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Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction

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Abstract—Preeclampsia and fetal growth restriction during pregnancy are associated with increased risk of maternal cardiovascular disease later in life. It is unclear whether this association is causal or driven by similar antecedent risk factors. Clarification requires recruitment before conception which is methodologically difficult with high attrition rates and loss of outcome numbers to nonconception/miscarriage. Few prospective studies have, therefore, been adequately powered to address these questions. We recruited 530 healthy women (mean age: 35.0 years) intending to conceive and assessed cardiac output, cardiac index, stroke volume, total peripheral resistance, mean arterial pressure, and heart rate before pregnancy. Participants were followed to completion of subsequent pregnancy with repeat longitudinal assessments. Of 356 spontaneously conceived pregnancies, 15 (4.2%) were affected by preeclampsia and fetal growth restriction. Women who subsequently developed preeclampsia/fetal growth restriction had lower preconception cardiac output (4.9 versus 5.8 L/min; P=0.002) and cardiac index (2.9 versus 3.3 L/min per meter^2; P=0.031) while mean arterial pressure (87.1 versus 82.3 mm Hg; P=0.05) and total peripheral resistance (1396.4 versus 1156.1 dynes sec cm^{-5}; P<0.001) were higher. Longitudinal trajectories for cardiac output and total peripheral resistance were similar between affected and healthy pregnancies, but the former group showed a more exaggerated fall in mean arterial pressure in the first trimester, followed by a steeper rise and a steeper fall to postpartum values. Significant relationships were observed between cardiac output, total peripheral resistance, and mean arterial pressure and gestational epoch. We conclude that in healthy women, an altered prepregnancy hemodynamic phenotype is associated with the subsequent development of preeclampsia/fetal growth restriction. **(*Hypertension*. 2018;72:442-450. DOI: 10.1161/HYPERTENSIONAHA.118.11092.)** ● **Online Data Supplement**

Key Words: fetal growth restriction ■ heart rate ■ hemodynamics ■ preeclampsia ■ pregnancy

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Preeclampsia and fetal growth restriction (FGR) affect 3% to 5% of all pregnancies. Both are significant contributors of maternal and perinatal morbidity and mortality.[1,2] Preeclampsia is characterized by de novo hypertension in pregnancy and maternal organ dysfunction in the form of renal, hepatic, clotting, or neurological abnormalities and FGR.[3] FGR describes a fetus that fails to achieve its genetic growth potential, usually diagnosed by a statistical deviation of fetal size from population-based standard in combination with functional changes in fetal and placental circulation.[4,5]

Although the pathogenic mechanisms of preeclampsia and FGR remain unclear, underlying causes are thought to overlap because of both conditions commonly occurring together. The most popular hypothesis is that of defective placental invasion in early pregnancy,[6–9] and for this reason, both disorders are commonly ascribed within the umbrella term: maternal placental syndromes.[10] This concept has largely arisen as the placenta has to be present for both disorders to develop and resolves with delivery of the placenta.[11] Furthermore, placentas from affected pregnancies are reported to have characteristic histological abnormalities (incomplete invasion of maternal spiral arteries, acute atherosis, villous ischemia, and hypovascularity).[12] However, the placental origins hypothesis has some inconsistencies.[11,13] One third of placentas from pregnancies affected by preeclampsia at term, and ≈26% of placentas from FGR pregnancies have normal histological appearances.[14–16] Preeclampsia can also present de novo in the postnatal period after the placenta has been delivered.[17]

Recent epidemiological observations suggest that maternal cardiovascular function may play an important role in these disorders. Women affected by preeclampsia/FGR have

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persistent postpartum abnormal cardiovascular function in the form of asymptomatic echo-diagnosed heart failure,[18,19] increased risk of developing hypertensive disease after pregnancy, and a long-term increased risk of developing or dying from cardiovascular disease later in life.[20,21] It is still unclear whether preeclampsia/FGR initiate damage to the mother's cardiovascular system which then lead to a higher risk of later-life cardiovascular disease or whether preeclampsia/FGR and cardiovascular disorders share common antecedent risk factors.[22]

The role of prepregnancy maternal cardiovascular function has not been comprehensively investigated primarily because of the logistical difficulty of recruiting a healthy preconception cohort of women, many of whom will be naive to medical services. Previous studies of cardiovascular function before pregnancy used retrospective data linkage from epidemiological and birth registries[22] or took postnatal assessments as surrogate prepregnancy measures.[23,24]

Therefore, to determine whether women who develop preeclampsia and FGR show hemodynamic differences before pregnancy, we prospectively assessed cardiovascular hemodynamics in healthy women from before pregnancy and followed subsequent pregnancy outcomes.

Materials and Methods

Analytic methods, materials, and data that support the findings of this study are available from the corresponding author on reasonable request.

We conducted a prospective cohort study of healthy women intending to conceive. As prospective preconception studies are methodologically complex, we conducted and published a pilot study (2010–2012, Cambridge) to assess the feasibility of recruitment, retention, and obtaining sufficient pregnancy outcomes after accounting for conception and spontaneous pregnancy loss rate.[25] After successful completion of the feasibility phase, the main study (2014–2017, London) was undertaken, which, for the assessments that we report, had an identical protocol to the feasibility study. Both studies received local site research authority approval and ethical approval from National Research Ethics Committees (reference numbers: 10/H0304/28 and 14/ES/1046).

All participants had an initial study visit to undergo initial cardiovascular hemodynamic assessments (detailed below in study protocol). Participants were then given 12 months to conceive a pregnancy. Those who conceived within study timeline had further follow-up through pregnancy: 2 visits in the first trimester (6 and 10 weeks gestation), once in the second trimester (22 weeks gestation), once in the third trimester (34 weeks gestation), and at 6 to 10 weeks postpartum. Participant study timeline is illustrated in Figure 1. At each visit, hemodynamic assessments were repeated, thus providing longitudinal assessments for individual participants. At the end of pregnancy, participants were analyzed based on whether the pregnancy was affected by preeclampsia and FGR or unaffected pregnancy. All diagnoses and management of preeclampsia/FGR were made by the participant's healthcare provider without involvement of the research team.

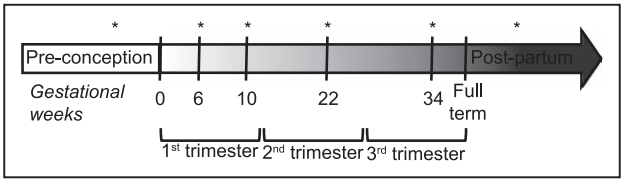


Figure 1. Timeline of study participant visits. *Study visit.

Recruitment and Study Entry Criteria

Healthy women planning a pregnancy were recruited via local and social media platforms and poster distributions to local general practice surgeries, community centers, hospitals, and universities in the London area. Those between the ages of 18 and 44 years who planned to conceive within 12 months of study entry were eligible. Women with a body mass index >35, current smokers, with preexisting conditions of essential hypertension (defined as systolic >130 mm Hg and diastolic >90 mm Hg), renal disease, diabetes mellitus, thrombophilia, polycystic ovarian syndrome, and irregular menstrual cycles (>42 days cycle length) were excluded. Those pursuing conception using artificial reproductive technology (ovarian reserve stimulation, in-vitro fertilization) were also excluded.

Sample Size

Suboptimal physiological cardiac output (CO) increments (to the degree of 0.7 L/min) in the first trimester have been reported in association with recurrence of preeclampsia/FGR in a subsequent pregnancy,[23,24,26] therefore preconception CO was selected as primary measure. Taking a conservative approach of detecting a smaller difference in CO of 0.5 L/min, at 80% power with 2-tailed α of 0.05, 196 unaffected pregnancies and 12 pregnancies affected by preeclampsia/FGR were required to power the study.

Based on conception and pregnancy loss data from the feasibility study, we predicted that at least 60% of women would conceive within 12 months.[25] We planned to recruit 500 women, predicted to result in ≈300 pregnancies, with a rolling recruitment target taking into account real-time pregnancy rates. Accounting for 25% proportional loss from miscarriage or chromosomal anomalies, and lost to study follow-up of ≈10%, 196 participants were projected to have viable pregnancies. Based on the incidence of preeclampsia and FGR (3% each), ≈12 pregnancies would be affected by preeclampsia/FGR.

Study Protocol

At the first study visit (preconception), participants were requested to refrain from caffeinated drinks at least 4 hours before their assessments. Baseline demographics and medical history including obstetric history were taken, and participant height and weight measured. All assessments were performed in a quiet temperature controlled room by 2 trained investigators. Participants were given a digital fertility monitor (Advanced Fertility Monitor, SPD Development Company Ltd) to track their menstrual cycles for 12 months, which allowed more accurate gestation specific study follow-up to be arranged based on dates of ovulation and first positive pregnancy testing (taken to relate to day of embryonic implantation[27]).

Cardiovascular function assessments were initiated after 10 minutes of rest in the left lateral supine position. Brachial blood pressure (BP) and heart rate were measured in the right arm using an automated sphygmomanometer (Omron-M7) which has been validated for use in pregnancy using standard cuff size according to the arm circumference of the woman.[28] All measurements were performed in duplicate.

Mean arterial pressure (MAP) was derived from the average of the 2 readings of systolic and diastolic pressures using the formula:

$$\text{MAP} = 1/3(\text{systolic pressure}) + 2/3\ (\text{diastolic pressure})$$

CO and stroke volume (SV) were assessed using a noninvasive, inert gas rebreathing technique, Innocor (Innovision A/S, Denmark) which has been validated against invasive assessments of cardiac function[29] and utilized in previous obstetric cohort research. Innocor applies pulmonary gas exchange as a means of measuring the pulmonary blood flow using a mixture. The subject continuously rebreathes a gas mixture: 1% sulfur hexafluoride, 5% nitrous oxide, and 94% oxygen for 20 seconds, with a breathing rate of 20/min. Expired gases are sampled continuously and analyzed by an infrared photoacoustic gas analyzer for the determination of CO and SV. The rate of dissipation of nitrous oxide is proportional to the pulmonary

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blood flow. A pulse oximeter simultaneously determines the heart rate from which SV (ie, the volume of blood ejected per heartbeat) is computed by the Innocor machine. Cardiac index was derived as CO divided by the participant's body surface area (which is derived from height and weight).

Total Peripheral Vascular Resistance (TPR)

TPR was derived from the formula:

$$\text{TPR}\ \left(\text{dynes}\cdot\text{sec}\cdot\text{cm}^{-5}\right) = \text{MAP}\ \left(\text{mm Hg}\right)\ \times\ 80/\text{CO}\ \left(\text{L/min}\right)$$

Clinical Outcomes

Clinical pregnancy outcomes including fetal scan reports conducted by maternity care providers were obtained from participant's electronic maternity records. If these were not available, informations from their discharge letters were obtained from general practitioner surgeries. The predefined clinical outcomes of interest was preeclampsia and FGR.

Preeclampsia was defined using information prospectively ascertained from participant's medical records, as per the consensus statement from the International Society of Study of Hypertension in Pregnancy[3]:

> *New-onset hypertension (systolic BP >140 mmHg and/or diastolic BP >90 mmHg) with one or more of the following: proteinuria, liver or renal function abnormalities, neurological abnormalities, clotting disorders and/or placental insufficiency manifesting as FGR.*

FGR was defined as per Delphi consensus statement[30]:

> *If FGR was diagnosed <32 weeks gestational age: Fetal abdominal circumference (AC) or ultrasound estimated fetal weight (EFW) <3rd centile, or absent umbilical artery (UA) end diastolic flow (EDF) or AC/EFW <10th centile combined with uterine artery (UtA) pulsatility index (PI) >95th centile and/or UA PI >95th centile.*
> *If FGR was diagnosed >32 weeks gestational age: AC/EFW <3rd centile or at least two out of three of the following: AC/EFW <10th centile, AC/EFW crossing centiles >2 growth quartiles, cerebro-placental ratio <5th centile or UA PI >95th centile.*

Birth Weight Correlations

Aside from clinical outcomes as described above, we also related preconception cardiovascular assessments to birth weight of subsequent pregnancy, which were obtained from participant's health records. The birth weights were adjusted for gestational age to a *z* score using a program based on a population-based standards, using a fetal weight equation proposed by Hadlock et al[31] with the customization proposed by Gardosi et al,[32] and SD derived from the 2004 to 2008 World Health Organization Global Survey on Maternal and Perinatal Health. Technical details of the *z* score calculator are described in the Appendix of Mikolajczyk et al.[33]

Statistical Analyses

Prepregnancy Group Comparisons

The distribution of each cardiovascular parameter was examined using the Shapiro-Wilk test. Prepregnancy cardiac measures were compared in women who subsequently developed preeclampsia/FGR and those who did not using a *t* test or a Mann-Whitney *U* test as appropriate. Continuous variables as reported as mean±SD (normal distribution) or median+interquartile range (non-normal distribution). All crude values were then adjusted using multivariable regression for maternal age, prepregnancy body mass index, and parity.

Birth Weight Correlations

Multivariable linear regression analysis was done to assess the relationship between prepregnancy cardiovascular parameters and birth weight *z* score using Stata14 (StataCorp, TX). These models were adjusted for potential confounders of maternal age, prepregnancy body mass index, parity, and gestational age at delivery (for birth weight *z* score).

Longitudinal Analyses

Longitudinal trajectories of each cardiovascular parameter from prepregnancy to postpartum were analyzed using a multilevel linear spline model as describe in Tilling et al.[34] In brief, to analyze the average pattern of change, each study visit was converted into a knot point, connected by linear splines. Knot points that did not show a marked difference in mean value from the preceding time point were excluded. Multilevel modeling was fitted to all available measures, and trajectory change per week was compared between the groups using a regression model.

Further, maximal information coefficient (MIC) as described in Reshef et al[35] was used to capture a large range of associations (functional or not) across the data set of all assessment and participant variables. Functional relationships were found between cardiovascular parameters and gestational age, and therefore an MIC score that roughly equals to the coefficient of determination (R^2) of the data relative to the regression function was assigned. This allowed us to determine nonlinear relationships between gestational status (ie, study visits at preconception, 6 weeks, 10 weeks, 22 weeks, 34 weeks, and postpartum) and change in cardiovascular parameters. Statistical significance of the MIC value was further assessed through permutation testing.

Results

Preconception Demographics of Healthy Women Wishing to Conceive

A total of 530 women were recruited into a pilot and a follow-on main study (see Methods for details), and cumulative recruitment flow chart is as shown in Figure 2. Mean participant age was 35.0 years (SD, 4.7), and mean time from assessment to conception was 3.1 months. After withdrawals and exclusions, there were 494 women from which 356 pregnancies were conceived, a study conception rate of 71.2%. After excluding pregnancies affected by first trimester complications, multiple pregnancies, and a stillbirth (confirmed aneuploidy), 218 singleton pregnancies were available for analyses. Of these, 15 pregnancies (6.8%) were affected by preeclampsia/FGR, consisting of 3 cases of preeclampsia, 8 cases of FGR, and 4 cases of preeclampsia occurring concurrently with FGR. Further characteristics of the study population by divided by subsequent pregnancy outcome are shown in Table 1, and details of pregnancies affected by preeclampsia/FGR are reported in Table S1 in the online-only Data Supplement. Maternal age, parity, body mass index, and ethnicity did not differ between affected and unaffected pregnancies, but women with a pregnancy complicated by preeclampsia/FGR had a shorter gestational length and smaller babies.

Association of Preconception Cardiovascular Function and Subsequent Pregnancy Outcome

Preconception CO and cardiac index (CO adjusted for body surface area) were lower in women affected by preeclampsia/FGR compared with women with an uncomplicated pregnancy, after adjusting for maternal characteristics (Table 2). The mean adjusted difference in our primary outcome measure, preconception CO was 0.8 L/min (95% confidence interval, −0.40 to −1.14). SV was also lower in women who subsequently developed preeclampsia/FGR.

Conversely, TPR was higher in women who developed preeclampsia/FGR, with a difference of 240.3 dynes·sec·cm^{-5}

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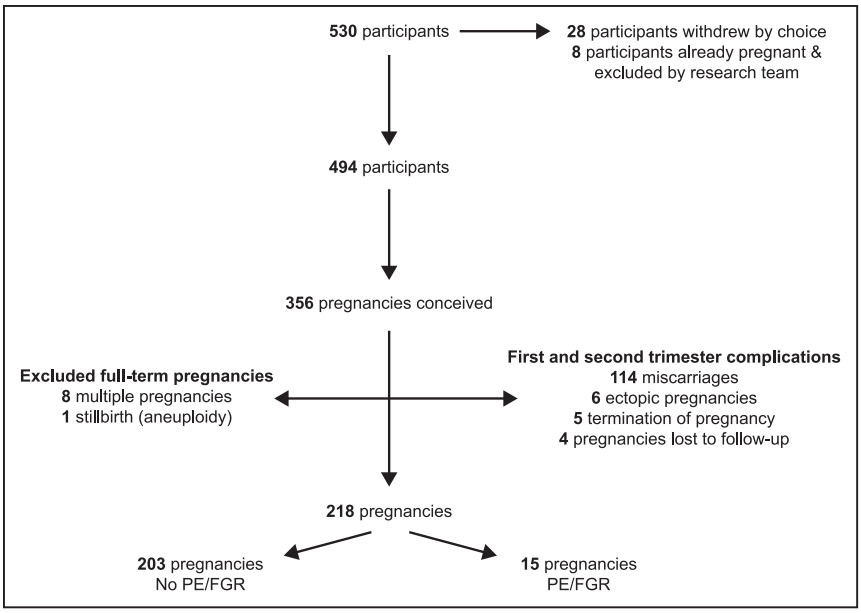


Figure 2. Study flow chart. FGR indicates fetal growth restriction; and PE, preeclampsia.

(95% confidence interval, −353.8 to −125.8). Components of peripheral BP measurements: systolic BP and MAP were different between the groups but not for diastolic BP. We performed a subanalysis for nulliparous women (women who had not had a previous live or stillbirth n=123) to ascertain if the differences found in the group as a whole were still evident in women whose cardiovascular system was not previously subjected to the effects of a pregnancy. Differences remained in CO (5.73±1.1; 5.12±0.64 L/min; P=0.017), cardiac index (3.35±0.66, 3.05±0.387; P=0.048), and TPR (median=1140.74 versus 1359.47; P=0.019) but not in peripheral BP and heart rate measurements.

Association of Preconception Cardiovascular Function and Birth Weight

We investigated the relationship between preconception cardiovascular parameters and birth weight, the latter being adjusted for gestation at delivery to derive a birth weight z score (Table S2). Associations were measured with R^2 to determine approximation of the data to a fitted regression line.

For the primary outcome measure, prepregnancy CO showed a positive association (R^2=0.07; P=0.022) with mean birth weight z score at term. A 1.0 L/min difference in CO was associated with a 0.164 increase in birth weight z score (95% confidence interval, 0.02–0.31), which translated to 53 g at term after adjustments for sex at delivery.

There were also small negative associations between MAP (R^2=0.05), systolic BP (R^2=0.05), heart rate (R^2=0.04), and TPR (R^2=0.07) while SV showed a positive corelation (R^2=0.06) with birth weight.

Longitudinal Trajectories of Cardiovascular Parameters Between Those That Had a Subsequent Normal Pregnancy and Those That Developed Preeclampsia/FGR

Participants who conceived a pregnancy within study timeline returned for follow-up visits during (6, 22, and 34 weeks gestation) and after pregnancy (6–10 weeks postpartum). Longitudinal changes in cardiovascular parameters from preconception until postpartum were recorded. We compared individualized trajectories between the groups based on subsequent pregnancy outcome and report here the main cardiovascular parameters of interests: CO, TPR, and MAP.

The trajectories for CO and TPR were no different between gestational time points (Table 3).

Trajectories of MAP from preconception to postpartum between both groups were significantly different between

Table 1. Baseline Maternal Characteristics and Birth Outcomes

Variable	Non-PE/FGR Pregnancies	PE/FGR Pregnancies	P Value
n	203 (93%)	15 (7%)	…
Maternal age, y	32.8 (3.9)	32.7 (4.1)	0.912
Maternal BMI, kg/m^2	24.4 (5.9)	26.0 (3.5)	0.328
Nulliparity (%)	113 (55.7)	10 (66.7)	0.337
Ethnicity (n)			
White	156	10	
Asian	22	5	
Black Caribbean	13	0	
Mixed	12	0	
Birth weight	3472.2 (454)	2341.53 (512.6)	<0.001
Birth weight z score*	0.3 (−0.3 to 0.9)	−1.7 (−2.1 to −0.9)	<0.001
Gestation at delivery*(days by USS EDD)	279 (273 to 286)	268 (264 to 279)	<0.001

BMI indicates body mass index; FGR, fetal growth restriction; PE, preeclampsia; and USS EDD, estimated due date determined by ultrasound scan.

*Non-normally distributed data. Normally distributed data presented as mean (SD), and non-normally distributed data presented as median (interquartile range).

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Table 2. Preconception Cardiovascular Parameters (Raw Data and Data Adjusted for Maternal BMI, Age, and Parity) Between Those That Subsequently Had a Pregnancy Affected by PE/FGR and Those That Had Unaffected Pregnancies

	Non-PE/FGR Pregnancy n=203		PE/FGR Pregnancy n=15		*P* Value	
Preconception Parameter	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
CO, L/min	5.8 (1.03)	5.8 (1.0)	5.0 (0.63)	4.9 (0.9)	<0.001	0.002
CI, L/min per meter^2	3.3 (0.6)	3.3 (0.6)	3.1 (0.42)	2.9 (0.6)	0.07	0.031
HR, bpm	67.3 (10.2)	67.3 (10.3)	66.4 (11.6)	66.2 (10.4)	0.781	0.685
SV, mL	82.2 (14.7)	82.2 (14.5)	74.4 (11.8)	73.9 (14.6)	0.027	0.047
TPR,* dynes·sec·cm^{-5}	1152.5 (1026.5–1292.8)	1156.1 (776.2–1819.7)	1392.6 (1283.0–1526.2)	1396.4 (891.3–1737.8)	<0.001	<0.001
Systolic BP, mm Hg	113.6 (10.4)	113.6 (10.5)	116.7 (13.5)	119.2 (10.5)	0.31	0.05
Diastolic BP, mm Hg	66.1 (7.6)	66.2 (7.3)	69.7 (8.5)	67.0 (7.3)	0.86	0.158
MAP, mm Hg	82.3 (7.5)	82.3 (7.3)	86.4 (8.5)	87.1 (7.3)	0.19	0.04

BMI indicates body mass index; BP, blood pressure; CI, cardiac index; CO, cardiac output; FGR, fetal growth restriction; HR, heart rate; PE, preeclampsia; SV, stroke volume; and TPR, total peripheral resistance.

*Non-normally distributed data. Normally distributed data presented as mean (SD), and non-normally distributed data presented as median (interquartile range).

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preconception to 6 weeks (controls: −0.5 U change/wk; preeclampsia/FGR: −1.1 U change/wk; *P*=0.03), 6 to 22 weeks (controls: −0.2 U change/wk; preeclampsia/FGR: +0.2 U change/wk; *P*=0.001), as well as 34 weeks to postpartum (controls: +0.1 U change/wk; preeclampsia/FGR: −0.8 U change/wk; *P*<0.001).

Nonlinear relationship of the change in CO, TPR, and MAP with gestation was assessed using MIC. Permutation testing of MIC demonstrated statistically significant relationships between CO and TPR and gestational epochs from before pregnancy to the postpartum period in both outcome groups (Table S3). Change in MAP was only significantly related to gestation in those with normal pregnancy outcome. MIC scores across all 3 parameters was higher in those who developed preeclampsia/FGR (Figure 3).

Discussion

We report that before pregnancy, women who are subsequently affected by preeclampsia and FGR have different hemodynamic function compared with those with subsequent normal pregnancy outcome. Although none of the participants were classified as hypertensive nor had features of overt cardiovascular disease before pregnancy, those that developed preeclampsia and FGR had a lower prepregnancy CO, higher resistance circulation, and higher BP.

It has been previously reported that higher prepregnancy BP (systolic of 130 mm Hg) is associated with a higher risk of developing preeclampsia.[22] These observations were from a large study that linked BP measurements in a public health program to registered birth outcomes. Of note, the mean interval between BP measurements and pregnancy was 3.5 to 4 years, therefore events in the intervening period such as development of essential hypertension, weight gain, or the use of artificial reproductive technologies for conception were unaccounted for. To contrast, the mean interval between prepregnancy assessments and pregnancy in our study was markedly shorter at 3 months and 3 days, and factors such as maternal anthropometrics and demographics just before index pregnancy were adjusted for in results.

We also demonstrate that the longitudinal trajectory of BP between our groups continued to differ significantly from preconception through the trimesters of pregnancy and up to the postpartum period. There is known to be a physiological fall in BP in the first trimester of pregnancy. In women who subsequently develop preeclampsia/FGR, this drop in the first trimester is significantly more pronounced compared with controls, perhaps as a compensatory mechanism given the higher prepregnancy BP starting point for the affected group. This observation, despite being on a modest number of women who developed preeclampsia/FGR, has potential clinical implications. Women commonly have their baseline pregnancy measurement of BP in the latter half of the first trimester; as this BP might be unexpectedly low in women at risk of preeclampsia/FGR, their pregnancy could be paradoxically categorized as low risk. Beyond the first trimester, there was a significant increase in BP per week from the late first trimester into the second trimester in women who subsequently develop preeclampsia/FGR. These women also experienced a more pronounced drop in BP from the third trimester to the postpartum period, which despite a late compensatory effect, does not reach the same levels as controls, resulting in a higher postpartum BP in women who developed preeclampsia/FGR. These findings suggest that targeted BP management or monitoring for affected women could be initiated in the late first trimester/early second trimester when incremental changes in BP are most marked.

Our findings of a relatively hypodynamic circulation with a lower CO and higher TPR in women who develop preeclampsia/FGR lend credence to reports of hemodynamic dysfunction observed in the subclinical and clinical stage of preeclampsia and FGR.[36–38] We find that these differences exist before pregnancy, preceding any sequalae of placental dysfunction, or perturbations exerted by preeclampsia/FGR on the maternal cardiovascular system. This raises the possibility of identifying a hemodynamic signature before pregnancy, in those women at risk of preeclampsia and FGR. A characteristic profile, integrated with more traditional cardiovascular risk factors such as body mass index, might identify

Table 3. Longitudinal Trajectories (Unit Change per Week) for CO (L/min per Week), TPR (Dynes·sec·cm^{-5}/wk), and MAP (mm Hg/wk)

	Non-PE/FGR Pregnancies	Pregnancies Affected by PE/FGR	95% CI	*P* Value
Changes in supine CO L/min				
Mean at time zero (prepregnancy)	5.77	4.95	…	…
Mean change per week from preconception to 6 wk	+0.13	+0.03	−1.3 to 0.1	0.87
Mean change per week from 6 to 22 wk	+0.01	+0.03	−0.02 to −0.6	0.41
Mean change per week from 22 to 34 wk	−0.39	−0.37	−0.05 to −0.8	0.70
Mean change per week from 34 to postnatal	−0.02	−0.09	−0.16 to 0.02	0.15
Changes in supine TPR, dynes·sec·cm^{-5}				
Mean at time zero (prepregnancy)	1152.5	1392.6	…	…
Mean change per week from preconception to 6 wk	−27.4	−42.8	−36.3 to 5.29	0.14
Mean change per week from 6 to 22 wk	−5.2	−4.3	−7.2 to 8.0	0.83
Mean change per week from 22 to 34 wk	+9.3	+10.6	−10.2 to 12.8	0.83
Mean change per week from 34 to postnatal	+6.7	+9.5	−14.4 to 20.0	0.75
Changes in supine MAP, mm Hg				
Mean at time zero (prepregnancy)	82.3	87.1	…	…
Mean change per week from preconception to 6 wk (inclusive)	−0.5	−1.1	−1.2 to −0.1	0.03
Mean change per week from 6 to 22 wk (inclusive)	−0.2	+0.2	0.2 to 0.6	0.001
Mean change per week from 22 to 34 wk (inclusive)	+0.3	+0.4	−0.2 to 0.4	0.55
Mean change per week from 34 to postnatal (inclusive)	+0.12	−0.8	−1.4 to 0.5	<0.001

CI indicates confidence interval; CO, cardiac output; FGR, fetal growth restriction; MAP, mean arterial pressure; PE, preeclampsia; and TPR, total peripheral resistance.

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women at risk of adverse outcome. Such models have been proposed after first trimester uterine artery Doppler and cardiovascular assessment.[39] The differences in CO and TPR in affected women also may inform targeted treatment in the form of manipulation of hemodynamic status. Women with preexisting hypertension, or those who subsequently develop preeclampsia, are commonly prescribed β-blocking agents as first line treatment[40]: these agents are negatively inotropic and may worsen an underlying low CO phenotype. Furthermore, the American Heart Association recognizes preeclampsia as a risk factor for future coronary heart disease and recommends lifestyle interventions after an affected pregnancy,[41] and our findings support the rationale of exploring the initiation of these interventions before pregnancy.

We also find that prepregnancy CO is positively associated with birth weight at term. It is tempting to speculate that increasing CO could be beneficial in FGR pregnancies, a condition for which there is currently no treatment. Plasma volume expanders and vasodilators have been shown to improve maternal CO and decreased TPR in pregnancies already affected by FGR and prolong gestation[42] while prescribed aerobic therapy has been shown to increase venous reserve in women with a previous preeclampsia-affected pregnancy.[43] However, several constitutional and environmental factors contribute to birth weight,[44,45] and it is unlikely that manipulation of maternal hemodynamics alone is sufficient to overcome all these factors.

We do not disregard an effect of the placenta in modulation of the disease process of preeclampsia and FGR in pregnancy. The majority of our cases represent late-onset disease (conventionally taken as occurring beyond 34 weeks gestation), which occurs more frequently then early-onset disease.[36] The phenotypes of late-onset disorders have greater associations with maternal factors such as dysregulation of angiogenic and oxidative processes and preexisting medical comorbidities compared with the phenotypes that present early in pregnancy.[46] Further examination of early-onset disease may reflect a preferential placental component to its pathogenesis and would be an avenue to explore for future studies.

The main strength of our study was the prospective design and short interval between prepregnancy cardiovascular measurements and pregnancy. Furthermore, we studied healthy women, hence the results were not biased by cardiovascular comorbidities, such as diabetes mellitus or preexisting hypertension, in themselves independent prepregnancy risk factors for developing preeclampsia.

A limitation of our study is the modest numbers of cases of preeclampsia/FGR, totaling 15 pregnancies. This number was anticipated based on the population incidence of these disorders, hence this study was adequately powered for the primary outcome, taking into account the large number initially recruited to anticipate for participants that did not conceive or conceived but miscarried. Our sample may have experienced a selection bias, in that healthier women who had an interest in medical research and healthy living were more likely to participate in a study on cardiovascular and preconception health. Furthermore, we have considered both disorders together, as

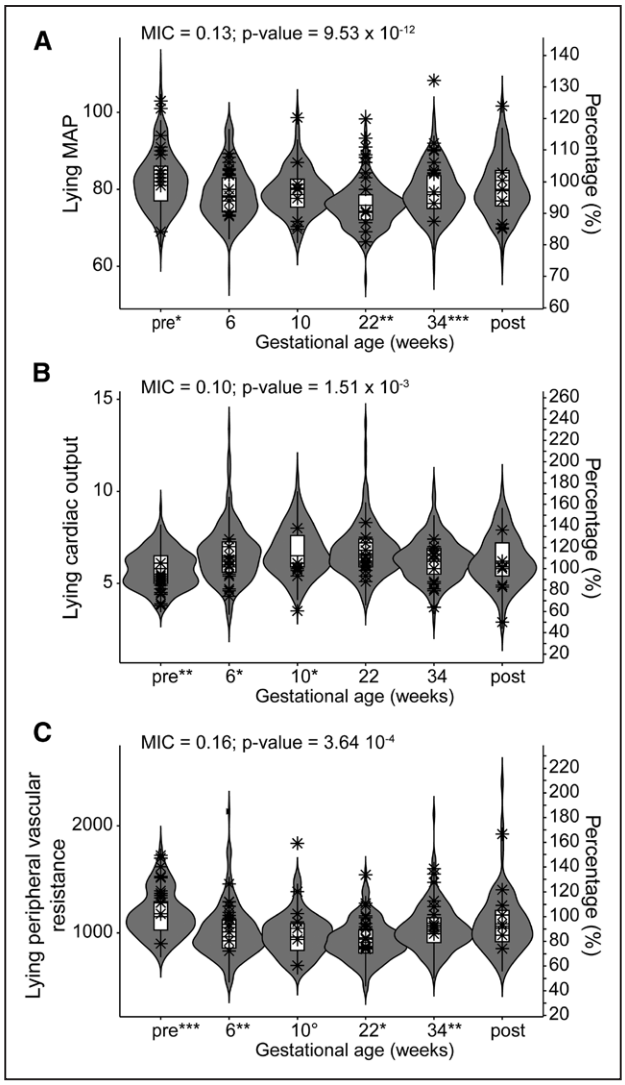


Figure 3. Maximal information coefficients (MIC) between supine cardiac output (**B**), mean arterial pressure (MAP; **A**), and total peripheral resistance (**C**) and longitudinal time change from prepregnancy to postpartum.

has been done in previous related studies.[23,24,47] This method acknowledges the overlay between the 2 phenotypes (15% of pregnancies with FGR have superimposed preeclampsia,[48] and conversely, 12%–58% of preeclampsia pregnancies[49,50] are affected by FGR); in keeping with long-held belief that both are part of the same pathophysiological spectrum.[51] It may not however address subtle differences in phenotypes of the conditions where underlying pathophysiology could be mutually exclusive.

Perspectives

We show that there are differences in hemodynamic phenotype from before pregnancy in healthy women who develop preeclampsia/FGR compared with those that do not develop these conditions. The women who develop preeclampsia/FGR have a hemodynamic profile characterized by low CO, high vascular resistance, and higher prepregnancy BP. These women demonstrate a greater decline of BP in the first trimester compared with controls; this compensatory mechanism may mask their inclination to hypertensive disease later in pregnancy. The findings suggest that cardiovascular hemodynamic dysfunction rather than placental maladaptation may play the initial pathogenic role in the origin of these disorders, particularly in late-onset manifestations of preeclampsia/FGR. From a clinical perspective, identifying a cardiovascular phenotype that is associated with future adverse pregnancy outcomes may be a useful target for prepregnancy screening and intervention. Future studies are needed to examine the feasibility of integrating maternal cardiovascular parameters into predictive models for preeclampsia/FGR and the possibility of manipulating maternal hemodynamics to improve pregnancy outcomes.

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Disclosures

None.

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Novelty and Significance

What Is New?

- In healthy women, a low-output, high resistance hemodynamic phenotype from preconception is associated with developing preeclampsia and fetal growth restriction in pregnancy.

What Is Relevant?

- Our findings may explain the link between pregnancy-specific disorders and increased risk of cardiovascular disease, including hypertension in later life.
- Hemodynamic aberrations that we report are potential targets for preconception intervention or tailored antihypertensive therapy in pregnancy.

Summary

A subset of healthy women have occult cardiovascular dysfunction which is associated with increased risk of developing preeclampsia/fetal growth restriction in pregnancy. This study highlights the shift of understanding in the paradigm of these disorders, classically thought to originate from placental dysfunction.

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Association Between Prepregnancy Cardiovascular Function and Subsequent Preeclampsia or Fetal Growth Restriction

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ONLINE SUPPLEMENT

Manuscript Title : Association between pre-pregnancy cardiovascular function and subsequent pre-eclampsia or fetal growth restriction

Short title: Pre-pregnancy cardiac function & pregnancy outcome

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Maternal age	Number of previous pregnancies (parity)	Previous adverse outcome pregnancy	Pregnancy outcome in study	Gestation at delivery (completed weeks)
36	0	-	FGR	39
39	1	FGR	FGR	38
30	1	PE	PE	38
35	0	-	FGR	39
35	0	-	FGR	40
25	0	-	PE + FGR	34
36	0	-	FGR	40
32	0	-	PE	40
30	0	-	FGR	38
30	0	-	PE + FGR	38
37	0	-	PE	40
37	1	PE + FGR	PE + FGR	29
29	0	-	FGR	35
32	1	FGR	FGR	39
27	1	No	PE + FGR	38

Table S1 Clinical details for 15 pregnancies affected by PE/FGR

		Mean diff	95%CI	R^2	P value
Systolic BP (mmHg)	Model 1	0.007	-0.02 – 0.001	0.002	0.516
	Model 2	-0.006	0.02 – 0.01	0.05	0.404
Diastolic BP (mmHg)	Model 1	0.01	-0.01 – 0.033	0.002	0.523
	Model 2	0.004	0.02 – 0.02	0.05	0.716
MAP (mmHg)	Model 1	0.009	-0.02 – 0.02	0.0002	0.823
	Model 2	-0.0012	-0.02 – 0.02	0.05	0.905
HR (bpm)	Model 1	0.007	-0.02 – 0.01	0.0003	0.788
	Model 2	-0.0012	0.02 – 0.01	0.04	0.867
CO (L/min)	Model 1	0.178	0.01 – 0.29	0.02	0.040
	Model 2	0.164	0.02 – 0.31	0.07	0.022
CI ($L/min/m^2$)	Model 1	0.014	-0.22 – 0.25	0.0001	0.905
	Model 2	0.0535	-0.18 – 0.30	0.04	0.663
SV (L)	Model 1	0.01	0.0 – 0.02	0.0203	0.036
	Model 2	0.0094	0.0 – 0.02	0.06	0.048
TPR ($dyness.sec.cm^{-5}$)	Model 1	-0.0007	-0.001 - -0.0001	0.02	0.030
	Model 2	-0.001	-0.001 - -0.0001	0.07	0.012

Table S2 Multi-variable associations between pre-conception CV parameters and birth-weight z-score. Model 1: Crude values; Model 2: Values adjusted for maternal factors of age, parity and BMI

Parameter	Non PE/FGR pregnancies (n=203)		PE/FGR pregnancies (n =15)	
	MIC	**P value**	**MIC**	**P value**
CO (L/min)	0.10	0.002	0.28	0.03
TPR (Dynes.sec.cm$^{-5)}$	0.16	<0.001	0.33	0.02
MAP (mmHg)	0.13	<0.001	0.21	0.63

Table S3 Maximal information coefficient (MIC) scores for gestation and changes in CO (L/min), TPR (Dynes.sec.cm^{-5}) and MAP (mmHg)