulation and vascular wall permeability contribute to the formation of hemodynamic and hemocoagulation components of PE pathogenesis.

Thus, the study of the associative relationships of vitamin D status with hemodynamic parameters in the uterine arteries in the 1st trimester of pregnancy in women with a high risk of PE development showed the following.

Conclusions

The data of echographic examination of the uterine arteries in pregnant women at risk of preeclampsia development indicate a pthological increase in the uterine vessels resistance in every fifth woman already in the 1st trimester of pregnancy; in every second pregnant woman the impedance indicator in the uterine arteries exceeds the 50th percentile of the reference interval. A strong inverse relationship was found between the level of vitamin D in the blood of pregnant women and the pulsation index in the uterine arteries: the lower the concentration of calciferol was, the higher the resistance of the uterine arteries.

The high specificity and sensitivity of the method for assessing the correlation between the level of calciferol and the value of the pulsation index in the UA suggests its practical orientation.

Timely diagnosis and correction of vitamin D deficiency in women of reproductive age subject to clear personalization and identification of risk

factors, starting from the preconception preparation, can be a promising direction in predicting and preventing pregnancy complications.

Correction of easily modifiable risk factors such as vitamin D deficiency with patient's participation is likely to significantly improve perinatal outcomes.

Further research is needed to obtain a strong evidence base.

Acknowledgments

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Table 1. Characteristics of the women examined by age, anthropometric data, reproductive and general somatic history

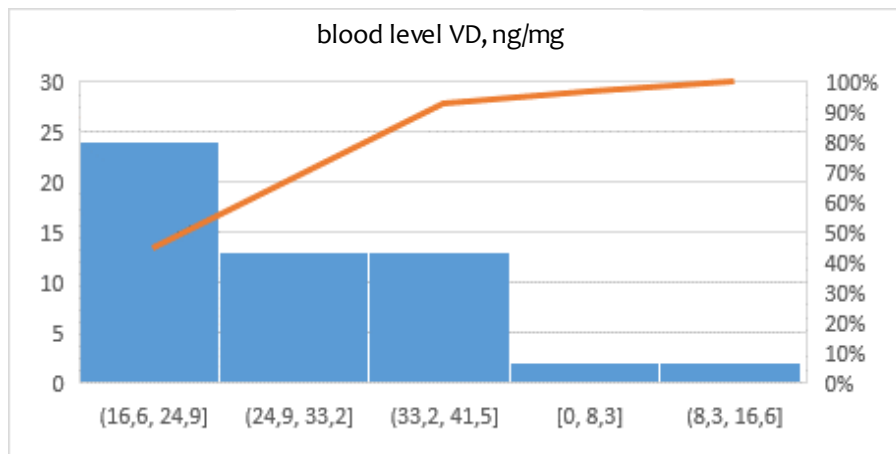| Indicator	Group under examination, n=54, abs. amount	Share of the indicator in the group, %
AGE		
18 – 25	20	37.04
26 – 35	27	50.0
36 – 40	7	12.9
BIRTH PARITY		
1 childbirt – 35 persons	35	64.8
2 childbirth -	15	27.8
3 childbirth - 3	3	5.6
4 childbirth - 1	1	1.8
BODY MASS INDEX, KG/M2		
BMI <18.5 - underweight	0	0
BMI> = 18.5 and <25 - normal body weight	4	7.4
BMI> = 25 and <30 - overweight	24	44.4
BMI> = 30 and <35 - obesity grade 1	18	33.3
BMI> = 35 and <40 - obesity grade 2	6	11.1
BMI> = 40 - obesity grade 3	2	3.7
EXTRAGENITAL PATHOLOGY		
Anomaly in the development of the urinary system	2	3.7
Chronic arterial hypertension, 1-2 degree	5	9.3
Autoimmune thyroiditis, hypothyroidism, medically compensated	3	5.6
Bronchial asthma	1	1.9
Vegetovascular dystonia, incl. hypertensive, mixed and tachycardial types	13	24.1
Diabetes mellitus type 2, mild, compensated	1	1.9
Chronic kidney disease	5	9.3
Cerebral angiodystonia of the hypertensive type, hypertensive-CSF syndrome against the background of osteochondrosis of the cervical spine 2	2	3.7
Chronic venous insufficiency	7	13.0

Figure 1. Distribution of indicators of the content of calciferol (25 (OH) D3; ng / l) in the blood of pregnant women

Table 2. Distribution of pulsation index indices in the uterine arteries at 11-13 weeks of gestation depending on the reference intervals (Gomez O. et al., 2008) [12].

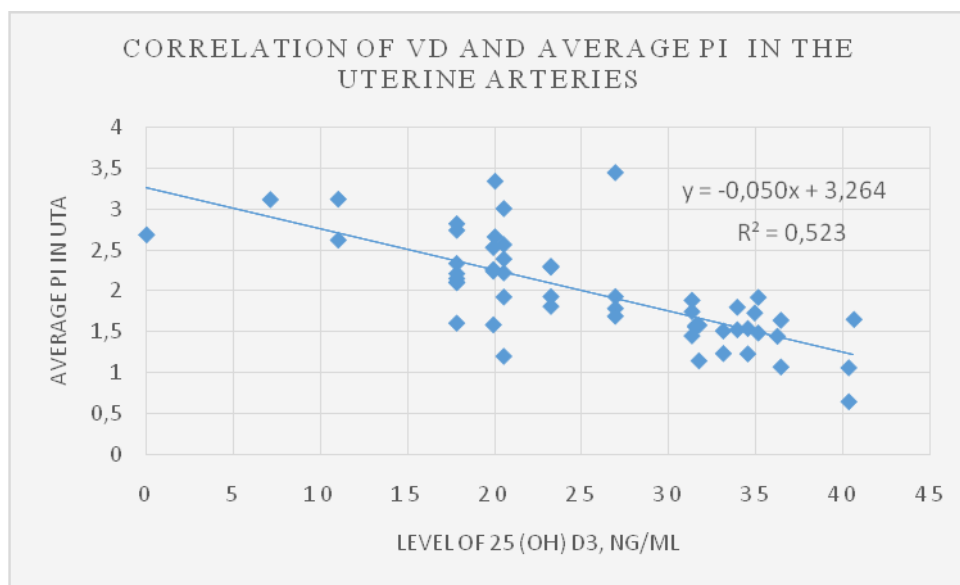| Percentile limits for PI in UA	Number of examined, n=54, abs. number	Share, %
<5 centle	1	1.85
> 5 and <50 centle	14	25.93
50 centle	9	16.67
> 50 and <95 centle	19	35.19
> 95 centle	11	20.37

Figure 2. Correlation between the level of calciferol (ng / ml) and pulsation index in the uterine arteries, 11-13 weeks of gestation

Figure 3. Transvaginal Doppler study of the uterine artery with fixation at the level of the internal os in the 1st trimester (screening). Normal uterine artery waveform.
Photo from the video archive of the doctor of ultrasound diagnostics Drozd A.B. (FMF certificate No 64936 dated 10.03.2009)

Figure 4. Transabdominal Doppler study of the uterine artery at the level of the internal os in the 1st trimester (screening). Normal waveform of the uterine artery.
Photo from the video archive of the doctor of ultrasound diagnostics Drozd A.B. (FMF certificate No. 64936 dated 10.03.2009)

Figure 5. Transvaginal Doppler study of the uterine artery with fixation at the level of the internal os in the 1st trimester (screening). Pathological waveform of the uterine artery.
Photo from the video archive of the doctor of ultrasound diagnostics Drozd A.B. (FMF certificate No. 64936 dated 10.03.2009)
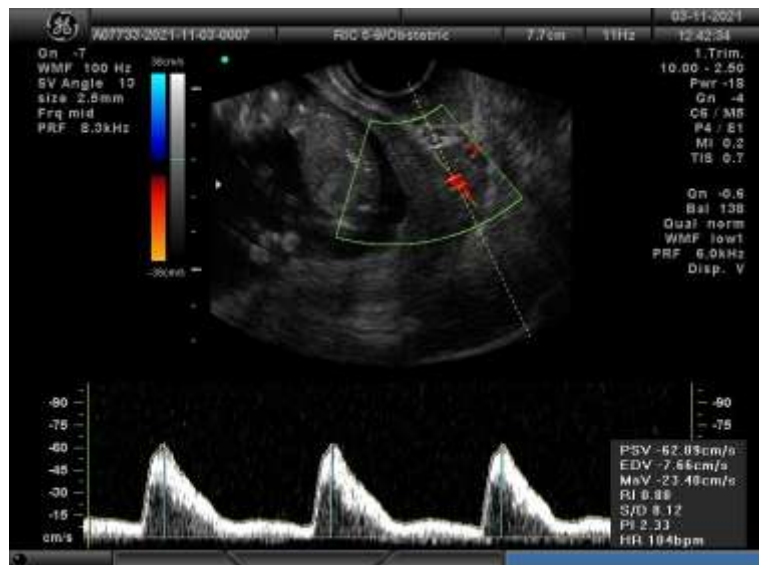

Figure 6. Transabdominal Doppler study of the uterine artery at the level of the internal os in the 1st trimester (screening) Pathological waveform of the uterine artery.
Photo from the video archive of the doctor of ultrasound diagnostics Drozd A.B. (FMF certificate No. 64936 dated 10.03.2009).