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## Alterations in maternal cardiovascular parameters and their impact on uterine and fetal circulation in hypertensive pregnancies and fetal growth restriction

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### ABSTRACT

**Objective:** To examine potential alterations in maternal cardiovascular parameters in hypertensive pregnancies with or without fetal growth restriction (FGR) in comparison to uncomplicated normotensive pregnancies, and to determine the correlation between maternal cardiovascular parameters and changes in umbilical and uterine artery circulation.

**Materials and methods:** This study enrolled 73 pregnant women starting from the 20th week of gestation, categorized into three groups: hypertensive conditions (pregnancy-induced hypertension, preeclampsia or eclampsia,  $n = 30$ ), hypertensive conditions with FGR ( $n = 8$ ) and a control group of healthy normotensive pregnant women ( $n = 35$ ). All participants underwent echocardiography to assess cardiac output and calculate peripheral vascular resistance. Additionally, fetal biometric measurements and Doppler ultrasound examinations of the uterine and umbilical artery were performed. The results were standardized into gestational age-adjusted z-scores.

**Results:** The mean pulsatility index (PI) of the uterine artery ( $1.36, p < 0.001$ ) and umbilical artery PI z-scores ( $1.32, p < 0.001$ ) showed significant increases in the hypertensive conditions + FGR group. Maternal cardiac output z-scores were notably lower in both the hypertensive + FGR group ( $-2.62, p = 0.001$ ) and the hypertensive group ( $-2.49, p < 0.001$ ). Peripheral vascular resistance was significantly elevated in the hypertensive + FGR group ( $7.43, p < 0.001$ ) and the hypertensive group ( $6.06, p < 0.001$ ). There was a positive correlation between maternal peripheral vascular resistance and uterine artery PI ( $R^2 = 0.172; p = 0.0004$ ), and a negative correlation between cardiac output and uterine artery PI ( $R^2 = 0.067; p = 0.031$ ). However, significant correlation between maternal cardiovascular parameters and umbilical artery PI was not identified.

**Conclusions:** Maternal cardiac output exhibits a significant decrease whereas peripheral vascular resistance increases in hypertensive pregnancies, irrespective of the presence of FGR. Both uterine and umbilical artery PI notably increase when hypertensive pregnancies are accompanied by FGR. A positive correlation exists between maternal peripheral vascular resistance and uterine artery PI, as well as a negative correlation between maternal cardiac output and uterine artery PI. However, changes in maternal cardiovascular parameters do not exhibit significant correlations with umbilical artery PI.

### 1. Introduction

Normal pregnancy is followed by substantial hemodynamic changes that support the uteroplacental circulation. It is now well studied that in normal pregnancy maternal cardiac output increases during the first

trimester because of an increased cardiac stroke volume. After the second trimester, the primary factor contributing to the rise in cardiac output is the elevation in heart rate, which culminates in its highest point during the initial stages of the third trimester. During early gestation, there is a reduction in peripheral vascular resistance

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attributable to the vasodilatory impact of progesterone and vasoactive agents, which aligns with the alterations in cardiac output, subsequently rebounding in the third trimester [1,2].

Maternal blood pressure has been used as a prosperous test to diagnose and classify hypertensive disorders in pregnancy. In the class of hypertensive disorders of pregnancy, preeclampsia is a major concern to long-term neonatal and obstetrical outcome for women with preeclamptic pregnancies. There are current studies about economic health burden, short-term costs of preeclampsia, also evidence revealed that in the fifth decade of life preeclampsia increases cardiovascular risk [3–5].

In these and many other studies elevated blood pressure had been the main classification criteria. Although blood pressure is easy to measure, it is a result of vascular resistance and changes in a cardiac output. Maternal vascular resistance is the result of various physiological factors, incorporating endothelial function, as well as maternal inflammatory reaction to metabolic and placental dysfunction [6].

There is a growing realization that deviation from the typical physiology of these maternal hemodynamic shifts not only coincide with pregnancy complications, notably preeclampsia and fetal growth restriction (FGR) but may also serve as early indicators of these conditions. Various patterns, which are shown in Fig. 1, can be identified based on maternal hemodynamic status, and can be linked specifically to preeclampsia, FGR, or the co-occurrence of both conditions [7].

In pregnancies where preeclampsia manifests independently of FGR, this condition typically emerges as a “late” complication and is characterized by a hyperdynamic overfilling state featuring elevated cardiac output, reduced peripheral vascular resistance, and larger left ventricular diameters in comparison to pregnancies unaffected by these conditions [9].

Conversely, when FGR is diagnosed, there is often an observed hypovolemic underfilling state characterized by decreased cardiac output, increased peripheral vascular resistance, smaller left ventricular diameters, and modified diastolic function. These characteristics are even more marked when FGR is concomitant with preeclampsia [9,10].

Research has explored the correlation between maternal cardiovascular alterations and changes in the uteroplacental circulation starting from 24 weeks of gestation in both uncomplicated pregnancies and in those affected by conditions such as preeclampsia, FGR, or both. The studies have revealed a connection with the uterine Doppler impedance, wherein a reduction in maternal cardiac output and an elevation in peripheral vascular resistance were linked to an elevated pulsatility index in maternal uterine arteries, regardless of the eventual pregnancy outcome. This study also investigated whether a correlation exists between maternal cardiovascular parameters and alterations in fetal umbilical artery Doppler indices from 24 weeks of gestation until term. The findings indicate that reduced maternal cardiac output and increased maternal peripheral vascular resistance are linked to elevated impedance in the fetal umbilical artery. Importantly, this association accounts not only in pathological pregnancies affected by conditions such as preeclampsia and/or FGR but also in healthy pregnancies [11]. Enhancing the connection between maternal cardiovascular

performance and fetal Doppler observations, the absence or reversal of end-diastolic flow in the umbilical artery was linked to decreased maternal cardiac output and elevated vascular resistance [12].

Consequently, now it is hypothesized that maternal cardiovascular dysfunctional adaptation in pregnancy may be more effective diagnostic marker than the time at the onset of increased blood pressure to comprehend different hypertensive disorders in pregnancy. Therefore, in our study we investigated maternal cardiac output and peripheral vascular resistance in three groups of pregnant women: normotensive healthy pregnancies, hypertensive pregnancies (gestational hypertension and preeclampsia or eclampsia) and hypertensive pregnancies with FGR. We sought to investigate whether maternal hemodynamical changes, cardiac output and peripheral vascular resistance, are associated with fetal and uterine circulatory changes in hypertensive pregnancies with or without FGR compared to healthy normotensive pregnancies.

**2. Materials and methods**

A prospective observational study was carried out at the Vilnius University Hospital Santaros Clinics from December 2021 to November 2023 after obtaining permission from the Biomedical Research Ethics Committee of the Vilnius region (approval date: November 24, 2020, No. 2020/11-1282-763). All participants provided informed consent. The participants, involving pregnant women starting from the 20th week of gestation, were categorized into three groups as follows.

- 1) Hypertensive disorders including gestational hypertension, preeclampsia or eclampsia diagnosed during pregnancy;
- 2) Hypertensive disorders and FGR diagnosed during pregnancy;
- 3) Uncomplicated normotensive pregnancy (control group).

Exclusion criteria were age <18 years, significant comorbidities such as renal or cardiovascular diseases, chronic hypertension, multiple pregnancies, and fetal malformations. Preeclampsia was diagnosed if a pregnant woman exhibited systolic blood pressure  $\geq 140$  mmHg and/or diastolic blood pressure  $\geq 90$  mmHg measured twice consecutively at least 4 h apart, along with  $\geq 0.3$  g of protein in a 24-h urine sample. FGR was characterized as an estimated predicted fetal weight below the 10th percentile.

Fetal ultrasound examinations were performed using a General Electric Voluson E8 Expert (GE Healthcare). To ensure that fetal growth was not compromised, all participants underwent fetal biometric assessments, including measurements of biparietal diameter, head and abdominal circumference, and femur length. Doppler ultrasound examinations were performed to assess uterine and fetal umbilical artery blood flow. The mean PI of the uterine artery was measured, with the average of the right and left uterine artery PI calculated. Additionally, the PI of the umbilical artery was measured. As the normal values for umbilical artery PI vary significantly with gestational age, we converted these values into corresponding z-scores based on gestational age. Mean

	FGR	Preeclampsia	Preeclampsia and FGR
Cardiac output	↓	↑ ↑	↓ ↓
Peripheral vascular resistance	↑	↓ ↓	↑ ↑
Heart rate	→	→	→
Augmentation index (AIx)	↑	↑	↑
Pulse wave velocity (PWV)	↑	↑	↑

Fig. 1. Alterations in maternal cardiovascular parameters in hypertensive disorders of pregnancy and/or fetal growth restriction. Adapted from Masini et al. [8].

estimates and standard deviations for this conversion were derived from widely used Doppler scales in clinical practice [13]. Mean uterine artery PI values were analyzed without conversion, as these Doppler indices exhibit minimal changes in the last trimester of pregnancy.

All participants had their blood pressure measured by an automatic device after sitting for 10 min. Mean arterial blood pressure (MAP) was calculated using the formula:  $MAP = \text{diastolic pressure} + (\text{systolic pressure} - \text{diastolic pressure})/3$ .

Cardiac output was calculated for the participants by echocardiography. The patients were scanned through parasternal and apical views. Left ventricular parameters were assessed for all participants, all measurements were calculated by taking the average of three consecutive measurements. Cardiac output (l/min) was calculated from the time integral of blood flow through the aortic valve using a transthoracic Doppler transducer, after manually inserting the patient's height and weight. Maternal peripheral vascular resistance was calculated using the following formula:  $\text{peripheral vascular resistance} = (MAP \times 80)/\text{cardiac output}$ .

Considering the significant changes in the maternal cardiovascular parameters throughout pregnancy, peripheral vascular resistance and cardiac output were likewise converted into corresponding z-scores. These scores were aligned with values observed in studies of uncomplicated normotensive pregnancies across various gestational weeks [14].

Statistical analysis was performed using SPSS software (version 29; SPSS Inc, Chicago, IL). Data were expressed as mean ± standard deviation. The Shapiro–Wilk test was used to test the normality of the data. Kruskal–Wallis test and ANOVA test were used to compare characteristics between the 3 groups. Kruskal–Wallis values were adjusted by Bonferroni's correction for multiple testing. The relationship between maternal hemodynamic performance and uterine and umbilical artery circulation was examined using 2nd degree polynomial regression analysis. A probability value (p-value) <0.05 was considered statistically significant.

### 3. Results

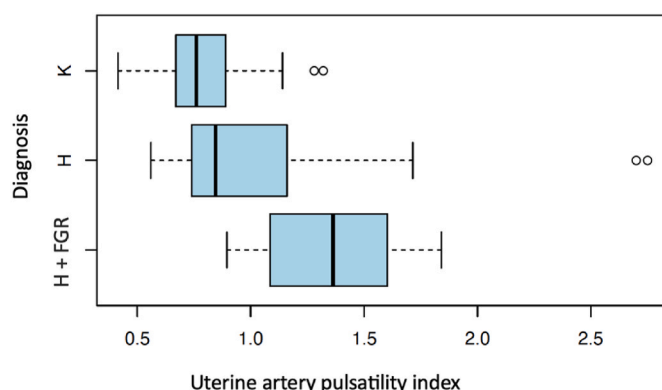
Table 1 shows the characteristics of the study participants. 73 individuals were enrolled in this study, including of 30 pregnant women with hypertensive conditions (gestational hypertension, preeclampsia, or eclampsia), 8 pregnant women with hypertensive conditions and FGR, and 35 healthy normotensive pregnant women with uncomplicated pregnancies (control group). There were no noteworthy distinctions among the groups regarding the participants' ages; however, the mean gestational age showed significant variance among them.

Fig. 2 illustrates the average PI indices of uterine artery across different groups. The mean PI of uterine artery was notably higher in the hypertensive conditions + FGR group (1.36) compared to both the control group (0.76,  $p < 0.001$ ) and the hypertensive conditions group (0.84,  $p = 0.015$ ). Significant differences in medians among the groups were observed (Kruskal–Wallis p-value <0.001).

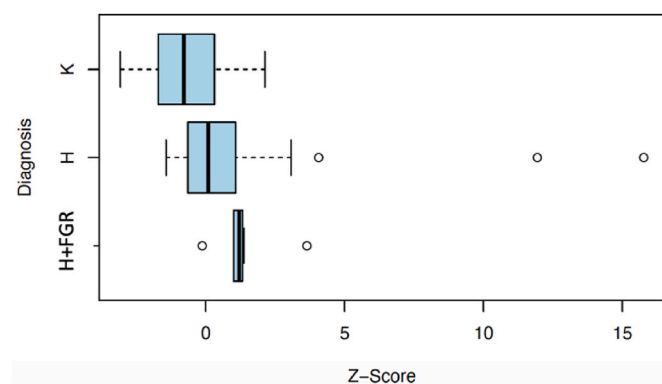
Similar findings were observed after the analysis of umbilical artery PI z-scores across the same groups (Fig. 3). As previously described,

**Table 1**  
Demographic characteristics of study participants.

Characteristics	Hypertensive disorders	Hypertensive disorders and FGR	Control group	P-value
Cases, n	30	8	35	
Mean maternal age, years (SD)	32.47 (0.85)	31.0 (1.98)	29.71 (0.75)	0.069
Mean gestational age at enrollment, weeks (SD)	32.43 (0.70)	31.88 (0.89)	27.57 (0.77)	<0.001



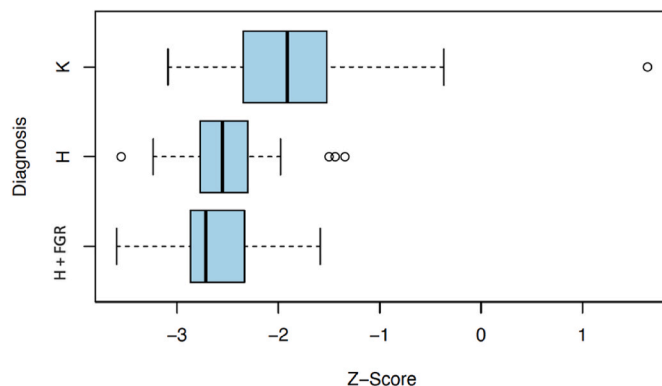
**Fig. 2.** Uterine artery pulsatility indices grouped according to pregnancy outcome. Independent samples Kruskal–Wallis test boxplot. K – control; H – hypertensive disorders; FGR – fetal growth restriction.



**Fig. 3.** Umbilical artery PI z-scores grouped according to pregnancy outcome. Independent samples Kruskal–Wallis test boxplot. K – control; H – hypertensive disorders; FGR – fetal growth restriction.

umbilical artery PI values were transformed into corresponding gestational age z-scores. The umbilical artery PI z-scores were notably higher in the hypertensive conditions + FGR group (1.32) compared to the control group ( $-0.71$ ,  $p < 0.001$ ). However, no statistically significant difference was noted between the group with only hypertensive conditions and the control group ( $1.10$ ,  $p = 0.051$ ). Significant changes in medians among the groups were also observed (Kruskal–Wallis p-value <0.001).

The z-scores, illustrating maternal cardiovascular performance,



**Fig. 4.** Cardiac output z-scores grouped according to pregnancy outcome. Independent samples Kruskal–Wallis test boxplot. K – control; H – hypertensive disorders; FGR – fetal growth restriction.

including cardiac output and peripheral vascular resistance across the groups, are shown in Figs. 4 and 5. Cardiac output z-scores, compared to the control group (-1.79), were significantly lower in both the hypertensive + FGR group (-2.62, p = 0.001) and the hypertensive only group (-2.49, p < 0.001). However, there were no significant differences in cardiac output z-scores between the hypertensive conditions + FGR group and the hypertensive conditions only group (Kruskal-Wallis p-value = 0.457).

Similar findings were observed after analyzing the z-scores of peripheral vascular resistance across same groups. Peripheral vascular resistance was notably higher in both the hypertensive + FGR group (7.43, p < 0.001) and the hypertensive only group (6.06, p < 0.001) in comparison to the control group (2.40). However, there were no significant differences in peripheral vascular resistance z-scores between the hypertensive conditions + FGR group and the hypertensive conditions only group (T-test p-value = 0.105).

The analysis of regression equations describing the relationship between maternal cardiovascular function and uterine and umbilical artery blood flow Doppler indices is summarized in Table 2. During analysis of the correlations of uterine artery PI with maternal cardiac output and peripheral vascular resistance z-scores, statistically significant differences between groups were found (p-value 0.031 and 0.0004, respectively). However, within the same groups, no statistically significant differences were observed analyzing the relationship between umbilical artery PI z-scores and the maternal cardiovascular parameters.

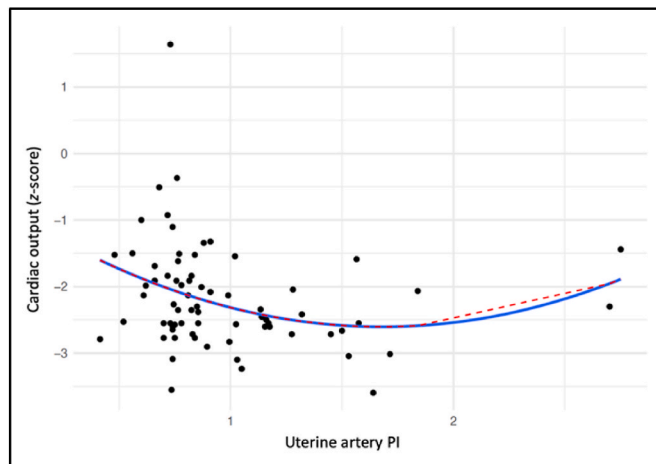
Although the strength of the correlation, as indicated by R<sup>2</sup> (0.067 and 0.172), was weak, it is noteworthy that the regression model itself is significant. Low p-value for the F-statistic suggests the model as a whole is statistically significant. Despite the weak correlation, the establishment of statistically significant differences between uterine artery PI and maternal cardiovascular indices within groups underscores the importance of the regression model (Figs. 6 and 7).

#### 4. Discussion

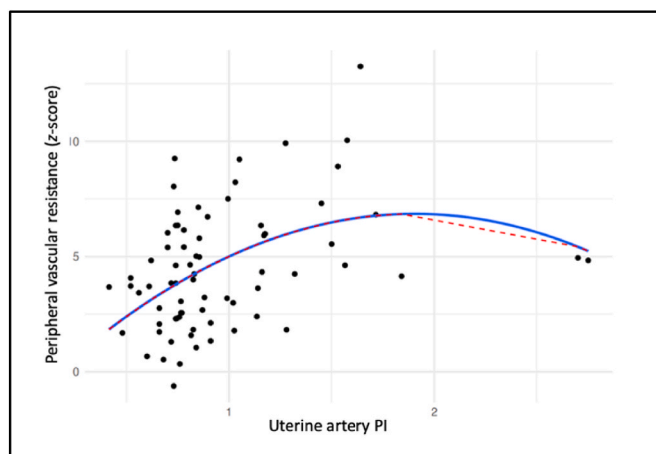
As previously described, in early-onset preeclampsia, there is a correlation with diminished cardiac output and increased peripheral vascular resistance. Consequently, women affected by this condition are susceptible to experiencing cardiovascular dysfunction – mainly a heart failure later in life [10,15]. These results contrast with those reported by Easterling et al., who identified a higher cardiac output in women with preeclampsia compared to healthy women in a longitudinal study [16]. The obvious disagreement in findings has been later explained by considering the gestational age at the onset of preeclampsia. Early-onset preeclampsia (starting before 34 weeks of gestation) is defined by a decreased cardiac output, elevated vascular resistance, and diminished intravascular fluid volume, whereas late-onset preeclampsia is

**Table 2**  
Correlation analysis between uterine and umbilical artery pulsatility index and maternal cardiovascular function.

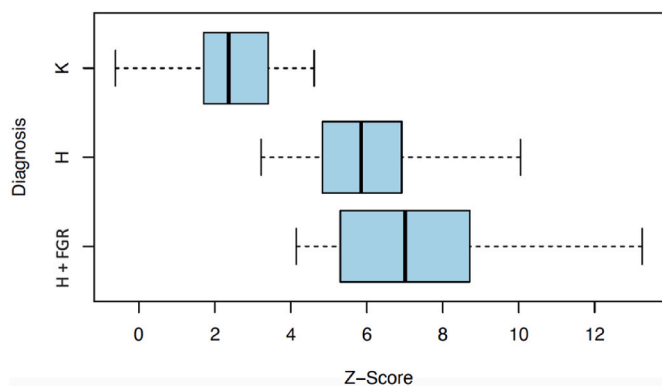
	R <sup>2</sup>	P value	Regression equation
<b>Uterine artery PI</b>			
Cardiac output (z-score)	0.067	0.031	$y = -1,1337x + 1,7047x^2 - 2,17361$
Peripheral vascular resistance (z-score)	0.172	0.0004	$y = 7,7686x - 6,1536x^2 + 4,45802$
<b>Umbilical artery PI (z-score)</b>			
Cardiac output (z-score)	-0.158	0.646	$y = -0,51386x - 0,53844x^2 + 2,17361$
Peripheral vascular resistance (z-score)	-0.015	0.642	$y = 2,50912x + 0,03251x^2 + 4,45802$



**Fig. 6.** Correlation between uterine artery PI and maternal cardiac output. Regression model.



**Fig. 7.** Correlation between uterine artery PI and maternal peripheral vascular resistance. Regression model.



**Fig. 5.** Peripheral vascular resistance z-scores grouped according to pregnancy outcome. Independent samples T test boxplot. K – control; H – hypertensive disorders; FGR – fetal growth restriction.

associated with increased cardiac output, normal or decreased vascular resistance, and intravascular fluid overload. In a more recent study involving women between 24 and 40 weeks of gestation, where all cardiovascular measurements were adjusted for the gestational age at the onset of the condition, it was proposed that the true differentiation lies between preeclampsia accompanied by FGR and preeclampsia with a fetus of normal size [9]. FGR is more commonly associated with early-onset preeclampsia and less frequently observed with late-onset preeclampsia [17]. When FGR is diagnosed, the maternal effects

resemble those seen in instances where preeclampsia coexists with FGR at any gestational age. Hence, it is now suggested that the primary differentiation between the two forms of preeclampsia lies less in whether the onset of the condition is early or late, and more in whether the condition is linked with FGR or not.

The results from our conducted study, consistent with those of other researchers, revealed that pregnant women with hypertensive conditions and FGR shows notably reduced cardiac output and elevated peripheral vascular resistance compared to the normotensive pregnant women. Contrary to our expectations, we did not observe any changes in the cardiovascular performance of women with hypertensive conditions when fetal growth is normal. Specifically, we did not observe an increased cardiac output or decreased peripheral vascular resistance compared to the control group. This disparity could potentially be associated to the inclusion of women not only with preeclampsia but also with gestational hypertension and small size of our study groups.

These findings carry significant implications for our comprehension of the condition and help elucidate the clinical observation, that treatments effective for one woman may not be as effective for another. For instance, strategies such as fluid restriction and administration of the negative chronotrope labetalol, which has the potential to lower cardiac output, are unlikely to ameliorate the clinical state of a woman experiencing intravascular volume depletion and a low cardiac output. Moreover, such approaches may not improve uteroplacental circulation or fetal condition. Nonetheless, these management strategies are typically ingrained in most protocols worldwide for the treatment of preeclampsia [8].

Traditionally, uterine artery Doppler impedance has been used as indicative of placental development, specifically mirroring the process of spiral arteries invasion by trophoblasts. Abnormally elevated uterine arteries PI was typically associated with narrow spiral arteries and inadequate trophoblast invasion [18]. The dopplerometry of uterine artery circulation in pregnant women is a broadly used procedure, often employed to indirectly assess placental vascular function. Appropriate uterine artery Doppler impedance during pregnancy is usually indicative of a healthy placenta, and is related to a reduced risk of pregnancy complications. Conversely, elevated uterine artery Doppler impedance is closely associated with impaired fetal growth and hypertensive disorders during pregnancy and is believed to indicate inadequate uteroplacental perfusion [19]. However, in this cohort, meticulously characterized for hypertensive disorders of pregnancy and FGR and compared with healthy pregnancies, uterine Doppler impedance abnormalities were only observed in cases of FGR. Conversely, uterine Doppler impedance remains normal in women without FGR, even if accompanied by hypertension.

The usage of uterine artery PI for screening purposes has become widespread as a predictor tool of preeclampsia and FGR. Initially, it was employed during the mid-second trimester to evaluate the individualized risk of adverse pregnancy outcomes. More recently it has evolved, as now measurements of uterine artery PI are applied in the first trimester and integrated with maternal medical history, mean arterial pressure, and serum biomarkers. This advancement allowed to initiate preventive therapy with acetylsalicylic acid from the early stages of pregnancy [20,21].

Normally the placentation begins with trophoblast invasion into the endothelium and muscular wall of the spiral arteries. This process in early-stage pregnancy leads to the formation of high-flow, low-resistance vessels capable of effectively perfusing the uterus and ensuring sufficient nutrient supply to the developing fetus. Deficiencies in this vascular invasion have long been regarded as the primary factor contributing to the onset of preeclampsia and fetal growth restriction. This belief is supported by observations that placentas from pregnancies complicated by these conditions often exhibit typical anatomopathological features, including vascular and villous abnormalities, fibrinoid deposition, intervillitis, and thrombotic vasculopathy [18]. Nevertheless, evidence of impaired placental invasion, as documented by

histopathological studies, is not exclusively confined to pregnancies affected by hypertensive disorders or restricted fetal growth. Additionally, it is not uniformly present in all pregnancies with the before mentioned adverse outcomes. The regulation of placental cellular function and development might be influenced by maternal systemic and local uterine cardiovascular perfusion, rather than the other way around [22].

The most significant adaptations of the maternal cardiovascular system during pregnancy occur predominantly in the early stages of the first trimester. Importantly, there is evidence suggesting that these adaptations can be anticipated even before conception. The hypothesis suggesting that maternal systemic and uterine vascular dysfunction precedes placental maldevelopment is backed by a recent prospective study involving 530 women [23]. According to the provided evidence, women who later developed preeclampsia, prior to the conception and trophoblast development exhibited lower cardiac output and higher systemic vascular resistance. Authors of this study concluded that an altered hemodynamic performance prior conception was linked to the subsequent onset of preeclampsia and/or FGR. Meaning that the timing of these changes is crucial, occurring prior to the establishment of a fully functional placental unit. This implies that maternal hemodynamics may play a pivotal role in influencing changes in uterine artery blood flow. This view is supported by research examining the link between maternal cardiovascular function and the changes in uterine circulation in both healthy normotensive pregnancies and those affected by preeclampsia or FGR. A connection was established with uterine Doppler impedance, revealing that an increased maternal uterine artery PI was associated with a lower in maternal cardiac output and higher peripheral vascular resistance regardless of the pregnancy outcome [11]. Our current research results contributes to understanding the association between maternal cardiovascular performance and uterine artery circulation, as we identified a statistically significant positive correlation between maternal peripheral vascular resistance and uterine artery mean PI, as well as a negative correlation with maternal cardiac output.

Fetal circulation, especially during physical activity is highly influenced by maternal cardiac function. Research shows that prolonged chronic exercise (i.e. professional athletes) lowers both fetal heart rate and umbilical artery PI without adverse effects, for example, fetal bradycardia [24]. However, strenuous exercise (exceeding 90 percent of maternal heart rate), can compromise fetal circulation, potentially leading to increased umbilical artery PI, harmful fetal bradycardia, and a half of reduction in uterine artery blood flow [25]. In pregnancies where uteroplacental insufficiency is present, maternal exercise may exacerbate umbilical artery Doppler results, including an elevated PI and temporary absence of end-diastolic flow. Consequently, FGR with abnormal Doppler findings in umbilical artery might warrant caution against aerobic exercise during pregnancy [26,27].

Potential association between maternal cardiac output/peripheral vascular resistance and fetal Doppler changes in umbilical artery have been investigated. Research indicate that lower maternal cardiac output and higher maternal peripheral vascular resistance correlate with elevated impedance in the fetal umbilical artery. This correlation was positive not only in pregnancies affected by preeclampsia and/or FGR but also in normotensive pregnancies with normal fetal growth [11]. Supporting the previously reported findings, it has been found that the absent or reversal of end-diastolic flow in the umbilical artery correlates with decreased maternal cardiac output and increased vascular resistance [12]. Our study design closely echoed of Tay et al., although we did not observe a significant association between fetal umbilical artery Doppler findings and maternal cardiovascular performance.

## 5. Limitations

Although our research presents significant evidence, it has limitations. Contrary to our expectations and findings of other researchers, we did not observe significant changes in the cardiovascular performance of

women with hypertensive conditions when fetal growth is normal, compared to those affected by FGR. This could potentially be explained by the inclusion of women not only with preeclampsia but also with gestational hypertension, as well as the limited small size of our study groups. Additionally, there was significant variance in mean gestational age among the groups.

## 6. Conclusions

Maternal cardiac output shows a significant decrease whereas peripheral vascular resistance increases in hypertensive pregnancies, irrespective of the presence of FGR. Both uterine and umbilical artery PI notably increase when hypertensive pregnancies are accompanied by FGR. A positive correlation exists between maternal peripheral vascular resistance and uterine artery PI, as well as a negative correlation between maternal cardiac output and uterine artery PI. However, changes in maternal cardiovascular parameters do not show significant correlations with umbilical artery PI.

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## Institutional review board statement

Not applicable.

## CRedit authorship contribution statement

**Tatjana Maseliene:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft. **Guoda Zukiene:** Data curation, Writing – original draft. **Anna Laurinaviciene:** Data curation, Project administration. **Dalia Breskuviene:** Formal analysis, Methodology. **Diana Ramasauskaite:** Conceptualization, Writing – review & editing. **Vilma Dzenkeviciute:** Conceptualization, Data curation, Supervision, Writing – review & editing.

## Declaration of competing interest

The authors declare no conflict of interest.

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