Correlation between central and uterine haemodynamics in hypertensive disorders of pregnancy

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ABSTRACT

Introduction: Pregnancies affected by hypertensive disorders (HDP) have increased uterine artery pulsatility index (UTA PI) compared to healthy pregnancies. De novo increases in UTA PI in the third trimester have been reported, making these changes less attributable to inadequate spiral artery invasion, which is typically recognised as an early pregnancy phenomenon. Women with HDP are also known to have lower cardiac output and increased systemic vascular resistance. The aim of this study was to investigate the relationship between central and uterine haemodynamics, in both HDP and uncomplicated pregnancies.

Methods: This was a prospective study in control pregnancies and those with HDP. Paired measurements of maternal haemodynamics, using a non-invasive device (USCOM-1A®), and uterine artery Doppler were performed in the third trimester.

Results: There were 231 women in the HDP group and 378 women in the control group. Women with preterm HDP had significantly lower cardiac output (median (IQR) 6.0 (5.1-7.2) vs. 6.6 (5.8-7.5) L/min, p=0.002) and higher systemic vascular resistance (median (IQR) 1394 (1189-1670) vs. 1063 (915-1222) dynes-sec-cm^5, p<0.001) and UTA PI (median (IQR) 1.0 (0.75-1.4) vs. 0.67 (0.58-0.83) p<0.001) compared to controls. Conversely, in women with term HDP, there were no significant differences in heart rate, cardiac output or UTA compared to controls (all P>0.05), while systemic vascular resistance was significantly higher (median (IQR) 1315 (1099-1527) vs 1063 (915-1222) dynes-sec-cm^5, p<0.001). In multiple regression analysis, heart rate, mean arterial pressure and stroke volume were significantly associated with the mean UTA PI (all p<0.001).

Conclusion: Differences observed in the uterine artery resistance in the third trimester of pregnancy are mirrored in the central maternal haemodynamic parameters. Late pregnancy

differences in the utero-placental circulation in preterm and term HDP are an index of maternal cardiovascular function rather than being related to inadequate spiral artery modelling and impaired placentation.

INTRODUCTION

In normal pregnancies, uterine artery pulsatility index (UTA PI) decreases with advancing gestation.[1,2] In hypertensive disorders of pregnancy (HDP), UTA PI is higher than in normal pregnancy from as early as the first trimester, and this difference persists throughout pregnancy although the PI still decreases with advancing gestation.[1,3–5] This difference is most apparent in early-onset HDP associated with fetal growth restriction.[1,3–5] High early pregnancy UTA PI has been attributed to impaired trophoblast invasion and poor spiral artery remodelling in pregnancies prone to HDP.[6–9] The subsequent fall in UTA PI with advancing gestation is thought to result from decreasing impedance to the uterine blood flow, as trophoblast invasion is eventually completed.[6,10,11] However, we, and others, have demonstrated that there is a de-novo increase in third trimester UTA PI in pregnancies that are at increased risk of HDP.[1,12,13] Furthermore, de novo increases of UTA PI in the third trimester are also associated with fetal growth restriction, stillbirth and adverse clinical outcomes even in the absence of HDP.[4,14–16] This late, third trimester increase in resistance cannot simply be explained by limited trophoblast invasion, which is irreversible and should be complete by this gestation.

An alternative explanation is that the changes seen in the uterine artery resistance are reflecting changes in the maternal systemic circulation, and that the maternal cardiovascular system is responsible for both the observed de-novo increase in UTA PI and the development of HDP in late pregnancy. Echocardiography studies have demonstrated structural and functional cardiac differences including diastolic and systolic dysfunction, left ventricular hypertrophy and impaired myocardial relaxation in those pregnancies

complicated by both term and preterm preeclampsia (PE), whilst studies of arterial stiffness have shown higher augmentation index in pregnancies complicated by PE, suggesting an underlying role of maternal cardiovascular function in HDP.[3,17–20] The aim of this study was to investigate the relationship between third trimester central and uterine haemodynamics, in both HDP and uncomplicated pregnancies.

METHODS

Study population and recruitment

This was a prospective study in HDP and normotensive control pregnancies presenting to a tertiary referral hospital between January 2012 and December 2017. The inclusion criteria were singleton pregnancies with a viable fetus at 28 weeks' gestation or greater with new-onset hypertension. The exclusion criteria were women with multiple pregnancies, a history of chronic hypertension or cardiac disease and pregnancies complicated by aneuploidy, genetic syndromes or major structural fetal abnormalities. HDP was defined as de novo hypertension (systolic BP $\geq$140mmHg and/or diastolic BP $\geq$90mmHg) after 20 weeks of gestation. For the purposes of this study, we analysed proteinuric and non-proteinuric HDP together. The control group had no pre-existing cardiac or metabolic disease. Those control pregnancies that subsequently developed HDP or resulted in the birth of a small for gestational age neonate were excluded from the analysis. Patients in the control group were recruited whilst attending an antenatal visit or a third trimester ultrasound assessment (placental localisation, presentation, measuring small or large for dates). Written consent

was obtained from all study participants and research ethics committee approval (12/LO/0810) was obtained prior to performing the study investigations.

Research Investigations

All haemodynamic assessments were performed in the same room, under standardized conditions for the entire cohort. Maternal height, weight and brachial blood pressure were obtained prior to hemodynamic assessment. Blood pressure was obtained using an upper arm automatic blood pressure (BP) monitor (Microlife, Microlife AG Swiss Corporation, Switzerland), in a semi-recumbent position and using an appropriate sized cuff. Mean arterial pressure (MAP) was calculated as (2xdiastolic blood pressure + systolic blood pressure)/3. USCOM-1A® is a non-invasive cardiac output device that has been validated against echocardiography in pregnancy.[21] It utilizes continuous wave Doppler, with a non-imaging probe in the suprasternal notch to obtain velocity time integrals (VTI) of transaortic blood flow at the left ventricular outflow tract. Using an anthropometric algorithm, which correlates the outflow tract diameter with the patient's given height, USCOM-1A® uses the VTIs to compute stroke volume (SV) and produce a complete hemodynamic profile, including heart rate (HR), cardiac output (CO) and systemic vascular resistance (SVR). Each Doppler acquisition used for analysis had a minimum of 2 consecutive Doppler profiles (cardiac cycles). Acquisitions with the least amount of interference and the best quality VTIs, deemed by the study investigators to best represent transaortic blood flow, were obtained in the device's flowtracer mode. CO, SV and SVR were converted into MoM to adjust for maternal characteristics and gestational age in weeks.[22] UTA PI was recorded by experienced practitioners using a standardised technique; the left and right uterine arteries were identified at the level of the cross-over of the external iliac artery using colour Doppler.

Pulsed wave Doppler was used to measure PI over 3 consecutive waveforms. The mean of the left and right UTA PI was calculated and subsequently converted into multiples of the median (MoM) to adjust for gestational age in weeks. [2]

Outcome of pregnancy

Data on the maternal characteristics and pregnancy outcomes were collected from the hospital obstetric and neonatal records. The study outcomes included the pregnancy outcome, gestational age at delivery and birthweight. Fetal growth restriction (FGR) was defined as birthweight <3rd centile for gestation and maternal obesity as a body mass index >30kg/m^2. Term was defined as ≥37 weeks' and preterm <37 weeks' gestation.

Statistical Analysis

Data distribution was assessed using the Shapiro-Wilk test as well as graphical methods. Categorical data were presented as number and percentage, while continuous data were presented as the median and interquartile range (IQR). Statistical analysis was performed using the Chi-squared test and Mann-Whitney test. Spearman's rank Coefficient was used to assess the correlation between the central and uteroplacental haemodynamics. Regression analysis was performed to assess the association of UTA PI MoM with independent variables (height, weight, HR, MAP, SV and maternal age). The independent variables were entered all together. All assumptions were met and 'raw' components such as MAP, HR, SV, weight and height were chosen as independent variables as supposed to BMI, CO and SVR to avoid multi-collinearity. A p value <0.05 was considered statistically significant. Statistical software (SPSS 25.0; SPSS Inc., Chicago, IL) was used to conduct the analysis.

RESULTS

There were 231 women with HDP (152 preterm and 79 with term) and 378 women with uncomplicated pregnancies included in the study. The demographic and pregnancy characteristics of the three groups are shown in Table 1. There were differences between

the three groups in maternal weight, which was significantly higher in the preterm and term HDP compared to the controls (both p<0.001) but not compared to each other (p= 0.420). Birthweight centiles were also significantly lower in the preterm HDP group compared to controls (median 12.0 vs 39.5, p<0.001) whilst there was no difference between the term HDP and control group birthweight centile (median 43.1 vs 39.5, p=0.701).

Haemodynamic indices in all three groups are shown in Table 2. Women with preterm HDP had significantly lower CO (median 6.0 vs. 6.6L/min, p=0.002) and significantly higher SVR (median 1394 vs. 1063 dynes-sec-cm^5, p<0.001) and UTA PI (median 1.0 vs. 0.67, p<0.001) compared to controls. Conversely, in women with term HDP there was no significant difference in CO (median 6.6 vs. 6.6L/min, p=0.685) or UTA PI (median 0.70 vs. 0.67, p<0.770) compared to controls, while SVR was significantly higher (median 1315 vs. 1063 dynes-sec-cm^5, p<0.001). The observed differences in the maternal haemodynamics persisted after conversion to MoMs correcting for maternal characteristics and gestational age (Table 2). When analysis was performed on the HDP group defined by the presence or absence of FGR, it demonstrated significantly higher UTA PI in the FGR group (median 0.79 vs. 1.4, p<0.001), but no significant difference in CO or SVR compared to HDP patients without FGR (Supplementary table 1). When analysis was performed on the HDP group defined by the presence or absence of maternal obesity, it demonstrated no significant differences in CO, SVR or UTA PI compared to non-obese HDP women (Supplementary table 2).

In the HDP group as a whole, there was a positive correlation between UTA PI MoM and SVR MoM (Fig 1: r_s= 0.22, p=0.001) and a negative correlation between UTA PI MoM and

CO MoM (Fig 2: r_s= -0.20, p=0.002). Subgroup analysis showed that these correlations remained significant for the preterm HDP group (UTA PI MoM and SVR MoM: r_s= 0.18, p=0.029, UTA PI MoM and CO MoM: r_s= -0.19, p=0.023) but not for term HDP (UTA PI MoM and SVR MoM: r_s= 0.01, p=0.937, UTA PI MoM and CO MoM: r_s= -0.12, p=0.916). Multiple regression analysis demonstrated that maternal height (cm), weight (kg), MAP (mmHg), HR (beats/min) and SV MoM significantly contributed to the prediction of UTA PI with HR making the largest unique contribution: (Table 3; *F* (6,585)=15.732, p<0.001, R^2=0.139, adjusted R^2=0.130).

DISCUSSION

Summary of study findings

Our study demonstrates that the differences observed in uterine artery resistance in the third trimester of pregnancy are mirrored in central maternal haemodynamic parameters; the higher the UTA PI, the higher the SVR and the lower the CO. In preterm HDP, UTA PI and SVR were significantly higher and CO was significantly lower than in controls. Pregnancies affected by HDP at term (≥37weeks) had a similar haemodynamic profile to controls with the exception of having higher SVR. Maternal HR made the greatest significant prediction of UTA PI in multiple regression analysis, suggesting a relationship of UTA PI with maternal cardiovascular function.

Interpretation of study findings and comparison with the existing literature

The association between abnormal uterine artery Doppler indices in the first and second trimester of pregnancy and subsequent development of HDP is well established [4,23], as is the evidence for altered maternal haemodynamics in HDP at presentation and prior to clinical disease onset[3,17,19,20,24]. However, few studies have looked at both parameters simultaneously in the third trimester. Ferrazi *et al*. found reduced HR and CO and increased SVR and mean UTA PI in a hypertensive cohort compared to control pregnancies, but it is unclear when the Doppler measurements were taken in temporal relation to the haemodynamic measurements and no attempt was made to account for the maternal characteristics or gestational age.[25] Similarly, Valensise *et al.* observed differences in the haemodynamic profile and uterine artery PI at mid-gestation (24 weeks) in women who

subsequently developed early or late HDP several weeks later. Their finding of a worse haemodynamic profile (lower CO and higher SVR and UTA PI) in those with early-onset HDP compared to late-onset HDP and controls is in agreement with our findings.[26] Finally, in a longitudinal study of healthy pregnancies, Flo *et al.* measured systemic maternal haemodynamics and uterine vascular resistance and uterine diameter. Although they did not include pathological pregnancies to compare differences in the haemodynamic profile, they showed a clear correlation between the systemic and uterine circulations throughout pregnancy.[27]

Our findings support the notion that UTA PI changes in late pregnancy correlate with maternal systemic haemodynamic parameters. This finding suggests that UTA PI is a consequence of underlying maternal cardiovascular functional differences rather than secondary to impaired trophoblast invasion. The fact that these differences can be observed in the third trimester of pregnancy, after completion of the spiral artery invasion, supports this theory. The previous finding of a de-novo increase in UTA PI in the third trimester in HDP is also better explained by differences in the maternal cardiovascular function than spiral artery invasion.[12] Similar haemodynamic indices in term HDP to healthy pregnancies do not necessarily indicate that two different pathologies are responsible for preterm and term HDP. In apparently healthy pregnancies, CO and SV peak in the early third trimester before falling towards term, with converse changes in SVR.[28,29] These changes are paradoxical when considering the increasing metabolic and haemodynamic demands of advancing pregnancy. Echocardiography studies have shown an excessive increase in the left ventricular mass and remodelling with associated diastolic dysfunction in a significant proportion of women at term - all of which revert to normal postpartum.[30,31] An alternative

interpretation to the finding that CO is the same in term HDP and controls may reflect the inability of apparently 'normal' pregnancies to increase CO further in response to physiological demand – rather than a lack of cardiovascular impairment in pregnancies with term HDP.

If the hypothesis that UTA PI is a reflection of the maternal cardiovascular function were true, we would expect similar differences in other maternal vessels. Studies of the ophthalmic artery Doppler have demonstrated clear differences between hypertensive and control pregnancies at the clinical stage of the disease[32] and in early pregnancy. At 11-14 weeks gestation, the ophthalmic artery Doppler performs as well as the uterine artery Doppler for the prediction of preeclampsia.[33,34] These findings demonstrate that the maternal vascular changes observed in HDP are not limited to the utero-placental vascular bed. Whilst historical studies have demonstrated abnormal trophoblast invasion in pregnancies with HDP[6,8,9], it is not clear that these changes cause HDP. It might be equally plausible that placental lesions occur secondary to maternal hypoperfusion of the utero-placental interface.[35,36] Further work is required to fully understand this relationship.

Study limitations and strengths

The strengths of this study include its prospective nature and the paired measurements of hemodynamic parameters and uterine artery Doppler assessment in a large population of complicated and normal pregnancies. Furthermore, indices that vary physiologically with gestation or maternal characteristics were corrected for by calculating MoM based on device-specific reference ranges. One limitation of our study is that it is cross-sectional in

nature and therefore we cannot draw conclusions about longitudinal changes in maternal haemodynamics or UTA PI in relation to the clinical course of HDP in this study population.

Clinical and research implications

Our findings have implications for future research as well as clinical assessment and management of women at risk of or presenting with HDP. A recently validated first trimester screening model for HDP including both UTA PI and MAP in addition to maternal factors and biomarkers had a detection rate of 100% for early-onset preeclampsia (<32 weeks), 75% for preterm preeclampsia and 43% for term preeclampsia - demonstrating the importance of MAP and UTA PI as markers of maternal cardiovascular function.[37] Looking at the value of maternal haemodynamic assessment in the third trimester to predict late HDP, Guy *et al.* found lower CO and HR and higher SVR in women who subsequently developed HDP.[38] These findings fit with our hypothesis of worsening haemodynamics in more severe, early-onset HDP. The role of measuring systemic and uterine haemodynamics for prognostic purposes will be an important area of future research.

Conclusion

Differences observed in uterine artery resistance in the third trimester of pregnancy are mirrored in central maternal haemodynamic parameters. Late pregnancy differences in the utero-placental circulation are an index of maternal cardiovascular function rather than being related to inadequate spiral artery modelling and impaired placentation.

Conflict of Interests

The authors report no conflicts of interest.

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Table 1: Demographic details and birthweights of pregnancies with hypertensive disorders (HDP) and control (normotensive) pregnancies. . Preterm HDP was defined as onset <37 weeks gestation and term HDP as onset ≥37 weeks gestation.

	Control (n= 378)	Preterm HDP (n=152)	Term HDP (n=79)	p-value (control vs preterm HDP)	p-value (control vs term HDP)	p-value (preterm vs term HDP)
Maternal age (years)	32 (28 to 35)	32 (28.0 to 36)	32 (29 to 36)	0.568	0.212	0.538
Gestation at assessment (weeks)	36.0 (33.5 to 36.8)	34.7 (32.3 to 36.0)	38.1 (37.6 to 39.0)	**<0.001**	**<0.001**	**<0.001**
Maternal weight (kg)	76.0 (68.0-85.2)	84.5 (72.4-94.8)	84.5 (75.0-98.0)	**<0.001**	**<0.001**	0.420
Maternal height (cm)	165 (159-169)	163 (158-167)	166 (160-169)	0.053	0.298	**0.024**
Body mass index (kg/ m^2)	28.3 (25.3-31.6)	31.2 (28.2-35.3)	31.8 (28.0-35.6)	**<0.001**	**<0.001**	0.917
Smoking in pregnancy	22 (5.8)	4 (2.6)	4 (5.1)	0.246	0.866	0.491
Nulliparous	191 (50.5)	81 (53.3)	53 (67.1)	0.565	**0.007**	**0.044**
Ethnicity						
Caucasian	232 (61.4)	76 (50.0)	59 (74.7)	**0.016**	**0.025**	**<0.001**
Afro Caribbean	46 (12.2)	32 (21.1)	12 (15.2)	**0.009**	0.463	0.282
Asian	80 (21.2)	40 (26.3)	7 (8.9)	0.200	**0.011**	**0.002**
Mixed/other	20 (5.3)	4 (2.6)	1 (1.3)	0.183	0.120	0.499
Antihypertensive medication in pregnancy	0 (0.0)	54 (35.5)	24 (30.4)	**0.016**	**<0.001**	0.433
Birthweight centile	39.5 (20.2-70.2)	12.0 (2.9-32.8)	43.1 (18.2-73.0)	**0.009**	0.701	**<0.001**
Birthweight z-score	-0.27 (-0.83--0.53)	-1.17 (-1.89- -0.45)	-0.17 (-0.91-0.61)	0.200	0.701	**<0.001**
Gestation age birth (weeks)	40.0 (39.0-41.0)	37.0 (35.0-38.6)	39.4 (38.6-40.3)	0.183	0.002	**<0.001**

All results are displayed as Median (IQR) or Number (%).

Table 2. Maternal central and utero-placental haemodynamic assessment in the group with preterm and term hypertensive disorders of pregnancy (HDP) and control (normotensive) pregnancies. Preterm HDP was defined as onset <37 weeks gestation and term HDP as onset ≥37 weeks gestation.

	Control (n= 378)	Preterm HDP (n=152)	Term HDP (n=79)	p-value (control vs preterm HDP)	p-value (control vs term HDP)	p-value (preterm vs term HDP)
MAP (mmHg)	88 (82 to 93)	107 (98 to 113)	107 (102 to 114)	**<0.001**	**<0.001**	0.397
Heart Rate (bpm)	86 (77 to 95)	79 (72 to 89)	84 (73 to 92)	**<0.001**	0.142	0.108
CO (L/min)	6.6 (5.8 to 7.5)	6.0 (5.1 to 7.2)	6.6 (5.7 to 7.3)	**<0.001**	0.685	**0.025**
SV (ml)	77.4 (66.7 to 89.1)	77.3 (65.9 to 89.0)	80.8 (64.0 to 94.4)	0.598	0.417	0.282
SVR (dynes-sec-cm^5)	1063 (915 to 1222)	1394(1189 to 1670)	1315 (1099 to 1527)	**<0.001**	**<0.001**	**0.046**
UTA PI	0.67 (0.58 to 0.83)	1.0 (0.75 to 1.4)	0.70 (0.57 to 0.81)	**<0.001**	0.770	**<0.001**
CO (MoM)	1.0 (0.88 to 1.12)	0.90 (0.77 to 1.0)	1.0 (0.90 to 1.1)	**<0.001**	0.256	**<0.001**
SV (MoM)	0.99 (0.87 to 1.12)	0.98 (0.86 to 1.1)	1.0 (0.88 to 1.2)	0.818	0.076	0.101
SVR (MoM)	1.0 (0.88 to 1.2)	1.4 (1.1 to 1.6)	1.1 (0.99 to 1.4)	**<0.001**	**<0.001**	**<0.001**
UTA PI (MoM)	0.96 (0.83 to 1.2)	1.4 (1.1 to 2.0)	1.0 (0.85 to 1.2)	**<0.001**	0.336	**<0.001**
Birthweight centile	39.5 (20.2 to 70.2)	12.0 (2.9 to 32.8)	43.1 (18.2 to 73.0)	**<0.001**	0.701	**<0.001**
Birthweight z-score	-0.27 (-0.83 to -.53)	-1.2 (-1.9 to -0.4)	-0.2 (-0.9 to 0.61)	**<0.001**	0.701	**<0.001**

All results are displayed as Median (IQR) or Number (%). MAP= mean arterial pressure, CO= cardiac output, SV= stroke volume, SVR= systemic vascular resistance, UTA PI= uterine artery pulsatility index, MoM= multiples of the median.

Table 3. Summary of multiple regression for the prediction of uterine artery mean pulsatility index

Variable	**Unstandardized regression coefficient**	**Standard Error of the coefficient**	**Standardised coefficient**	**P value**
Intercept	3.317	0.547		
Age (years)	-0.004	0.003	-0.055	0.162
Height (cm)	-0.012	0.003	-0.185	<0.001
Weight (kg)	0.005	0.001	0.172	<0.001
MAP(mmHg)	0.007	0.001	0.191	<0.001
Heart Rate (bpm)	-0.009	.001	-0.271	<0.001
Stroke volume MoM	-0.237	0.100	-0.101	<0.001

MAP= mean arterial pressure

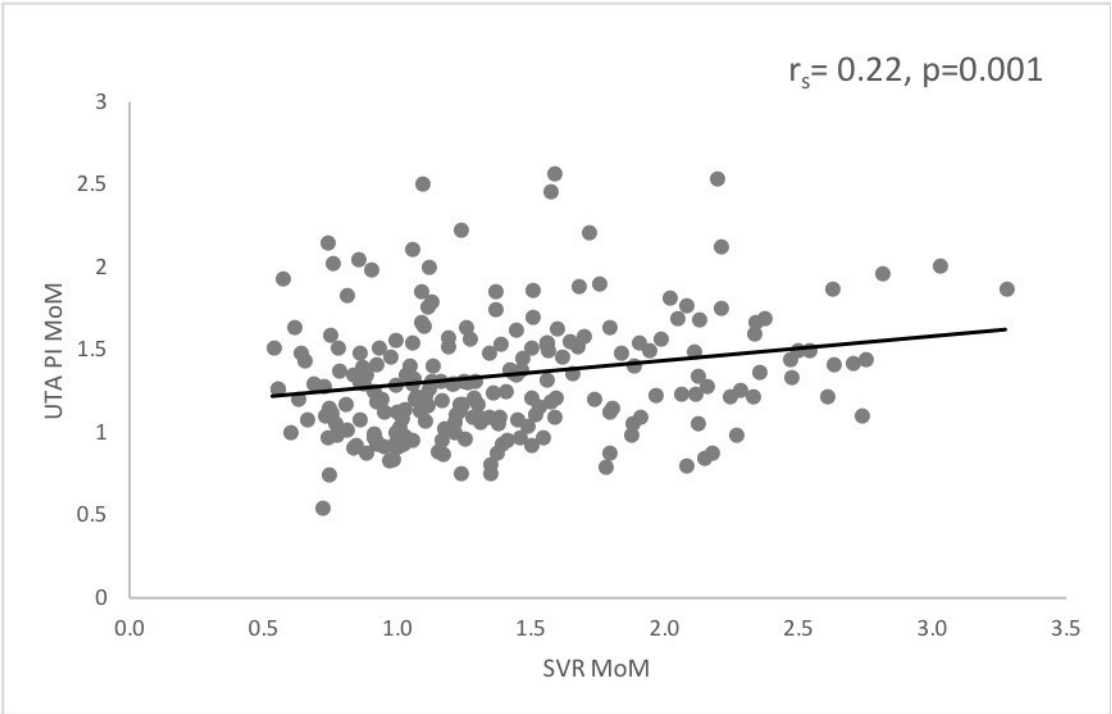
Figure Title and Legends:

Figure 1: Correlation between UTA PI MoM and SVR MoM

UTA PI= Uterine artery pulsatility index, SVR = systemic vascular resistance, MoM= multiples of the median.

Figure 2: Correlation between UTA PI MoM and CO MoM

UTA PI= Uterine artery pulsatility index, CO= cardiac output, MoM= multiples of the median.



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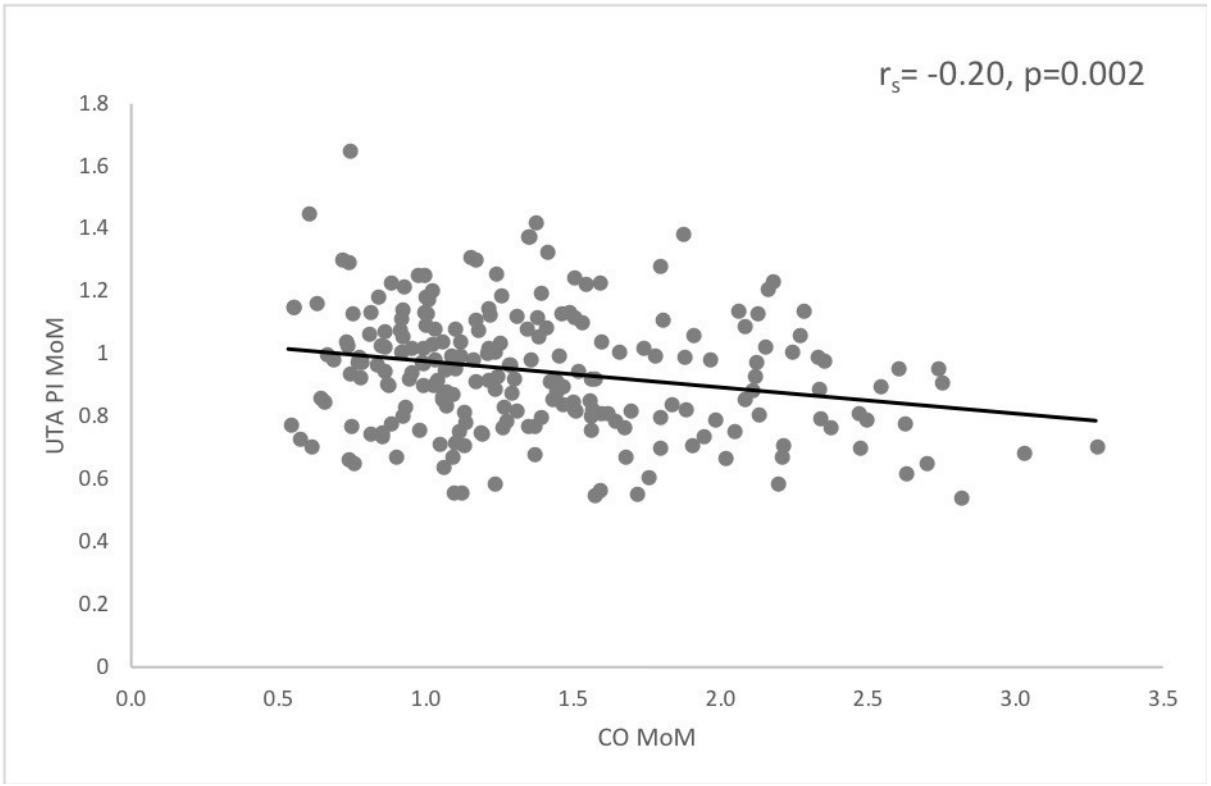

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