Utility of Doppler parameters at 36–42 weeks' gestation in the prediction of adverse perinatal outcomes in appropriate-for-gestational-age fetuses

Michał Migda[1,2], Katarzyna Gieryn[1], Bartosz Migda[3],

Marian Stanisław Migda[2], Marek Maleńczyk[1]

[1] Obstetrics, Women's Disease and Gynecological Oncology Teaching Department, Voivodeship Hospital Complex, Collegium Medicum of the Nicolaus Copernicus University in Toruń, Poland

[2] Civis Vita Medical Center in Toruń, Poland

[3] Diagnostic Imaging Division, Second Faculty of Medicine with the English Division and the Physiotherapy Division, Medical University of Warsaw, Warsaw, Poland

Correspondence: Michał Migda, Civis Vita Centrum Medyczne, ul. Warszawska 20, 87-100 Toruń, Polska, tel. +48 607 398 446, e-mail: mchmigda@gmail.com

Abstract

Aim: To investigate the potential value of Doppler ultrasound and to assess cerebroplacental ratio (CPR) in the prediction of adverse perinatal outcome defined as Apgar score < 7 at 1 minute. **Material and methods:** This was a retrospective cross-sectional study in selected pregnant women undergoing an ultrasound examination between 36 and 42 weeks of gestation. We measured estimated fetal weight (EFW), mean umbilical artery pulsatility index (UA PI), mean middle cerebral artery pulsatility index (MCA PI), CPR, and Apgar score in 1 minute. Multiples of medians (MoM) were calculated for MCA PI and UA PI. **Results:** The study group consisted of 446 women, 236 were primipara and 210 were multipara. The average age was 29.6 years (range 16–46 years). The average week of delivery is 39.5 weeks of gestation (range 36–42). Mean MCA PI and UA PI were 1.3 (0.1–2.45) and 0.8 (0.39–1.66), respectively. The mean values were 1.03 (0.1–1.9) for MCA PI MoM and 1.04 (0.5–2.1) for UA PI MoM. Primiparas had lower values of MCA PI (1.27 vs. 1.34), MCA PI MoM (1.00 vs. 1.05), CPR (1.62 vs. 1.73), EFW (3479.53 g vs. 3579.25 g) and birth weight (3513.50 g vs. 3617.79 g). For CPR cut-off point of 1.08: sensitivity was (0.945), specificity 0.1, positive predictive values 0.979, negative predictive values 0.04 and accuracy 0.926. The ROC curves for CPR were: area under the curve was 0.52 at CI 95% (0.342–0.698), $p = 0.8271$. **Conclusion:** Screening in pregnancies with appropriate-for-gestational-age fetuses at 36–42 weeks of gestation using Doppler parameters is not useful in the prediction of adverse perinatal outcomes like an Apgar score < 7 at 1 minute.

Introduction

Doppler ultrasound[1] is used to assess the flow in umbilical artery (UA) and fetal middle cerebral artery (MCA). The pulsatility index (PI) is used to calculate the cerebroplacental ratio (CPR), which is used for the assessment of fetal oxygenation[2–3]. Abnormal Doppler findings in the third trimester are typically associated with adverse perinatal outcome[4–6]. Most studies on the clinical use of Doppler and CPR have been focused on the assessment of small-for-gestational-age[7] fetuses, who are at increased risk for adverse perinatal outcomes and long-term neurodevelopmental impairment[8–11]. However, a large study of Bakalis *et al.* regarding singleton pregnancies at 30–34 weeks of gestation reports that the majority of cases for each type of adverse perinatal outcomes concerned fetuses that were appropriate-for-gestational-age (AGA). For instance, 70% of stillbirths and 80% of cesarean sections for fetal distress occur in AGA group[12]. Consequently, prenatal care should identify hypoxemic rather than small fetuses, and screen for low CPR regardless of the fetal size[5,13]. It was also reported that the prediction of an adverse perinatal outcome by low CPR was better if the time interval between assessment and delivery was ≤ 2 weeks and that the screening by CPR at 36 weeks may be more valuable than at 32 weeks[2,12,14].

The objective of this study has been to investigate the usefulness of Doppler parameters obtained in third-trimester AGA fetuses for the prediction of adverse perinatal outcomes.

Material and methods

We performed a retrospective cross-sectional study between January 2012 and December 2013 in a group of pregnant women with appropriate-for-gestational-age fetuses, undergoing a routine third-trimester ultrasound examination between 36 and 42 weeks of gestation. The study was approved with an institutional review board consent of the Obstetrics, Women's Disease and Gynecological Oncology Teaching Department, Voivodeship Hospital Complex, Collegium Medicum of the Nicolaus Copernicus University in Toruń, Poland.. All the exams were performed at our Department by accredited examiners using Voluson GE E 6 (General Electric, Zipf, Austria). The inclusion criteria for this study were as follows: singleton pregnancy, gestational age determined by last menstrual period (LMP) and confirmed with crown-rump length measurement at 11–13 weeks, absence of fetal structural malformation or a genetic condition confirmed either pre- or post-natally, ultrasound examination performed no further than 2 weeks before delivery. All pregnant women included in the study were Caucasian, conception was spontaneous, were non-smokers and had no medical history of chronic hypertension, diabetes mellitus, systemic lupus erythematosus (SLE) or antiphospholipid syndrome (APS). The following ultrasound parameters were assessed: estimated fetal weight (EFW) calculated automatically using Hadlock's formula, mean UA PI, mean MCA PI, CPR was calculated dividing MCA PI by UA PI. Doppler measurement of UA and MCA was performed according to ISUOG (International Society of Ultrasound in Obstetrics and Gynecology) guidelines. For UA Doppler, a free loop measurement was performed, with an insonation angle of <20^0 (Fig. 1).

The proper technique of MCA Doppler measurement was as follows[15]:

1. Axial section of the brain (including thalami and sphenoid wings) and magnified.
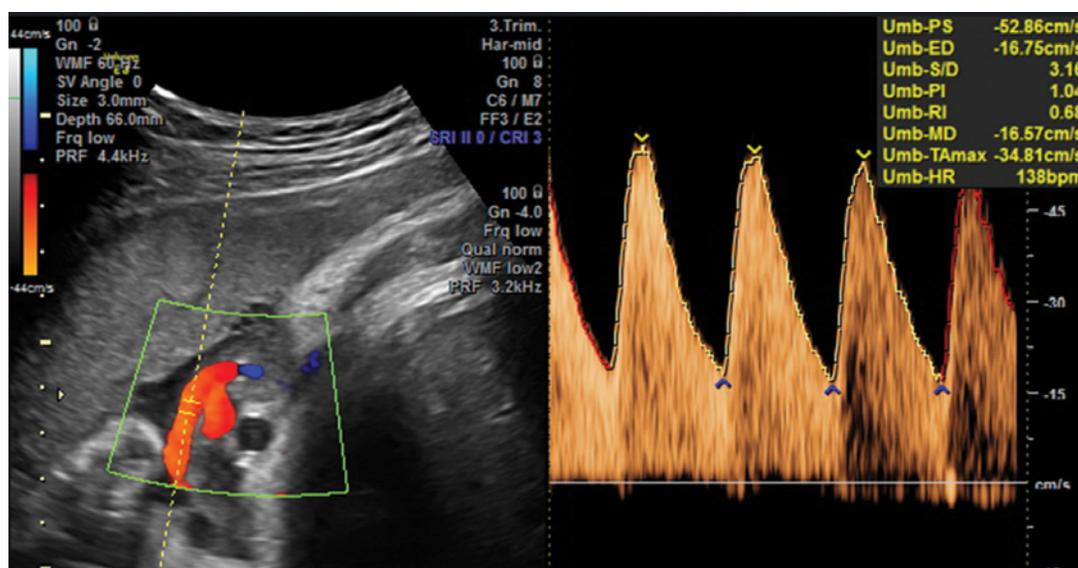

Fig. 1. *Doppler assessment of pulsatility index (PI) in umbilical artery (UA)*
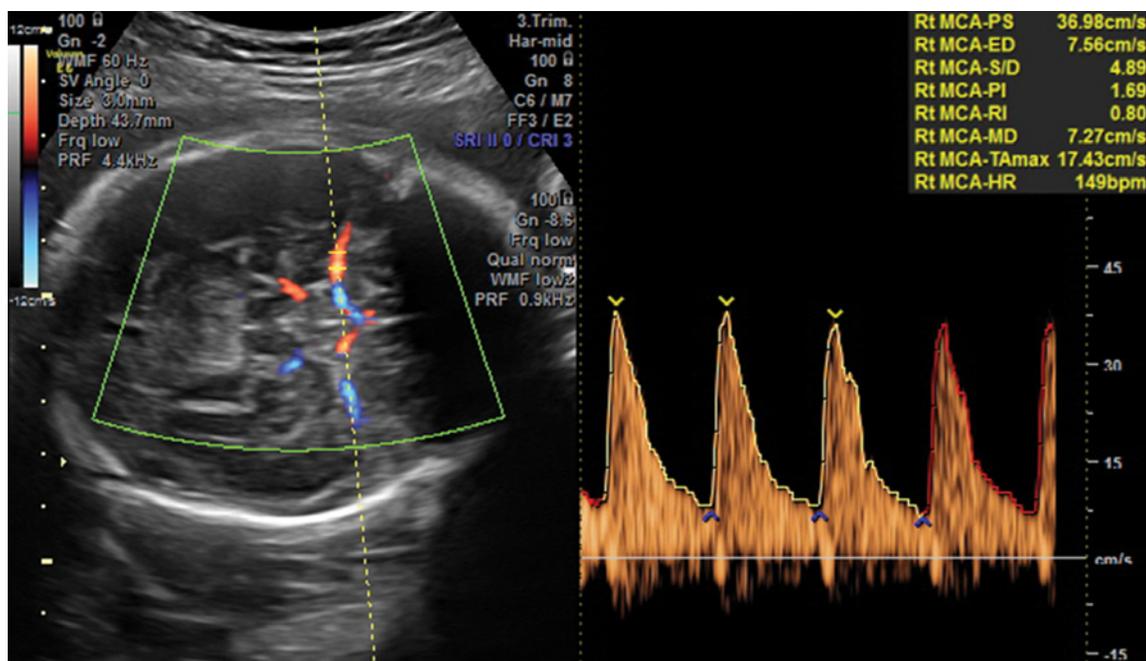
Fig. 2. *Doppler assessment of pulsatility index (PI) in middle cerebral artery (MCA)*

2. Color flow mapping should be used to identify the circle of Willis and the proximal MCA (Fig. 2).
3. The pulse-wave Doppler gate should then be placed at the proximal third of the MCA, close to the origin in the carotid artery.
4. The angle between the ultrasound beam and the direction of blood flow should be kept as close as possible to 0^0 (Fig. 2).
5. At least three to 10 consecutive waveforms should be recorded.
6. PI is usually calculated using autotrace measurement.

We defined adverse perinatal outcomes as Apgar score of < 7 at 1 minute. In cases where the same pregnant women underwent repeated ultrasound examinations, we took into account the last exam before delivery. We did not analyze umbilical cord pH after delivery, due to the fact that our group consisted of low-risk pregnancies. Moreover, the mode of delivery was assessed with special attention to fetal distress as an indication for operational delivery (vacuum, forceps, cesarean section).

Statistical analysis

Statistical analysis of the obtained data was performed using Statistica 10 software (StatSoft.Inc). Continuous variables were predominant: mother age, gestational age, UA PI, UA PI MoM, MCA PI, MCA PI MoM, CPR, EFW on ultrasound (US), birth weight. In addition, there was a single qualitative variable: mode of delivery.

The W-Shapiro-Wilk test was used to evaluate the normal distribution of continuous variables. The Mann-Whitney U test and Student's t-test were used to compare continuous variables according to the distribution of data. ROC curves were used to determine the suitability of CPR as an Apgar score predictor, giving the area under the curve (AUC) with 95% confidence interval and a significance level. For measurable variables, the average, median, minimum, maximum and standard deviation were calculated. In addition, plots for UA PI and MCA PI were plotted against gestation age expressed at 95% confidence intervals.

For all calculations, $p < 0.05$ was considered as the statistical significance level.

Results

The study group consisted of 446 pregnant women, of which 236 were primiparas and 210 were multiparas. The average age was 29.6 years (range 16–46 years). The average age of primiparas was 27.7 years (range 16–41 years) and of multiparas 31.7 years (range 19–46 years).

Table 1 shows the characteristics of the whole group. The average week of delivery was 39.5 weeks of gestation (range 36–42). The mean values of MCA PI and UA PI were 1.3 (0.1–2.45) and 0.8 (0.39–1.66), respectively. The mean values based on multiple of medians were 1.03 (0.1–1.9) for MCA PI MoM and 1.04 (0.5–2.1) for UA PI MoM (Tab. 1).

Seventy women were at least 35 years of age. None of the tested fetal parameters was found to be significantly different between the groups of women more and less than 35 years of age (Tab. 2).

Age (years)	Descriptive statistics							
	N	Mean	Median	Min.	Max.	Lower Quartile	Upper Quartile	SD
Mother age	446	29.6	30	16	46	27	33	5.044
Gestational age	446	39.5	40	36	42	39	41	1.420
MCA PI	446	1.30	1.27	0.10	2.45	1.09	1.50	0.306
MCA PI MoM	446	1.03	1.00	0.10	1.90	0.90	1.20	0.242
UA PI	446	0.80	0.78	0.39	1.66	0.69	0.90	0.159
UA PI MoM	446	1.04	1.00	0.50	2.10	0.90	1.20	0.206
CPR	446	1.67	1.62	0.16	3.87	1.39	1.90	0.472
EFW USG	446	3526.48	3553	2230	4680	3200	3860	457.060
Birth weight	446	3562.61	3550	2700	4480	3250	3860	412.195
N – number of cases; SD – standard deviation. MCA – middle cerebral artery. UA – umbilical artery. PI – pulsatility index. CPR – cerebroplacental ratio. EFW – estimated fetal weight. US – ultrasound. MoM – multiple of medians								

Tab. 1. *Maternal and obstetric characteristics of the study population*

Age (years)	N		Mean		Min.		Max.		SD		p
	<35	≥35	<35	≥35	<35	≥35	<35	≥35	<35	≥35	
Mother age	376	70	28.1	37.6	16	35	34	46	3.880	2.441	0.0000
Gestational age	376	70	39.5	39.3	36	36	42	42	1.431	1.353	0.0942
MCA PI	376	70	1.29	1.34	0.10	0.57	2.45	2.16	0.299	0.342	0.2150*
MCA PI MoM	376	70	1.02	1.06	0.10	0.40	1.90	1.70	0.235	0.74	0.1734
UA PI	376	70	0.80	0.80	0.39	0.44	1.66	1.14	0.160	0.157	0.9694
UA PI MoM	376	70	1.04	1.03	0.50	0.60	2.10	1.50	0.207	0.200	0.9521
CPR	376	70	1.66	1.74	0.16	0.53	3.87	3.51	0.463	0.516	0.3084
EFW US	376	70	3523.9	3540.39	2230	2500	4680	4525	458.578	451.826	0.7820*
Birth weight	376	70	3564.6	3552.14	2700	2710	4480	4330	414.126	404.435	0.8174*
N – number of cases; Std. – standard deviation; p* – t-Student test; p – U Mann-Whitney test, MCA – middle cerebral artery, UA – umbilical artery, PI – pulsatility index, CPR – cerebroplacental ratio, EFW – estimated fetal weight, US – ultrasound, MoM – multiple of medians											

Tab. 2. *Statistical analysis of two groups <35 and ≥ 35 years old*

Parity (0 = primipara; 1 = multipara)	N		Mean		Min.		Max.		SD		p
	0	1	0	1	0	1	0	1	0	1	
Mother age	236	210	27.7	31.7	16	19	41	46	4.644	4.633	0.0000
Gestational age	236	210	39.5	39.4	36	36	42	42	1.468	1.366	0.3477
MCA PI	236	210	1.27	1.34	0.10	0.57	2.05	2.45	0.298	0.311	0.0119*
MCA PI MoM	236	210	1.00	1.05	0.10	0.40	1.60	1.90	0.233	0.249	0.0432
UA PI	236	210	0.80	0.80	0.49	0.39	1.45	1.66	0.152	0.167	0.9574
UA PI MoM	236	210	1.04	1.04	0.60	0.50	1.90	2.10	0.199	0.214	0.9504
CPR	236	210	1.62	1.73	0.16	0.53	2.99	3.87	0.437	0.503	0.0354
EFW US	236	210	3479.53	3579.25	2330	2230	4613	4680	471.895	434.880	0.0213*
Birth weight	236	210	3513.50	3617.79	2700	2710	4470	4480	429.786	385.075	0.0075*
N – number of cases; Std. – standard deviation; p*– t-Student test; p – U Mann-Whitney test, MCA – middle cerebral artery, UA – umbilical artery, PI – pulsatility index, CPR – cerebroplacental ratio, EFW – estimated fetal weight, US – ultrasound, MoM – multiple of medians											

Tab. 3. *Statistical analysis of two groups of patients: primiparas vs multiparas*

Apgar	N		Mean		Min.		Max.		SD		p
	≤7	>7	≤7	>7	≤7	>7	≤7	>7	≤7	>7	
Mother age	10	436	29.6	29.6	25	16	35	46	2.875	5.085	0.9921
Gestational age	10	436	40.0	39.5	38	36	41	42	1.247	1.423	0.2476
MCA PI	10	436	1.29	1.30	1.01	0.10	1.90	2.45	0.285	0.307	0.9347
MCA PI MoM	10	436	1.02	1.03	0.80	0.10	1.50	1.90	0.225	0.242	0.7992
UA PI	10	436	0.80	0.80	0.63	0.39	0.98	1.66	0.120	0.160	0.8934
UA PI MoM	10	436	1.04	1.04	0.80	0.50	1.30	2.10	0.165	0.207	0.8165
CPR	10	436	1.67	1.67	1.05	0.16	2.97	3.87	0.531	0.471	0.8310
EFW USG	10	436	3618.80	3524.37	2650	2230	4330	4680	485.323	456.763	0.5189
Birth weight	10	436	3445.00	3565.30	2810	2700	3950	4480	393.340	412.656	0.3621

N – number of cases; Std.-standard deviation; p – t-Student test; p – U Mann-Whitney test, MCA – middle cerebral artery, UA – umbilical artery, PI – pulsatility index, CPR – cerebroplacental ratio, EFW – estimated fetal weight, US – ultrasound, MoM – multiple of medians*

Tab. 4. *Statistical analysis of two groups of patients that deliver a fetus with: <= 7 Apgar vs >7 Apgar*

When compared to multiparas, primiparas had lower values of MCA PI (1.27 vs. 1.34), MCA PI MoM (1.00 vs. 1.05), CPR (1.62 vs. 1.73), EFW USG (3479.53 g vs 3579.25 g) and birth weight (3513.50 g vs. 3617.79 g) (Tab. 3).

None of the parameters tested (mother age, MCA PI, MCA PI MoM, UA PI, UA PI MoM, CPR, EFW USG, birth weight) showed a difference across the groups with respect to Apgar score, or the method of delivery (Tab. 4 and Tab. 5). In our study, we used the cut-off point of 1.08, and we report a high sensitivity (0.945) but a low specificity (0.1), positive predictive values (PPV) 0.979, negative predictive values (NPV) 0.04 and accuracy (ACC) 0.926.

The results for the analysis of ROC curves for CPR were: AUC was 0.52 at CI 95% (0.342–0.698), $p = 0.8271$ (Fig. 3). Figures 4 and 5 show the relationships between UA PI and MCA PI and gestational age in weeks with a 95% confidence interval.

Discussion

In our study, we have assessed the utility of Doppler parameters as predictors of adverse perinatal outcomes in selected groups of pregnancies with AGA fetuses in the third trimester of pregnancy. CPR is more predictive of adverse perinatal outcomes compared to a single Doppler measurement like UA PI or MCA PI[1]. Grammellini *et al.*, as well as other researchers, report that CPR values are constant throughout the last ten weeks of pregnancy, and have established a value of 1.08 as a cut-off point, beyond which (<1.08) the ratio is regarded as abnormal[8]. Other authors suggest a value of CPR <1.05 to be a good predictor of an adverse perinatal outcome, but included high-risk pregnancies, e.g. complicated with arterial hypertension or gestational diabetes[16]. It is of paramount importance to properly define the MCA and UA PI values as normal or abnormal, since such parameters are to reflect placental insufficiency, especially in prolonged pregnancies between 41 and 42 + 6 weeks, where perinatal morbidity and mortality increase due to frequently postulated placental

Mode of delivery	N		Mean		Min.		Max.		SD		p
	ND	OP	ND	OP	ND	OP	ND	OP	ND	OP	
Mother age	273	173	29.2	30.2	16	17	42	46	4.890	5.237	0.1252
Gestational age	273	173	39.6	39.3	36	36	42	42	1.371	1.481	0.0390
MCA PI	273	173	1.29	1.31	0.10	0.60	2.45	2.16	0.309	0.303	0.5002
MCA PI MoM	273	173	1.02	1.03	0.10	0.50	1.90	1.70	0.244	0.239	0.8431
UA PI	273	173	0.80	0.80	0.39	0.49	1.66	1.45	0.167	0.146	0.9645
UA PI MoM	273	173	1.03	1.04	0.50	0.60	2.10	1.90	0.215	0.190	0.6633
CPR	273	173	1.67	1.68	0.16	0.61	3.87	3.51	0.492	0.439	0.6156
EFW US	273	173	3505.19	3560.08	2230	2330	4526	4680	461.068	449.938	0.2169
Birth weight	273	173	3539.24	3599.48	2700	2700	4460	4480	414.982	406.218	0.1328

N – number of cases; ND – natural delivery; Op – operational delivery; SD. – standard deviation; p – t-Student test; p – U Mann-Whitney test, MCA – middle cerebral artery, UA – umbilical artery, PI – pulsatility index, CPR – cerebroplacental ratio, EFW – estimated fetal weight, US – ultrasound, MoM – multiple of medians*

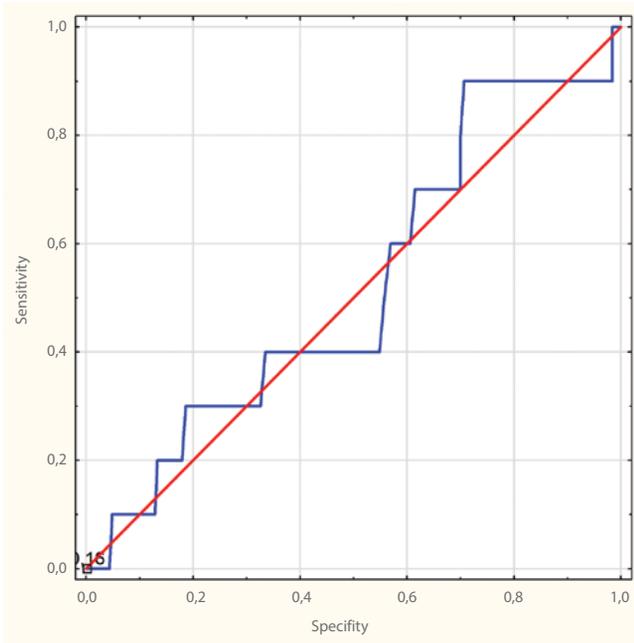**Tab. 5**. *Statistical analysis of two groups of patients according to mode of delivery*

Fig. 3. *ROC curve for the cerebroplacental ratio (CPR)*

obsolescence[17]. Even in uncomplicated pregnancies with no symptoms of abnormal placental function, an adaptive mechanism of brain-sparing effect is activated to protect the brain throughout the adverse conditions manifested as decrease of MCA PI values even before UA alterations appear[1]. In our study, we demonstrate that during the third trimester of pregnancy, MCA PI and UA PI decrease with gestational age. Such findings are similar to results presented in previous studies[7,18–19]. However, we found none of the analyzed Doppler parameters to be statistically significant in the prediction of adverse perinatal outcomes. In our opinion, this could have been expected, as we examined a low-risk pregnancy population. Our data are similar to Korbelak *et al*., who also report a low prediction rate of UA PI in predicting adverse perinatal outcomes in a low-

-risk population group[20]. Yet, a major weakness of their study is a relatively small group of only 24 patients that were enrolled to the cohort. Recent studies, in contrast, investigate the power of Doppler parameters in predicting adverse perinatal outcomes using non-selected groups of patients, where the included complications, like small gestational age (SGA), fetal growth restriction (FGR), gestational hypertension or gestational diabetes mellitus, could influence significantly the results[2,9,12,14,16,18,21–23]. In our study, we found no significant correlation of Doppler parameters with Apgar score < 7 at 1 min. Yet, we report that nulliparous women, compared to multiparas, had significantly lower values of: age, MCA PI, MCA PI MoM, CPR, EFW and fetal birth weight. In our population, there was a significantly higher number of patients younger than 35 years. Natural delivery was more frequent than operational delivery, and all were emergency cesarean sections. Our results contrast with those in a study by Valino *et al*., where half of the cases had elective cesarean section due to a maternal or fetal condition[24].

Our study had some limitations. Firstly, it was a retrospective study. Secondly, it was a relatively small cohort of one center-based study, with a small number of Apgar score < 7 cases. The strong side of the study is the homogeneity of population of Caucasian women without risk factors and the fact that examinations were performed within a short period of time before delivery by experts trained in Doppler examinations.

Screening in pregnancies with AGA at 36–42 weeks of gestation using Doppler parameters is not useful in the prediction of adverse perinatal outcomes like an Apgar score < 7 at 1 minute.

Conflict of interest

Authors do not report any financial or personal connections with other persons or organizations that might negatively affect the contents of this publication and/or claim authorship rights thereto.
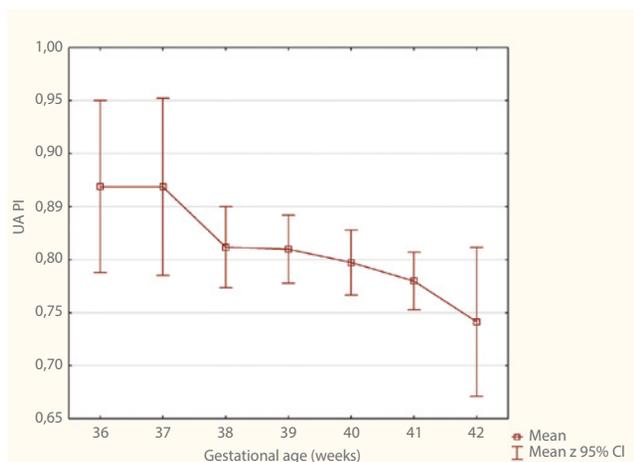

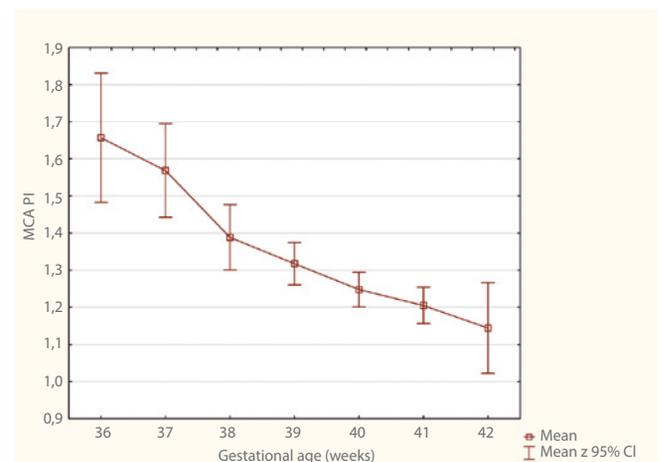**Fig. 4.** *Relationship between UA PI and gestational age in weeks with a 95% confidence interval*

Fig. 5. *Relationship between MCA PI and gestational age in weeks with a 95% confidence interval*

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