Original Paper

Intraplacental Villous Artery Doppler can Improve the Ability to Predict Placenta-Mediated Disease

ADRIANA TUDOR[1], LILIANA NOVAC[1], IOANA VICTORIA CAMEN[1,2], MARIA MAGDALENA MANOLEA[1,2], SIDONIA CATALINA VRABIE[1], MARIA SIDONIA SANDULESCU[1,2], MIRCEA SEBASTIAN ȘERBĂNESCU[1,2], MIHAIL VIRGIL BOLDEANU[1], SIMONA DANIELA NEAMȚU[1,2], ANCA MARIA ISTRATE OFIȚERU[1], ANDA LORENA DIJMARESCU[1,2], MARIUS BOGDAN NOVAC[1,2]

[1]*University of Medicine and Pharmacy of Craiova, Romania*

[2]*"Filantropia" Hospital, Craiova, Romania*

ABSTRACT: Objective. Evaluation of Intraplacental Villous Artery Doppler (IPVA) as a predictive factor compared to umbilical artery (UA) Doppler in placenta-mediated disease (PMD). Methods. This prospective study included a group of 106 pregnant women, of which 76 patients constituted the PMD group: preeclampsia (PE) and small for gestational age (SGA), and 30 pregnant women constituted the control group. IPVA and UA Doppler evaluation was performed in 2 pregnancy periods: 20.0-23.6 weeks, and 28.0-32.6 weeks of gestation. Results. From the study of maternal characteristics and risk factors for the presented pathology, we found that no studied risk factor was statistically involved in the evolution toward PMD during pregnancy. In the control group, we noticed a decrease in IPVA PI and RI, along with an increase in gestational age, while in the PMD group, these indices increased. Both in the 2nd and the 3rd trimester, we had a significant statistical difference between the two groups ($p<0.001$). Regarding the degree of prediction of the changes that occurred at this level, we found a good statistical correlation. A higher degree of positive predictability is noted, for IPVA-PI, but also for UA-PI, but with better sensitivity (72.27%) for UA PI in the 2nd trimester. Conclusions. We can conclude that both Doppler measurements, IPVA and UA can be used to evaluate and detect pregnancy complications that belong to PMD, preeclampsia, and/or fetal growth restriction.

KEYWORDS: *IPVA, UA, Doppler, PE, SGA.*

Introduction

Adequate placentation is necessary for good fetal development and for a successful pregnancy.

PE and SGA are part of the placenta-mediated disease, which affects 4-7% of pregnancies, representing an important risk factor for maternal and fetal health [1].

It is known that an increase in UA-PI, as it occurs in pregnancies complicated with PE and SGA, shows that there is an increase in vascular resistance at the placental level.

But it is also known that these changes occur only if at least two-thirds of the placental vasculature is affected, which makes us suspect that the UA Doppler change occurs only in the advanced stages of the reduction of the placental vasculature [2].

On the other hand, an interpretation of the meaning of these changes in UA Doppler at the placental level is not possible due to ethical principles [3].

In this context, it has been demonstrated that a fetoplacental Doppler assessment can be obtained not only from the level of the umbilical arteries but also from the level of several branches of the placental vessels [4].

The Doppler evaluation of the intraplacental villous arteries was thus proposed for the early detection of insidious changes occurring in the placental vascularization.

This is in the context of cases with SGA infants at birth and cases with placentally mediated stillbirth, which presented normal UA Doppler and important placental changes, cases that have been intensely debated [5,6].

Materials and Methods

This is a prospective study conducted at Clinical Hospital "Filantropia" Craiova in Obstetrics and Gynecology Department, between January 2018-May 2022, which included a group of 106 pregnant women with a singleton gestation.

The studied population consisted of two groups of pregnant women: the first group, called the PMD group, consisted of 76 pregnancies with infants with SGA at birth and pregnancies with/without PE, compared to the second group composed of 30 pregnancies with normal

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evolution, which they constituted the control group.

Ultrasound Doppler scans of IPVA and UA were performed in two periods of pregnancy: in the 2nd trimester between 20.0-23.6 weeks of gestation and the 3rd trimester between 28.0-32.6 weeks of gestation.

Patients who had accurate dating (first-trimester ultrasound) were included in the study.

At the time of inclusion in the study, a detailed interview was carried out, through which the necessary demographic, clinical, and medical history data were obtained.

UA Doppler measurement was performed in a free cord loop.

IPVA Doppler was performed after scanning the intraplacental area, examining at least 2 intraplacental vessels, at the level of the middle placental segment of each main stem vessel, with a corrected angle of 30° between the Doppler beam and the vessel.

SGA was sonographically defined as the estimated fetal weight (EFW) below the 10th percentile at any gestational age after the enrollment period.

We defined preeclampsia as a new onset of hypertension (BP⩾140/90mmHg) and proteinuria (0.3g in 24-hour sample or⩾2+dipstick) after 20 weeks of gestation in a previously normotensive woman.

All patients were volunteers in this study, in which they participated after signing the informed consent.

Based on the Declaration of Helsinki, the study received the approval of the Ethics Committee of the University of Medicine and Pharmacy of Craiova.

Statistical Analyses

The differences between the groups were tested with a Fisher exact test and a Student-test for normal distribution and homogeneity of variances.

Positive and negative predictive values were calculated with their 95% Confidence Intervals, of each parameter.

We used the median and range (Minimum and Maximum) for nonparametric data and the mean and standard deviation for parametric data. Statistical significance was considered to be $p<0.05$.

Results

We examined a total of 106 pregnant women, of which 76 patients developed SGA, PE, or PE in association with SGA during pregnancy, and the second group consisted of 30 pregnancies with a normal evolution.

The average age of the patients included in the study was 28.4 years, similar between the two groups, 28.5±6.25 years in the control group and 28.4±6.2 years in the PMD group, without a statistically significant difference ($p>0.001$).

Maternal BMI was approximately the same in the two groups, 25.5kg/m^2 so the maternal weight did not present a significant statistical difference in this study either ($p>0.001$).

Studying other risk factors for the presented pathology, we found that no studied risk factor was statistically involved in the evolution toward PMD during pregnancy.

The data are presented in Table 1.

Table 1. Demographic characteristics and risk factors for PMD of the study population.

	Control group	PMD Group	p-value
Maternal characteristics			
Maternal Age (years) (Mean±SD)	28.5±6.25	28.4±6.2	p=0.923
BMI (kg/m2, (Mean±SD)	25.5±5.1	25.4±3.3	p=0.933
Nulliparity (n, %)	12 (11.32%)	43 (40.56%)	p=0.108
History of recurrent abortion (n, %)	7 (6.60%)	20 (18.86%)	p=0.750
Previous birth (n, %)	18 (16.98%)	33 (31.13%)	p=0.123
Previous premature birth (n, %)	4 (3.77%)	12 (11.32%)	p=0.101
Previous PE (n, %)	3 (2.83%)	16 (15.09%)	p=1.786
Previous SGA (n, %)	2 (1.88%)	9 (8.49%)	p=0.619
Birth characteristics			
Gestational age at birth (weeks) (Mean±SD)	38.32±0.51	36.21±1.91	p<0.001
Birthweight (percentile) (Mean±SD)	36.1±14.20	10.81±7.55	p<0.001
Birthweight (grams) (Mean±SD)	3130.3±212.24	2355.60±391.36	p<0.001
Apgar score 1 min	8.43±0.62	7.15±1.24	p<0.001
Apgar score 5 min	9±0.45	8.13±0.99	p<0.001
Hospitalization in Neonatal Intensive Care Department (n, %)	2 (1.88%)	36 (33.96%)	p<0.001

Also, in this table, a series of characteristics for new-borns from the pregnancies included in this study are presented.

We noticed a significant statistical difference ($p<0.001$), regarding gestational age at birth, birthweight, Apgar score, and hospitalization in Neonatal Intensive Care.

As expected, gestational age at birth and birthweight was lower in the group with PMD complications, as was the Apgar score or the percentage of new-borns who required hospitalization in the Neonatal Intensive Care Department.

One of the aims of our study was the assessment of the intraplacental villous artery's Doppler capacity to detect early the increase in resistance in the placental flow concerning the UA Doppler.

As noted in Table 2, in the control group that analysed normal pregnancies, we had a mean of 0.42±0.12 and 0.33±0.07 for IPVA PI and IPVA RI, respectively, with maxima that did not exceed the value of 1, which is within normal limits.

In the PMD group, the mean IPVA was 1.01±0.24 and 0.61±0.11 for IPVA PI and IPVA RI respectively, with maximums of 1.58 for IPVA PI, which shows us an increase in placental blood flow resistance.

Table 2. Statistical correlation of mean Doppler IPVA in the second trimester.

	IPVA-PI	IPVA-RI
Mean IPVA	0.82	0.51
Control group		
Mean	0.42	0.33
SD	0.12	0.07
Maximum	0.77	0.53
Minimum	0.27	0.24
PMD Group		
Mean	1.01	0.61
SD	0.24	0.11
Maximum	1.58	0.86
Minimum	0.25	0.32
p<0.001	**p=0.000**	**p=0.000**

Calculating the mean value of IPVA PI and IPVA RI in the 3rd trimester in the two groups, it was 0.9 and 0.6, respectively (Table 2).

In the PMD group, the mean IPVA PI was 1.1±0.3 compared to 0.5±0.1 in the control group.

The resistance index in the PMD group was higher (IPVA RI=0.7±0.2) compared to the control group, 0.4±0.1.

Table 3. Statistical correlation of mean Doppler IPVA in the third trimester.

	IPVA PI	IPVA RI
Mean IPVA	0.9	0.6
Control group		
Mean	0.5	0.4
SD	0.1	0.1
Maximum	1.0	0.5
Minimum	0.4	0.3
PMD Group		
Mean	1.1	0.7
SD	0.3	0.2
Maximum	1.7	1.6
Minimum	0.4	0.3
p<0.001	**p=0.000**	**p=0.000**

The statistical correlation of the two groups shows a strong statistical significance, $p<0.001$, for the changes that occur at the IPVA level in pregnancies with possible growth restriction and/or preeclampsia, in the 2nd and 3rd trimesters.

The statistical correlation of IPVA PI with gestational age showed us a positive linear correlation, an increase of IPVA PI with the increase of gestational age, while in pregnancy with normal evolution, these values tend to decrease, the linear correlation being negative (Fig 1).

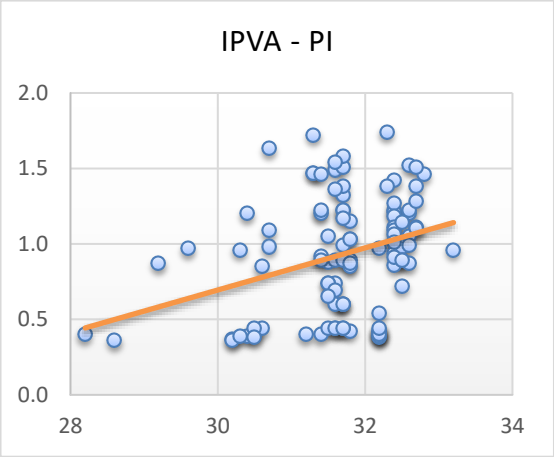

Figure 1. Correlation of IPVA PI with gestational age in 3rd trimester.

We performed the Doppler evaluation of the fetoplacental circulation not only at the level of the IPVA but also at the level of the umbilical arteries.

As noted in Table 4, the PMD group had a higher mean UA PI than the control group, 1.3±0.2 and 1.0±0.2 respectively.

We noticed the same thing at UA RI, but with a smaller difference between the values, 0.6±0.1 and 0.7±0.1 respectively.

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And the value of the percentiles at UA PI was higher in the PMD group, having maximum values of the 95th percentile, with an average of 61.5±24.2 percentiles, compared to the control group, which presented normal values, below the 95th percentile and with an average of 8.2±8.4 percentiles.

This analysis shows that there is a significant statistical correlation, p<0.001.

Table 4. Statistical correlation of mean Doppler UA in the second trimester.

	UA PI	UA PI (percentiles)	UA-RI
mean UA	1.1	46.4	0.7
Control group			
Mean	1.0	8.2	0.6
SD	0.2	8.4	0.1
Maximum	1.3	31.0	0.7
Minimum	0.7	1.0	0.5
PMD Group			0.7
Mean	1.3	61.5	
SD	0.2	24.2	0.1
Maximum	1.8	95.0	0.9
Minimum	0.8	1.0	0.5
p<0.001	**p=0.000**	**p=0.000**	**p=0.000**

The PI UA measurement in the 3rd trimester showed us an average value of 0.9±0.2 in the control group, compared to 1.2±0.2 in the PMD group.

While in the control group, we did not have UA-PI values above 95 percentiles, in the PMD group we found maximum values of 98 percentiles (Table 5).

Table 5. Statistical correlation of mean Doppler UA in the third trimester.

	UA PI	UA PI (percentiles)	UA-RI
Mean UA	1.1	65.4	0.7
Control group			
Mean	0.9	39.5	0.6
SD	0.2	19.8	0.1
Maximum	1.3	82.0	0.8
Minimum	0.6	6.0	0.4
PMD Group			
Mean	1.2	75.6	0.7
SD	0.2	22.3	0.1
Maximum	1.7	98.0	1.0
Minimum	0.6	8.0	0.4
p<0.001	**p=0.000**	**p=0.000**	**p=0.000**

In pregnancies with normal evolution, the IPVA PI/UA PI ratio is less than 1.

When the ratio becomes above unity, it shows an increase in vascular resistance at the placental level, which will also affect the Doppler values of the umbilical artery (Table 6).

In the second trimester, we had only 7 cases with this ratio >1, while in the third trimester, 23 cases presented this ratio>1.

Table 6. IPVA/UA ratio in the 2nd and 3rd trimesters.

	IPVA-PI/UA-PI 2nd /3rd trimester	IPVA-RI/UA-RI 2nd /3rd trimester
IPVA/UA Fraction (Mean)	0.8/0.8	0.5/0.9
Control Group		
Mean	0.4/0.5	0.3/0.6
SD	0.1/0.2	0.1/0.2
Maxim	0.8/1.2	0.5/1.2
Minim	0.3/0.3	0.2/0.4
PMD Group		
Mean	1.0/0.9	0.6/0.9
SD	0.2/0.1	0.1/0.2
Maxim	1.6/1.4	0.9/1.9
Minim	0.3/0.3	0.3/0.4
p<0.001	**p=0.000**	**p=0.000**

Making a comparison between the two parameters, IPVA PI and UA PI regarding the degree of prediction of the changes occurring at this level, we found a good statistical correlation.

A higher degree of positive predictability is noted, with PPV of 100% for IPVA, compared to 84.5% for UA, in the second trimester and 100% vs 85.29% in the third trimester, as reported by other specialized studies (Table 6, Table 7), but with better sensitivity (72.27%) for UA PI in the 2nd trimester.

Table 7. Predictive accuracy of IPVA PI and UA PI in the second trimester.

2nd Trimester	Sn (CI 95%)	Sp (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
IPVA PI	45.45%	100%	100%	52.63%
UA PI	72.27%	56.66%	84.52%	93.42%

Table 8. Predictive accuracy of IPVA PI and UA PI in the third trimester.

3rd Trimester	Sn (CI 95%)	Sp (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
IPVA PI Trim III	50%	100%	100%	60.52%
UA PI Trim III	52.63%	66.66%	85.29%	76.31%

A parallel between IPVA PI and UA PI, the two groups being analysed both separately and together in the two trimesters, showed us that there is a significant statistical correlation (p<0.001) (Table 8).

Table 9. Statistical correlation between IPVA-PI and UA-PI in the two trimesters.

IPVA/UA	Control group n=30	Complication group n=76	Control group + Complication group N=106	p-value
IPVA PI/2nd trimester	0.4±0.1	1±0.2	0.8±0.2	<0.001
UA PI/ 2nd trimester	1±0.2	1.3±0.2	1.2±0.3	<0.001
IPVA PI/3rd trimester	0.5±0.1	1.1±0.3	0.9±0.4	<0.001
UA PI/3rd trimester	0.9±0.2	1.2±0.2	1.1±0.3	<0.001

We can thus make the statement that both Doppler measurements, IPVA and UA can be used to evaluate and detect the evolution of pregnancy towards complications that belong to PMD, preeclampsia, and/or fetal growth restriction (Table 9).

Discussion

We examined IPVA Doppler and UA Doppler in a cohort of 106 pregnancies both with normal evolution and with PE and/or SGA.

Considering that SGA birthweight infants have an increased risk of stillbirth, fetal distress, increased morbidity, and long-term negative effects, including delayed neurological development, all this suggests that the birth of an SGA child, with or without preeclampsia, not be a benign condition [3,5,7].

This is especially since even in the presence of a normal UA Doppler waveform, the placenta shows histopathological changes specific to maternal and fetal malperfusion [8,9].

That is why it is also necessary to query the impedance indices at the placental level, which are closely related to the number and functioning of the placental vascular tree, considering that in PMD there is a reduction of it.

Since 1990, Thompson and Trudinger [10] have predicted the effect of the decrease in placental arterial impedance both within PMD and by increasing gestational age or a smaller placenta, according to a mathematical model.

According to this model, with the increase in the level of obliteration of the vessel, when it reaches a sufficiently high value, UA PI starts to increase abruptly, reaching very high values, above the 95th percentile, associated with fetal compromise.

Nevertheless, there are cases in which, although we have abnormally high UA PI, the intraplacental villous blood flow is within normal limits, as we also encountered in our study.

And then what would be the explanation?

By Doppler scanning of an artery, we only measure the blood flow in that artery, while the function of other occluded arteries is compensated by other arteries that, by increasing the lumen, can give normal results in the ultrasonographic scan.

This phenomenon was explained by Lacin et al. taking into account the structure of the villous arteries and the adaptability of the placenta [11].

In our study, we found that starting early, from 20 weeks of pregnancy, in cases with risk factors for PE and/or SGA and who eventually developed this pathology, IPVA PI values were higher than in the group of control, a phenomenon that intensified in the 3rd trimester.

Previous studies have shown that in a normal pregnancy, due to the constant multiplication of tertiary villi, there is a progressive reduction of placental resistance [12,13,14], while in high-risk pregnancies, there is greater resistance to the intraplacental flow in cases of PE and/or SGA, and in which neonatal outcomes are poor [15,16].

We noted an increase in vascular resistance at the placental level, manifested by an increase in the IPVA/UA>1 ratio, which presented a significant statistical difference, $p<0.001$, demonstrating that Doppler investigation of intraplacental vessels is feasible, even if some studies did not identify a benefit through IPVA Doppler screening [11,12,17].

But subsequent studies have shown that measuring IPVA PI has at least the advantage of detecting pregnancies at risk of producing PMD, a beneficial advantage for the fetus [3,15,18].

Making a comparison between the two parameters, IPVA and UA Doppler, regarding the degree of prediction of the changes occurring at this level, we found in the conducted study, a good statistical correlation.

A higher degree of positive predictability is noted, similar in the 2nd and 3rd trimesters, as reported by other specialized studies, with better sensitivity for UA PI in the 2nd trimester [3,19].

It would be a shame if, having a non-invasive intervention at our disposal, we did not use the related benefits, with the influence on perinatal mortality and did not introduce it into clinical care, because IPVA can offer, at least theoretically, but also following the results of this study, early detection of PMD.

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Conclusions

We can conclude that both Doppler measurements, IPVA and UA can be used to evaluate and detect the evolution of pregnancy towards PMD, preeclampsia, and/or fetal growth restriction, starting from the second trimester.

But it seems that larger prospective studies are needed to validate IPVA as an individual prognostic factor for PMD.

Conflict of interests

None to declare.

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Corresponding Author: Mircea Sebastian Șerbănescu, University of Medicine and Pharmacy of Craiova, "Filantropia" Hospital, Craiova, Romania, e-mail: mircea_serbanescu@yahoo.com