OBSTETRICS

Uterine and fetal placental Doppler indices are associated with maternal cardiovascular function

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BACKGROUND: The mechanism underlying fetal-placental Doppler index changes in preeclampsia and/or fetal growth restriction are unknown, although both are associated with maternal cardiovascular dysfunction.

OBJECTIVE: We sought to investigate whether there was a relationship between maternal cardiac output and vascular resistance and fetoplacental Doppler findings in healthy and complicated pregnancy.

STUDY DESIGN: Women with healthy pregnancies (n=62), preeclamptic pregnancies (n=13), preeclamptic pregnancies with fetal growth restriction (n=15), or fetal growth restricted pregnancies (n=17) from 24–40 weeks gestation were included. All of them underwent measurement of cardiac output with the use of an inert gas rebreathing technique and derivation of peripheral vascular resistance. Uterine and fetal Doppler indices were recorded; the latter were z scored to account for gestation. Associations were determined by polynomial regression analyses.

RESULTS: Mean uterine artery pulsatility index was higher in fetal growth restriction (1.37; P=.026) and preeclampsia+fetal growth restriction (1.63; P=.001) but not preeclampsia (0.92; P=1) compared with control subjects (0.8). There was a negative relationship between uterine pulsatility index and cardiac output (r^2=0.101; P=.025) and umbilical pulsatility index z score and cardiac output (r^2=0.078; P=.0015), and there were positive associations between uterine pulsatility index and peripheral vascular resistance (r^2=0.150; P=.003) and umbilical pulsatility index z score and peripheral vascular resistance (r^2= 0.145; P=.001). There was no significant relationship between cardiac output and peripheral vascular resistance with cerebral Doppler indices.

CONCLUSION: Uterine artery Doppler change is abnormally elevated in fetal growth restriction with and without preeclampsia, but not in preeclampsia, which may explain the limited sensitivity of uterine artery Doppler changes for all these complications when considered in aggregate. Furthermore, impedance within fetoplacental arterial vessels is at least, in part, associated with maternal cardiovascular function. This relationship may have important implications for fetal surveillance and would inform therapeutic options in those pathologic pregnancy conditions currently, and perhaps erroneously, attributed purely to placental maldevelopment. Uterine and fetal placental Doppler indices are associated significantly with maternal cardiovascular function. The classic description of uterine and fetal Doppler changes being initiated by placental maldevelopment is a less plausible explanation for the pathogenesis of the conditions than that relating to maternal cardiovascular changes.

Key words: cardiac output, circulation, fetal growth restriction, hypoxia, peripheral vascular resistance, placenta, preeclampsia, pulsatility index

Fetal growth restriction, with or without associated preeclampsia, is classically thought to be due to placental insufficiency[1] and results in progressive fetal hypoxia and acidemia and leading to compensatory changes in the fetal circulation.[2] The interaction between preeclampsia, uteroplacental insufficiency, and fetal growth restriction and circulatory changes is of direct clinical relevance as a major determinant of preeclampsia-related healthcare costs arise from the neonatal costs of premature delivery.[3] Delivery in early onset

EDITORS' CHOICE

disease is often undertaken because of fetal growth restriction,[4] and the increasing severity of fetal growth restriction is associated with worse neonatal morbidity.[5]

The fetal circulatory adaptation to chronic hypoxia that is detected noninvasively with the use of Doppler ultrasound scanning is characterized by increased impedance in the umbilical artery and a reduction in cerebral impedance in the fetus, the so-called "brain sparing" response.[6,7] Increased vascular resistance within the umbilical arteries in compromised pregnancy may result from either structural changes or functional adaption within the umbilical-placental bed. Both abnormal placental villous morphologic condition[8,9] and reduced villous count[10] are associated with fetal growth restriction and abnormal Doppler waveforms in the umbilical artery. Umbilical vasoreactivity also varies with oxygen tension, the pH of circulating blood,[11] and the influence of vasoactive agents.[12,13] For instance, differences in the vasoconstrictor activity on umbilical arteries of noradrenaline,[14] endothelin,[12] thromboxane,[15] and serotonin[16] have been described between control and pregnancies with abnormal umbilical artery flow velocity waveforms. However, the umbilical cord is not innervated by the autonomic nervous system.[17]

Pregnancy that is affected by chronic fetal hypoxia triggers a maintained adaptive redistribution of the fetal cardiac output away from peripheral circulations towards essential vascular beds, such as fetal brain,[18] that leads to the typical asymmetric fetal growth restriction.[19] In addition, the sustained increase in fetal peripheral vascular

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AJOG at a Glance

Why was this study conducted?

The study was undertaken to investigate the association between maternal cardiovascular function and fetal circulatory changes in growth restriction, preeclampsia, and healthy pregnancy.

Key Findings

In pregnancy, maternal uterine and fetal umbilical Doppler impedance is higher; maternal cardiac output is low, and vascular resistance is high.

What does this add to what is known?

Assessment of maternal cardiovascular function may be an important adjunctive modality in the determination of fetal health, with implications for surveillance of at-risk pregnancies and the opening possible therapeutic options.

resistance transfers to increased impedance of blood flow returning to the placenta, which clinically is diagnosed by an increased umbilical artery Doppler pulsatility index (PI) in compromised pregnancy.[6,20]

Abnormalities in the early placental circulation[21] and structure have long been implicated in the pathogenesis of both preeclampsia and fetal growth restriction,[22] and the concept of placental dysfunction has led to strategies to stratify high-risk pregnancies.[23] Though the theory of abnormal placentation is classically thought to explain abnormally high resistance uterine artery flow, little direct evidence supports a causative association. Our group has shown that healthy normotensive women who experience preeclampsia and/or fetal growth restriction have altered prepregnancy hemodynamics compared with those women who have normal outcomes.[24]

Early onset preeclampsia and fetal growth restriction commonly coexist and are associated with abnormal maternal cardiovascular function, which is predominantly low cardiac output and high vascular resistance.[25,26] Our group has refined this observation further to establish that it is fetal growth restriction (with or without coexisting preeclampsia) that is associated with this low cardiac output–high peripheral vascular resistance maternal phenotype, irrespective of gestation.[27] By contrast, preeclamptic pregnancies with appropriately grown fetuses are associated with high maternal cardiac output–low peripheral vascular resistance, in other words the opposite maternal cardiovascular phenotype.[28] This distinction between 2 types of preeclampsia are, we believe, critical to an understanding of the corresponding changes in maternal cardiovascular function: if women with both forms of preeclampsia are considered together, the opposing changes in cardiac output and peripheral vascular resistance of these 2 "clinical phenotypes" are negated by statistical averaging.

In this study, we recruited a carefully phenotyped cohort of pregnant women who were undergoing detailed cardiovascular and Doppler examinations and classified them into 4 categories: preeclampsia, preeclampsia with fetal growth restriction, fetal growth restriction, and healthy pregnancy. Cardiovascular function and Doppler indices change with gestational age; therefore, to allow comparison, we transformed all data in relation to that obtained from women with healthy pregnancies using the statistical technique of *z* scoring.[29] By adjusting parameters for the effect of gestational age changes in this way, we were able to investigate the relationship between maternal cardiovascular function and the classically described fetal cardiovascular changes during complicated pregnancy across the entire third trimester of pregnancy.

Materials and Methods

We performed a prospective study that included a cohort of pregnant women from 24 weeks of gestation who were affected by fetal growth restriction alone (FGR group), by preeclampsia alone (PE group), or by the combination of both (PE+FGR group) and a group of healthy unaffected pregnant women (control group). Recruitment was at a single tertiary level referral hospital in London between January 2015 and June 2017. The study was approved by the National Research Ethics Service Committee London Riverside (REC reference 15/LO/0341), and written consent was obtained. Participants were nonsmokers, were 18–44 years old, had a body mass index <35 kg/m^2, and had no comorbidities such as chronic hypertension, diabetes mellitus, or cardiovascular or renal disease. Exclusion criteria were the presence of fetal malformations and multiple pregnancies. Women who were included were part of the PRECEPT study, whose cardiovascular function has been reported recently.[27]

Preeclampsia was defined as maternal blood pressure at diagnosis of $>140/90$ mm Hg and urine protein creatinine ratio of >30. *Fetal growth restriction* was defined as fetal abdominal circumference or estimated fetal weight <10th percentile[30] and umbilical Doppler PI >95th percentile on ultrasound scan.[31]

Participants with preeclampsia or fetal growth restriction were enrolled either at the time of first manifestation of the disease or at the time of transfer of care to our hospital if they were booked elsewhere. Women who were included in the control group had healthy pregnancies and were enrolled at different gestational ages, when they attended their routine antenatal clinic assessment. Gestational age was determined from measurement of crown-rump length at 11–13+0 weeks of gestation.

Maternal cardiovascular measurements were performed according to a standardized protocol in all participants. Abstinence from caffeine for at least 4 hours before the assessments was required, and participants rested for 10 minutes in the research room before the tests. Cardiac output was obtained in the standing position with an inert gas rebreathing device (Innocor; Innovision A/S, Glamsbjerg, Denmark),[32] which previously was validated against thermodilution for the measurement of cardiac output in nonpregnant populations.[33]

TABLE 1
Maternal characteristics at recruitment

Characteristic	Control subjects	Fetal growth restriction	Preeclampsia	Preeclampsia with fetal growth restriction	Kruskal-Wallis *P* value
Cases, n	62	17	13	15	—
Median gestational age at recruitment, wk (range)	32 (24–40)	32 (24–39)	36 (25–39)	30 (24–36)	.50
Median parity, n (range)	1 (0–3)	0 (0–2)	0 (0–2)	0 (0–3)	—
Median age, y (interquartile range)	34 (31.5–36.5)	35 (31–39)	32 (27.5–36.5)	33 (31–35)	.11
Mean booking body mass index, kg/m^2 (standard deviation)	24.0 (3.2)	25.7 (5.6)	29.1 (4.5)[a]	25.8 (5.4)	.007
Mean birthweight *z* score (standard deviation)	0.61 (1.04)	−2.603 (0.86)	0.78 (1.96)	−2.5 (1.27)	—
Mean uterine artery pulsatility index (standard deviation)	0.8 (0.24)	1.37 (0.51)[b]	0.92 (0.33)	1.63 (0.6)[c]	<.001

[a] *P*=.001 between control subjects and subjects with preeclampsia; [b] *P*=.026 between control subjects and subjects with fetal growth restriction; [c] *P*=.001 between control subjects and subjects with preeclampsia and fetal growth restriction.

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Maternal blood pressure was measured with an automatic device (Omron M-7; OMRON Healthcare Europe BV, Hoofddorp, The Netherlands) that has been validated in pregnancy.[34] Blood pressure was measured on the right arm after 5 minutes of standing. Mean arterial pressure was calculated by following equation: diastolic pressure+(systolic pressure−diastolic pressure)/3. Maternal peripheral vascular resistance (PVR) was derived from mean arterial pressure that was measured standing with the following formula: peripheral vascular resistance=mean arterial pressure×80/cardiac output.[35]

All women underwent serial ultrasound scans with Samsung WS80 (Samsung Medison, Seoul, Republic of Korea) or GE Voluson E8 (GE Healthcare Austria GmbH & Co OG, Zipf, Austria) within 72 hours from the maternal cardiovascular assessment. Fetal biometry and Doppler velocimetry were assessed to determine whether the fetal growth met the criteria for diagnosis of fetal growth restriction. Doppler vascular parameters that were examined were mean PI in the uterine artery (mean of right and left uterine arteries), umbilical artery, and fetal middle cerebral artery when indicated.

To assess the relationship between maternal cardiovascular function and fetal vascular impedance, PI values in the fetal circulation (umbilical artery and middle cerebral artery) were transformed into the corresponding *z* scores for gestational age, with mean and standard deviations obtained from widely used Doppler reference ranges.[31] Uterine artery PI values were examined untransformed because these values change little over the third trimester. Because maternal cardiovascular function also changes with gestational age, cardiac output and peripheral vascular resistance were also transformed into *z* scores by a comparison of the values with a large cohort of measurements that were obtained in healthy pregnancies at different gestational epochs, as our group has described recently.[27]

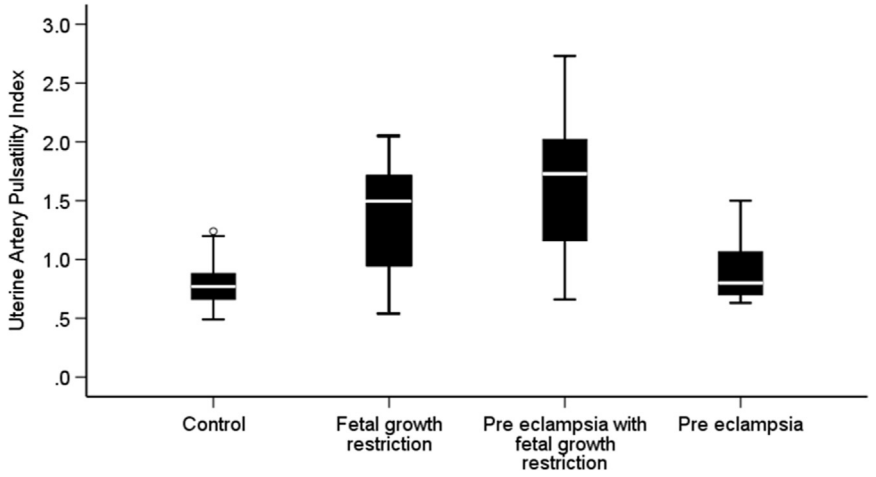
Statistical analyses were performed with SPSS software (version 24; SPSS Inc, Chicago, IL). The Kruskal-Wallis test was used to compare the demographic characteristics and among the 4 groups. The associations between hemodynamic indices and PI were examined with the use of polynomial regression analyses. Quadratic models were chosen after we established that these provided the closest fit to the data, using curve-fitting analyses. Unless otherwise stated, data are expressed as means±standard deviation, and a probability value of <.05 was considered statistically significant.

Results

Subject characteristics are listed in Table 1. Forty-five pregnancies with pathologic outcome (17 FGR group, 13 PE group, and 15 PE+FGR group) and a further 62 women with healthy pregnancies and normal pregnancy outcomes were recruited (control subjects). There were no statistically significant differences in gestational age or median age of the women among groups, although body mass index at booking was significantly higher in women with preeclampsia than in control subjects (29.1±4.5 kg/m^2 vs 24.0±3.52 kg/m^2; *P*=.007). Of the 62 control subjects and 45 cases of pathologic outcome, umbilical artery Doppler indices were available in all; middle cerebral artery Doppler indices were available in 15 control subjects s and 35 pathologic outcome cases, and uterine artery Doppler indices were available in 50 control subjects and 24 pathologic outcome cases.

The relationships between uterine artery PI in the normal and abnormal pregnancy groups are shown in Figure 1. Uterine artery PI was elevated

FIGURE 1
Uterine artery pulsatility index in women, grouped according to pregnancy outcome



The mean uterine artery pulsatility index *z* score was higher in fetal growth restriction (1.37; *P*=.026) and preeclampsia+fetal growth restriction (1.63; *P*=.001) but not preeclampsia (0.92; *P*=1) compared with control subjects (0.8).

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significantly in women in the FGR group or the FGR+PE group, but not the PE group, when compared with women with healthy pregnancies.

Regression equations that describe the relationship between maternal hemodynamic indices and Doppler impedance in the uterine and placental and fetal circulations are presented in Table 2. Uterine artery PI independent of pregnancy health was inversely and nonlinearly associated with maternal cardiac output *z* score (R^2=0.101; *P*=.025; Figure 2, A) but was directly and nonlinearly associated with peripheral vascular resistance *z* score (R^2=0.150; *P*=.003; Figure 2, B). Similar trends were observed with umbilical artery *z* scores, although the strengths of the associations were more modest (cardiac output z score: R^2=0.078; *P*=.015 [Figure 3, A]; peripheral vascular resistance *z* score: R^2=0.145; *P*<.001 [Figure 3, B]). There were no associations identified between maternal hemodynamic indices and middle cerebral artery PI.

Comment

We demonstrate a relationship between maternal cardiovascular function and fetal-placental Doppler indices in a mixed population of healthy pregnancies and those affected by preeclampsia and/or fetal growth restriction. Specifically, low maternal cardiac output and high maternal peripheral vascular resistance are associated with raised impedance in the maternal uterine and fetal umbilical arteries.[36] Interestingly, there was no relationship with fetal cerebral Doppler impedance that indicated that the mechanism is unlikely to be mediated by hypoxia.

Uterine artery Doppler impedance classically is thought to represent placental development through spiral artery invasion,[1] with high impedance reflecting inadequate trophoblast invasion[37] and narrow spiral arteries.[38] Its sensitivity is particularly poor for preeclampsia and fetal growth restriction that occur at term.[39–44] By contrast in this cohort where preeclampsia and fetal growth restriction were carefully phenotyped and compared with healthy pregnancies, uterine Doppler impedance is only abnormal where fetal growth restriction is present (with or without preeclampsia) and is normal in preeclampsia where fetal growth restriction is not present.[45] Our present work adds evidence of the connection between abnormal and normal uterine Doppler velocimetry and maternal cardiac output phenotype; fetal growth restriction with or without preeclampsia and preeclampsia are associated with a low and high cardiac output, respectively.[27] This relationship was possible to unravel only because recruitment was from an entire gestation range and because both maternal cardiovascular and fetoplacental Doppler indices were adjusted to remove gestational age as a confounder. Although preeclampsia with fetal growth restriction is certainly more common at early gestations,[46] it is the condition that defines the cardiovascular phenotype rather than the gestation at onset.

Although a relationship between pregnancies that are affected with both fetal growth restriction and preeclampsia and reduced cardiac output/high vascular resistance has been known for a decade,[47,48] the mechanisms that underly this observation remain unclear. One scenario places the placenta as the primary cause of the hemodynamic changes. On the fetal side, there is a reduction in nutrient and oxygen delivery that leads to growth restriction. The reduced umbilical vein oxygenation leads to fetal hypoxia and triggers redistribution of the fetal cardiac output away from peripheral circulations to maintain perfusion to the fetal brain, which characteristically increases impedance in the umbilical artery and a relative reduction in that of the middle cerebral artery.[6,7,49] On the maternal side, increased placental vascular resistance and measurement of the tertiary villi increases maternal uterine artery impedance, which contributes to an increase in maternal peripheral vascular resistance.[50] This, in turn, leads to an increase in maternal cardiac afterload, which opposes maternal cardiac output and could explain the established relationship among adverse pregnancy outcome, impaired cardiac output, and high vascular resistance.

An alternative scenario that is supported by a recently published preconception study from our group is that a low maternal cardiac output/high vascular resistance state initiates reduced placental perfusion with oxygenated

TABLE 2
Associations between maternal haemodynamic indices and Doppler pulsatility indices

Association	R^2	*P* value	Regression equation
Uterine artery pulsatility index			
Cardiac output z score	0.101	.025	$y=-0.115x+0.044x^2+0.918$
Peripheral vascular resistance *z* score	0.150	.003	$y=0.142x-0.009x^2+0.957$
Umbilical artery pulsatility index			
Cardiac output *z* score	0.078	.015	$y=-0.655x+0.136x^2+1.161$
Peripheral vascular resistance *z* score	0.145	<.001	$y=0.612x+0.045x^2+1.058$
Middle cerebral artery pulsatility index			
Cardiac output *z* score	0.028	.51	$y=0.182x-0.069x^2-0.392$
Peripheral vascular resistance *z* score	0.081	.14	$y=-0.150x-0.028x^2-0.355$

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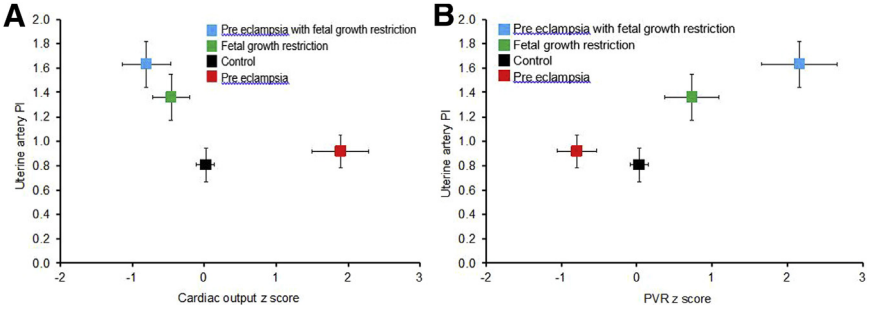
blood and triggers the consequences described earlier on the fetal and maternal side of the placenta.[51] This sequence is compatible with the idea of maternal cardiovascular rather than primary placental dysfunction being the origin of complicated pregnancy. The quality of the maternal cardiovascular function may determine the quality of the placental and fetal circulation, which links maternal cardiac output with changes in the maternal uterine and fetal umbilical circulations. Further evidence for maternal cardiac output changes that drive, rather than respond to the maternal uterine and fetal circulation, is that the effects are dose-dependent. In other words, a lower maternal cardiac output and higher peripheral vascular resistance are associated with both a higher umbilical and uterine artery impedance; both parameters are important descriptors of fetal growth restriction.[52] This is consistent with the observation that incremental change in cardiac output from early pregnancy onwards is associated with birthweight.[53,54]

Interestingly, we report that a reciprocal relationship between maternal cardiac output and impedance in the uterine and umbilical arteries also exists in the whole cohort that includes healthy pregnancy. This suggests that the interplay between maternal cardiac output may be a normal physiologic regulatory mechanism. In the lung, hypoxic pulmonary vasoconstriction, also known as the von Euler–Liljestrand mechanism, is a physiologic response to alveolar hypoxia that ensures the distribution of pulmonary capillary blood flow to alveolar areas of highest oxygen partial pressure. Therefore, perfusion is matched to ventilation in poorly and richly oxygenated parts of the lungs. It could be argued that within the placenta, to ensure efficient maternofetal transfer of flow-limited oxygenation, the equivalent would be to match the level of maternal uterine arterial oxygenation with the magnitude of placental perfusion. Thus, a reduction in oxygen delivery to the placenta via the maternal uterine arteries is matched by an increase in placental vascular resistance. This will slow the passage of blood through the placenta and improve gaseous exchange, which is the reciprocal relationship between maternal cardiac output and placental vascular resistance that represents a von Euler–Liljestrand mechanism within the placenta. Because maternal arterial blood pressure is determined by the product of cardiac output and peripheral vascular resistance, a fall in maternal cardiac output is buffered by an increase in maternal peripheral vascular resistance to maintain maternal arterial blood pressure. Thus, it is plausible that a direct relationship between increased maternal peripheral vascular resistance and increased placental vascular resistance represents an analogous physiologic mechanism. Low maternal cardiac output equates to lower uterine blood flow and hence reduced oxygen availability to the feto-placental unit, and the oxygen content in blood is not reduced per se. This is important when one considers that human and animal data suggest that

FIGURE 2
Uterine artery pulsatility index vs *z* scores for cardiac output and peripheral vasculare resistance according to pregnancy outcome



Uterine artery pulsatility index vs **A,** cardiac output *z* score and **B,** peripheral vascular resistance *z* score in women whose data were grouped according to pregnancy outcome. There is a negative relationship between uterine pulsatility index and cardiac output (r^2=0.101; *P*=.025) and positive association between uterine pulsatility index and peripheral vascular resistance (r^2=0.150; *P*=.003).

PI, pulsatility index; *PVR*, peripheral vascular resistance; *SEM*, standard error of the mean.

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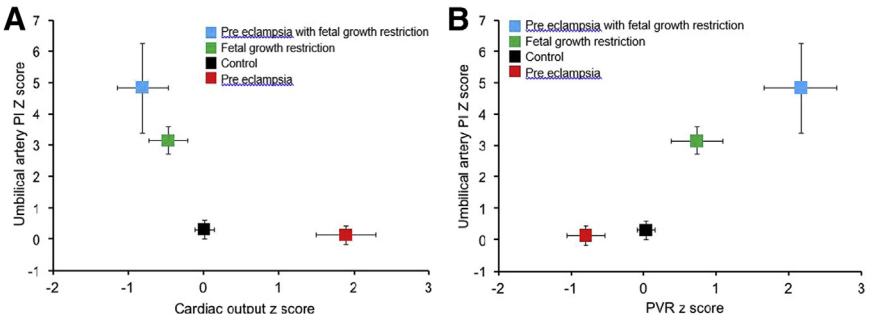
FIGURE 3
Umbilical artery pulsatility index vs *z* scores for cardiac output and peripheral vascular resistance according to pregnancy outcome



Umbilical artery pulsatility index *z* score vs **A,** cardiac output *z* score and **B,** peripheral vascular resistance z score in women whose data were grouped according to pregnancy outcome. There is a negative relationship between umbilical pulsatility index and cardiac output (r^2=0.078; *P*=.015) and positive associations between umbilical pulsatility index and peripheral vascular resistance (r^2= 0.145; *P*=.001).

PI, pulsatility index; *PVR*, peripheral vascular resistance; *SEM*, standard error of the mean.

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intrauterine growth restricted fetuses show lower oxygen extraction.[55] This acute localized adaptation should be distinguished from chronic generalized hypoxia, which leads to pulmonary hypertension.

There are limitations to our interpretation of these findings. The correlations, although highly significant, are of moderate strength and suggest that contributions other than maternal cardiovascular function are important in the modulation of fetoplacental impedance. It may be that the relationships hold particularly in the case of pathologic pregnancy that is associated with fetal growth restriction and preeclampsia; these cases are, by their nature, rare. Some Doppler values were missing; this was not a systematic bias but rather reflected the challenge of obtaining a full set of maternal and fetal cardiovascular observations in an acute setting.

These findings have relevance in the surveillance of compromised pregnancies. If cardiac output does, in part, determine fetal circulatory changes, then this raises a question about what might happen in the late third trimester when cardiac output reduces from its peak value.[56] In normally grown fetuses that are stillborn, uterine and umbilical artery Doppler impedance have been shown to be higher than those fetuses who are live born.[57] Might this reduction in maternal cardiac output imperil the uteroplacental circulation and be a mechanism for unexplained stillbirth?

These findings also have potential therapeutic relevance. In later pregnancy, treatment with negatively inotropic drugs (such as beta blockers) have been associated with fetal growth restriction and stillbirth,[58] perhaps through a direct effect on the uteroplacental and fetoplacental circulations. Vasodilator drugs do not have a primary negatively inotropic mode of action and are effective in the treatment of acute hypertension in pregnancy;[59] plasma volume expansion combined with vasodilator therapy in women with high vascular resistance and fetal growth restriction is reported to increase fetal growth.[60] This raises the possibility of intervention to optimize maternal cardiovascular function before or in established preeclampsia and/or fetal growth restriction.

The uterine artery Doppler relationship with pathologic pregnancy has, from the first studies of 3 decades ago, been troubled by an apparent contradiction: its usefulness in screening "early onset" preeclampsia and fetal growth restriction, but not for late onset complications.[61] The explanation appears to be linked closely to the cardiovascular characteristics that are associated with the specific subtype of fetal growth restriction and/or preeclampsia. We suggest that the differential performance of uterine artery Doppler impedance arises because it is most frequently abnormal in fetal growth restriction and fetal growth restriction that is associated with preeclampsia; these conditions coexist particularly frequently at <34 weeks of gestation. Our data support that uterine artery Doppler impedance is no different from that of healthy pregnancy in "pure" preeclampsia and is unaffected by fetal growth restriction, which is more common at later gestation.

In conclusion, uterine and fetal placental Doppler indices are associated significantly with maternal cardiovascular function. Although we cannot ascribe causality, emerging evidence supports that cardiovascular dysfunction precedes fetal growth restriction and preeclampsia, possibly even from before pregnancy rather than their resulting from the conditions. The classic description of uterine and fetal Doppler changes being initiated by placental maldevelopment is a less plausible explanation for the pathogenesis of the conditions than that relating to maternal cardiovascular changes.

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