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Maternal hemodynamics in screen positive and negative women of the ASPRE trial

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Abstract

Objective**:** To compare maternal hemodynamics and perinatal outcomes in women identified at 11-13 weeks' gestation as being screen positive (N=170) or negative (N=926) for preterm preeclampsia (PE) by a combination of maternal factors, mean arterial pressure, uterine artery pulsatility index and serum placental growth factor and pregnancy associated plasma protein-A.

Methods: This was a prospective, longitudinal cohort study of maternal cardiovascular function, assessed by a bioreactance method, in women undergoing first trimester screening for PE. We investigated screen positive and screen negative women that did not have medical co-morbidities, did not develop PE or pregnancy induced hypertension (PIH) and delivered livebirths at term with birthweight between the 5^{th} to 95^{th} percentiles. A multilevel linear mixed-effects model was performed to compare the repeated measures of the cardiac variables controlling for maternal characteristics.

Results: The screen negative group had normal cardiac function changes across gestation, whereas, the screen positive group demonstrated static or reducing cardiac output and stroke volume and higher mean arterial pressure and peripheral vascular resistance with advancing gestation. In the screen-positive, compared to screen-negative women, the birth-weight z-score was shifted to the left with about 70% higher prevalence of babies below the 35th, 30th or 25th percentile, and the rate of operative delivery for fetal distress in labour.

Conclusions: Patients who screen positive for impaired placentation, even if they do not develop PE or deliver SGA neonates, have pathological cardiac adaptation in pregnancy and increased risk of adverse perinatal outcome.

Introduction

In normal pregnancy, cardiac output (CO) increases with gestational age and by 24 weeks the increase is up to 45% compared to non-pregnant levels.[1, 2] Conversely, peripheral vascular resistance (PVR) decreases by about 35% from pre-pregnancy levels, reaches a nadir during the middle of the second trimester and subsequently increases for the remainder of the pregnancy.[3, 4] These changes are the required mechanisms for the body to meet the increased metabolic demands of the mother and fetus and to ensure adequate uteroplacental circulation and fetal growth.[5, 6]

Maladaptation of the maternal cardiovascular system, from as early as the first trimester of pregnancy, plays a pivotal role in the pathophysiology of hypertensive disorders of pregnancy (HDP) and delivery of small for gestational age (SGA) neonates.[7] Birth of SGA neonates is associated with a lack of maternal intravascular volume expansion, low CO and increased PVR.[8-10] This distinct hemodynamic phenotype in SGA is not only observed in pregnancies with HDP[11] but also in normotensive pregnancies.[12, 13]

Early-onset PE and SGA are associated with impaired placentation, but it is uncertain whether the hemodynamic pattern observed in pregnancies complicated by PE and SGA are also present in pregnancies identified by first-trimester screening as having evidence of impaired placentation but do not subsequently develop PE or deliver SGA neonates. This study attempts to address this question by examining the hemodynamic profile and perinatal outcome in pregnancies identified by first-trimester screening as being at increased risk of impaired placentation but did not develop PE or pregnancy induced hypertension (PIH) and delivered livebirths at term with birthweight between the 5th to 95th percentiles. The hemodynamic profile and

perinatal outcome of these pregnancies were compared to those who were identified by first-trimester screening as being at low-risk of impaired placentation.

Methods

Study population

This prospective, longitudinal study of singleton pregnancies is a sub study of the ASPRE trial (Combined multi-marker screening and randomised patient treatment with aspirin for evidence-based preeclampsia prevention), involving women with singleton pregnancies attending routine pregnancy care at 11^{+0} to 13^{+6} week's gestation. The sub-study was conducted from November 2015 to May 2016 in six maternity hospitals in the UK. Ethical approval was granted (REC reference: 13/LO/1479) and R&D approvals were obtained for respective sites.

During the first visit, PE screening was performed based on a previously reported algorithm for first-trimester assessment of risk for preterm-PE by maternal factors, mean arterial pressure (MAP), uterine artery mean pulsatility index (UtA-PI), pregnancy-associated plasma protein A (PAPP-A) and placental growth factor (PlGF).[14] Women screen-positive for preterm-PE were offered participation in a double blind, randomized trial of Aspirin vs. Placebo in the prevention of PE. They were also offered to participate in this sub-study involving hemodynamics monitoring. The two study groups of the hemodynamics study comprised of 1) women who screened positive for PE (N=430) (Risk of preterm PE $\geq$1 in 100) and 2) gestation age matched screen-negative controls (N=1148) (Risk of preterm PE <1 in 100). Maternal factors, biomarkers, hemodynamics and fetal wellbeing scans were assessed upon recruitment (at 11-14 weeks) and repeated at 19-24, 30-34 and 35-37 weeks. For the ASPRE trial exclusion criteria were maternal age <18 years, women already on Aspirin, pre-existing maternal cardiac conditions, fetal abnormalities, incomplete follow-up and termination of pregnancy or miscarriage.

As both the screen-positive and screen-negative groups were heterogeneous, we excluded from this study women with multiple comorbidities (chronic hypertension, pre-existing or gestational diabetes mellitus, systemic lupus erythematous or anti-phospholipid syndrome, asthma, other autoimmune diseases, HIV, hepatitis B or C), those using any medication, those that developed PE or GH and those delivering preterm or babies with birthweight <5th or >95th percentiles, because these factors would have a significant impact on maternal hemodynamic parameters.

Maternal factors

Maternal factors recorded included maternal age, height, weight at each visit, racial origin (White, Black, South Asian, East Asian and mixed), method of conception (spontaneous or assisted by in-vitro fertilization or use of ovulation drugs), cigarette smoking during pregnancy (yes or no), medical history, medications and obstetric history (parous or nulliparous if no previous pregnancies at >24 weeks' gestation), and previous PE or FGR (yes or no).

Maternal cardiovascular function

Cardiovascular function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) validated both in pregnant and non-pregnant populations.[10, 15, 16] Bioreactance calculates the stroke volume via the relative phase shifts occurring when an alternating electrical current traverse the thoracic cavity. Four dual-surface electrodes were applied across the maternal back and after 15 minutes of rest, cardiovascular variables [CO, stroke volume (SV), heart rate (HR), PVR and MAP] were recorded in a sitting position for 10 minutes at 30-second intervals (20 cycles). The averages of the final 10 cycles of hemodynamic recordings were used as the variables included in the analysis.

Definitions

The definitions of non-proteinuric gestational hypertension (GH) and PE were those of the International Society for the Study of Hypertension in Pregnancy.[17] SGA and LGA were defined as birthweight for gestational age <5th percentile and >95th percentile, respectively.[18]

Statistical analysis

Maternal demographic and pregnancy outcome characteristics between the two groups were compared using the chi-square test or Fisher's exact test for categorical variables. For the comparison of the maternal race and method of conception, we present only the overall chi-square test statistic. The Kolmogorov – Smirnov test was used to assess the normality of the distribution of the data. As the data were not normally distributed, the Mann – Whitney U-test was used to compare continuous data. Data are presented as median (interquartile range) for continuous variables and as n (%) for categorical variables.

Comparison of repeat measures of maternal weight, body surface area, CO, SV, HR, MAP and PVR between the four visits was performed using Friedman's test with the Dunn-Bonferroni correction for the post-hoc analysis.

For the repeated measures analysis of the maternal hemodynamic variables, controlling for demographic characteristics and time (the four visits), a multilevel linear mixed-effects model was performed. Linear mixed effects are statistical models for repeated data analysis. They incorporate both fixed and random effects and provide information for both the within and between subject variability. Fixed effects are considered those variables that all possible values in which a researcher is interested are present in the study, whilst random effects are those that the study

contains only a random sample of possible variable values.[19] They are more robust when dealing with missing values in longitudinal studies, compared to the traditional repeat measures ANOVA, and hence it is gradually becoming the preferred method for repeat measures analysis.

The distribution of maternal weight, CO, SV, MAP and PVR were made Gaussian after $\log_{10}$ transformation. The fixed-effect component included time (the four visits), group (screen-negative versus screen-positive), maternal age, weight, height, race, conception, smoking, family history of a hypertensive disorder of pregnancy, nulliparity and first-order interaction between time and group. The likelihood radio (LR) test was used to define the best multilevel model (including only the random slope for time or random intercept versus including both the random intercept and slope) and to compare it with the base-model (with no random effects). The fixed and random effects of the multilevel models and the estimated marginal means at the four visits are presented.

The software program IBM SPSS Statistics 23 (SPSS Inc., Chicago, IL, USA) were used for the statistical analysis (IBM Corp, Released 2015, IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp).

Results

For the maternal hemodynamic studies, 1520 and 505 women with singleton pregnancies who were screen-negative and positive for preterm-PE, respectively, were recruited at the initial visit of the ASPRE trial. We excluded from the study 373 patients of the screen-negative and 78 from the screen-positive cohort due to miscarriage, preterm delivery, fetal anomalies, poor signal from the bioreactance monitor and incomplete follow-up (Figure 1). The remaining study population of 1146 from the screen-negative group and 427 from the screen-positive group were included for the hemodynamic studies. For the current study, we included 926 from the screen-negative group and 170 women from the screen-positive group. respectively, who fulfilled the entry criteria. In the screen positive group, 88 patients were randomised to aspirin and 82 to placebo.

Maternal demographics and pregnancy outcomes

The maternal characteristics for the two groups of women at the screening visit are presented in Table 1. The screen-positive women were heavier and taller, were more likely to be primiparous and of Black race and were more likely to have a family history of PE and to have conceived by in-vitro fertilization. Conversely, in the screen-negative group, multiparous women with no previous history of PE/FGR, White race and spontaneous conception were significantly more prevalent when compared to the screen-positive cohort. Despite being normotensive, the systolic, diastolic and MAP during the screening visit was significantly higher in the screen-positive compared to the screen negative group.

Both cohorts delivered babies between the 5^{th} and 95^{th} centiles and at similar gestational ages at term, they had the same rate and reasons for induction of labour

and rates and days of admission to the neonatal unit (NNU) (Table 1 and Supplementary table 1). Only seven patients in the screen-negative and two in the screen-positive group were induced for estimated weight between the 5th and 10th percentile with normal fetal Dopplers, a non-statistically significant difference (Supplementary table 1). All of them delivered babies with birthweight above the 5th percentile. However, the distribution of birth-weight z-score was shifted to the left with about 70% higher prevalence of babies below the 35th, 30th or 25th percentile in the screen-positive compared to screen-negative women (Table 1, Figure 2). Furthermore, the rate of emergency caesarean section and operative delivery for fetal distress in labour was higher in the screen positive compared to the screen negative group (Table 1). There were no differences between the two groups in terms of NNU admission, ventilation, respiratory distress syndrome, sepsis or neonatal hypoglycemia (Table 1).

Multilevel linear mixed-effects models (see supplementary results)

The fixed and random effects of the best multilevel models are shown in Supplementary Table 2 and the estimated marginal means are shown in Supplementary Table 3 and Figures 3 and 4.

$Log_{10}CO$ in the screen-negative group, demonstrated an increase during the first three visits and a decline thereafter. On the contrary in the screen-positive group, $Log_{10}CO$ demonstrated a linear decline with gestation. The two groups demonstrated opposing changes with gestation in $Log_{10}SV$. The screen-negative group demonstrated an increase in SV in the first three visits with a decline after that, whilst the screen-positive group showed a progressive decline with gestation. HR in both groups, demonstrated an increase with gestation during the first three visits. In the

fourth visit, the HR reached a plateau in the screen-negative group whilst the screen-positive group showed a decline. Log_{10}MAP in both groups, demonstrated a similar change with gestation with a decline in the first three visits followed by an increase in the fourth visit. Log_{10}MAP levels were higher throughout gestation in the screen-positive group. Log_{10}PVR in the screen-negative group, demonstrated a decline during the first three visits and a slight increase after that. On the contrary, in the screen-positive group, Log_{10}PVR demonstrated an increase with gestation.

Discussion

The results of this study demonstrate that healthy women, who screen-positive for preterm-PE,[20] even if normotensive and delivered at term, exhibit a pathological cardiovascular adaptation in pregnancy. They have a static hemodynamic profile with a decline in CO and SV and higher MAP and PVR compared to healthy women who screen-negative. The birthweight distribution of this group was skewed to the left with about 70% higher prevalence of babies below the 35th, 30th or 25th percentile compared to screen-negative women, indicating a higher prevalence of placental insufficiency. As a surrogate marker for placental disease, they had about 50% more operative deliveries due to fetal distress in labour.

Our results in the screen-negative group, agree with the known changes of maternal cardiac function in normal pregnancy with a decline in PVR and MAP from the first trimester and a concomitant increase in maternal CO and SV until early in the third trimester.[21-24] Thereafter, an increase in MAP and PVR and a decline in CO and SV until term denote an increase in afterload and a decline in left ventricular systolic function.[21, 23, 24] Furthermore, the magnitude of change from the screening visit at 11-14 weeks to the second visit at 19-24 weeks is comparable to that described in a recent meta-analysis that showed about 10% and 5% increase in CO and SV, respectively, and a 20% decline in PVR between the first and second trimester.[23] Like other studies in normal pregnancy, we also identified a peak CO early in the third trimester, followed by a decline towards term.[21, 24-26] The majority of the increase in CO in the second visit appears to be mainly due to the persistent rise in HR, rather than the modest 5% increase in SV. Thereafter, the maternal CO appears to be driven by the rise in HR, as SV declines towards term, possibly as a result of the increase in afterload.[26]

On the contrary, CO and PVR in the screen-positive women demonstrated an opposite pattern. The decline in SV throughout gestation could not be compensated by the rise in HR, resulting in mild drop of CO. PVR remained static across gestation, a failure of the cornerstone of hemodynamic maternal adaptation in early pregnancy. Previous studies on maternal hemodynamics performed either in hypertensive populations[27-29] or on normotensive cohorts[10-12, 30-36] had similar findings of a low CO and raised PVR in pregnancies with FGR.

The fact that this hemodynamic pattern was associated with a shift to the left in the distribution of birthweight and with a higher prevalence of operative deliveries for fetal distress is suggestive of a degree of placental insufficiency. This was either mild enough not to be manifested clinically during pregnancy, or it was a false negative of the serial growth scans in the background of maternal normal blood pressure, or it evolved during the last five weeks of gestation, after the last visit at 36 weeks. In any case, the maternal hemodynamic profile demonstrates that the FMF algorithm screens positive a group of women at high risk for placental insufficiency who warrant close surveillance at term.

We have excluded from our study babies with birthweight below the 5th and above the 95th percentiles to avoid reporting on adverse outcomes secondary to severe growth restriction or macrosomia. Despite the population selection, the screen-positive group contained a high proportion of mothers with impaired cardiovascular adaptation and hence it is not surprising that their babies had undiagnosed placental insufficiency with higher rates of operative birth due to fetal distress. The inability of an undiagnosed growth restricted fetus to cope with the stress of labour may be linked to the impaired expansion of maternal CO. The screen-positive women would struggle to accommodate the 12% and 34% increase in CO associated with the first

and second stage labor, respectively,[2, 37] or the hypovolemic stress after epidural anesthesia.[38, 39] It is thus unsurprising that women with low CO and high PVR had more intrapartum feto-maternal complications,[40] as also demonstrated in this study.

This is the first study that utilises a validated combined multi-marker screening method to select a 'high and low risk for PE' cohort for comparison of maternal hemodynamics. The longitudinal nature of the study and the large sample size are its main strengths. Furthermore, the selection of an operator independent,[16, 41] non-invasive cardiac monitor maximised patient participation and reduced bias across the multiple sites of the study. The stringent methodology in patient selection meant that we could reliably examine the serial changes in pregnancy of the maternal hemodynamics without the confounding effect of medical co-morbidities, medications or potentially compromised cardiovascular systems in women with previous HDP and FGR.

A limitation of this study is that we do not have postnatal follow-up and were unable to ascertain whether these hemodynamic patterns are evident only during a period of cardiovascular strain, such as pregnancy, or whether they persist in the non-pregnant state. Furthermore, the design of the ASPRE trial included assessments up until 37 weeks' gestation. It is possible that had more visits been performed until delivery, a higher proportion of babies with suspected growth restriction would have been detected and hence their pregnancy management modified. However, with the constraints of routine clinical care, this may not be possible to achieve and therefore, the maternal hemodynamic profiles may play a significant role in highlighting pregnancies that need closer surveillance at term. Another limitation of the study is the high proportion of women in the screen negative group that withdrew consent

from the study or did not attend for all four visits (194/1519); consequently, there is a risk of a certain degree of selection bias.

In conclusion, patients who screen-positive for preterm-PE have impaired cardiac adaptation in pregnancy and smaller birthweights. Therefore, they should have increased surveillance late in the third trimester and should not be regarded as 'normal' despite remaining normotensive at term as they are at greater risk of occult placental insufficiency. Current efforts in creating a prediction model to identify FGR[10] and those at risk of operative delivery for fetal compromise in SGA fetuses at term[42] could be improved by incorporating maternal PE screening status and hemodynamic studies. Given the inherent error of third trimester fetal biometry measurements,[43] repeated maternal hemodynamics using a non-operator dependant technique in the third trimester could potentially risk-stratify screen-positive pregnancies to guide timing of induction of labor if SGA was suspected.

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Figure legends:

Figure 1. Flow diagram of recruitment for the maternal hemodynamics studies after screening for the ASPRE trial

Figure 2. Birth-weight Z-score distributions for screen-negative (white bars) and screen-positive (black bars) women

Figure 3. Linear mixed-effects model: Estimated marginal means of Log_{10}Cardiac output (A), Log_{10}Stroke volume (B) and Heart rate (C) in the four visits after controlling for demographic characteristics in the screen-negative (dotted line, white circles) and screen-positive (solid line-black circles) groups.

Figure 4. Linear mixed-effects model: Estimated marginal means of Log_{10}Mean arterial pressure (A and Log_{10}Peripheral vascular resistance (B) in the four visits after controlling for demographic characteristics in the screen-negative (dotted line, white circles) and screen-positive (solid line-black circles) groups.

Table 1. Demographics and pregnancy outcomes in screen-negative and positive women.

	Screen negative (n=926)	Screen positive (n=170)	p-value
Age (years)	31.4 (27.28 –	31.3 (27.8 –	0.874
Weight at booking (kg)	66.8 (60.0 – 77.0)	70.7 (61.5 - 84.9)	0.002
Height (cm)	165.4 (6.4)	163.7 (7.0)	0.001
Smoking, n (%)	54 (5.8)	6 (3.5)	0.220
Primiparous, n (%)	448 (48.4)	140 (81.9)	<0.0001
Multiparous, no previous PE/FGR,	478 (51.6)	30 (18.1)	<0.0001
Family history of PE (%)	39 (4.2)	18 (10.5)	0.001
Conception, n (%)			<0.0001
Spontaneous, n (%)	905 (97.7)	159 (93.5)	
Ovulation drug, n (%)	7 (0.8)	0 (0.0)	
In vitro fertilization, n (%)	14 (1.5)	11 (6.4)	
Ethnicity			<0.0001
White, n (%)	745 (80.5)	102 (59.6)	
Black, n (%)	97 (10.5)	49 (28.7)	
South Asian, n (%)	36 (3.9)	10 (5.9)	
East Asian, n (%)	21 (2.3)	6 (3.5)	
Mixed, n (%)	27 (2.9)	3 (1.8)	
Systolic blood pressure (mmHg)	113.3 (106.7 –	118.5 (111.2 –	<0.0001
Diastolic blood pressure (mmHg)	73.6 (68.7 – 78.5)	77.5 (72.3 –	<0.0001
Mean arterial pressure (mmHg)	86.7 (81.7 – 92.3)	90.3 (85.2 –	<0.0001
Gestational age at delivery (wks)	40.1 (39.3 – 41.0)	39.7 (39.0 –	0.004
Birth-weight (g)	3500 (3229 – 3800)	3280 (3060 –	<0.0001
Birth weight z-score	-0.19 (-0.77 - -0.39)	-0.66 (-1.1 –	<0.0001
Birth weight percentile	42.5 (22.2 – 65.0)	25.2 (13.6 –	<0.0001
5^{th} -10^{th} percentile, n (%)	69 (7.4)	24 (14.1)	0.002
<25^{th} percentile, n (%)	266 (28.7)	84 (49.0)	<0.0001
<30^{th} percentile, n (%)	319 (34.4)	97 (57.1)	<0.0001
<35^{th} percentile, n (%)	371 (40.0)	111 (65.3)	<0.0001
Induction of labor, n (%)	228 (24.6)	45 (26.5)	0.630
Emergency LSCS, n (%)	119 (12.9)	32 (18.7)	0.041
Operative birth for fetal distress, n	96 (10.4)	28 (16.4)	0.023
NNU admission, n (%)	44 (4.8)	3 (1.8)	0.077
NNU number of days	3.0 (3.0 – 5.0)	5.0 (1.0 – 5.0)	0.548
Ventilation, n (%)	10 (1.1)	3 (1.8)	0.454
Respiratory distress syndrome, n	19 (2.0)	0 (0.0)	0.058

Sepsis, n (%)	20 (2.2)	2 (1.2)	0.396
Neonatal hypoglycemia, n (%)	6 (0.6)	1 (0.6)	0.928

PE: pre-eclampsia, FGR: fetal growth restriction, NNU: neonatal unit

Figure 1

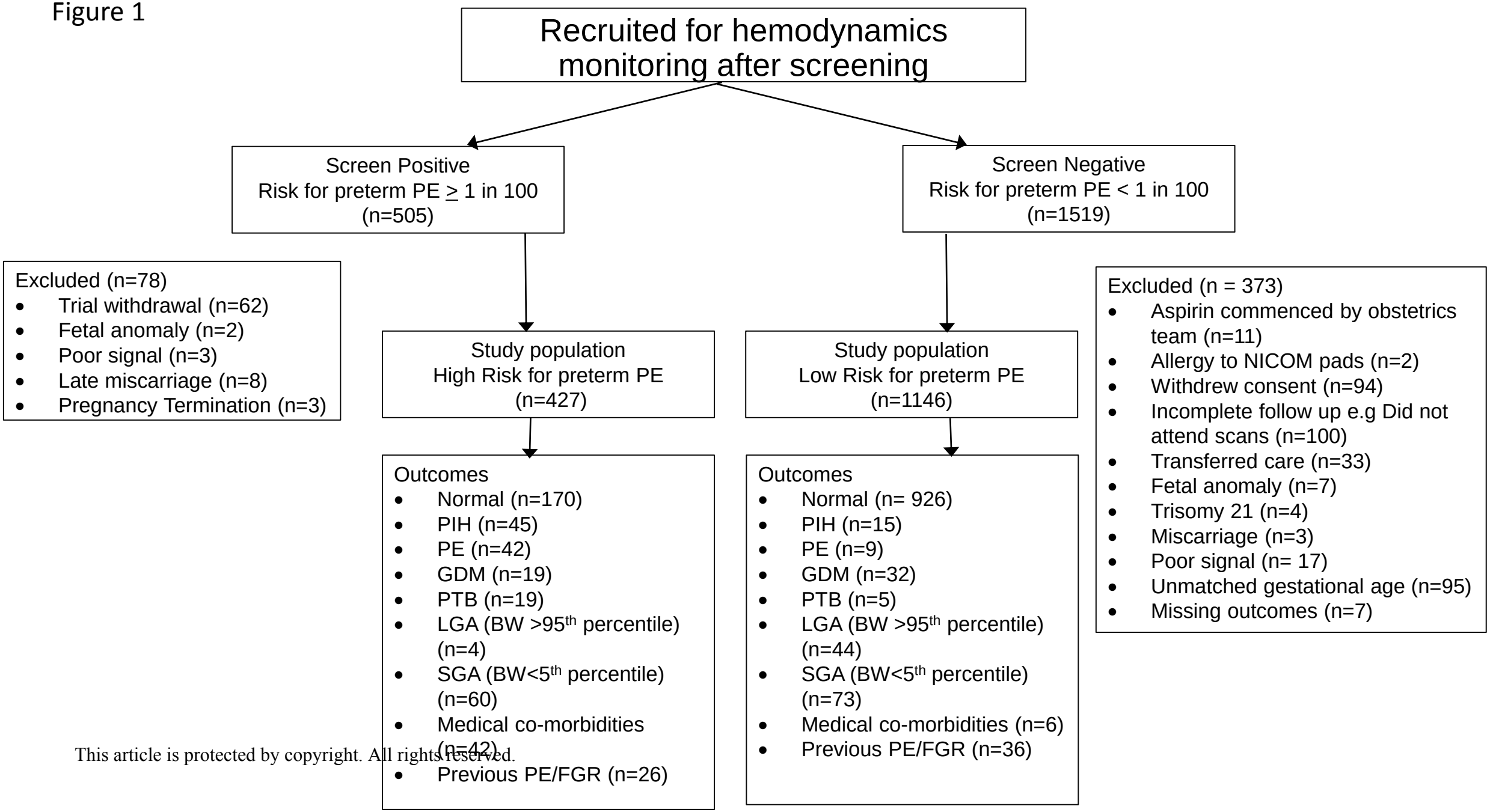

Figure 2

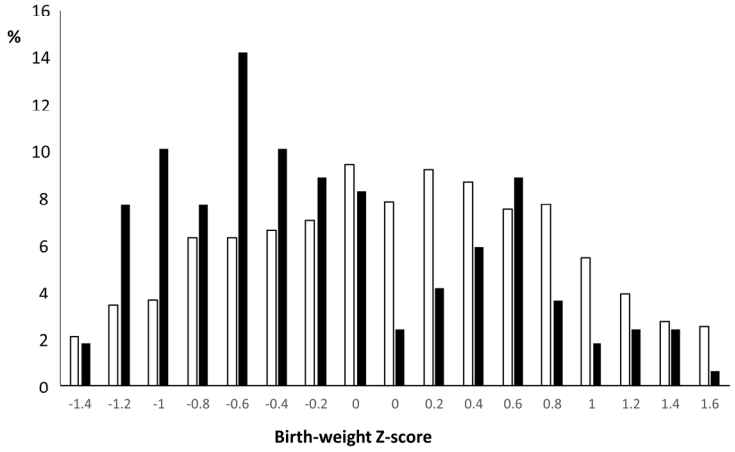

Figure 3

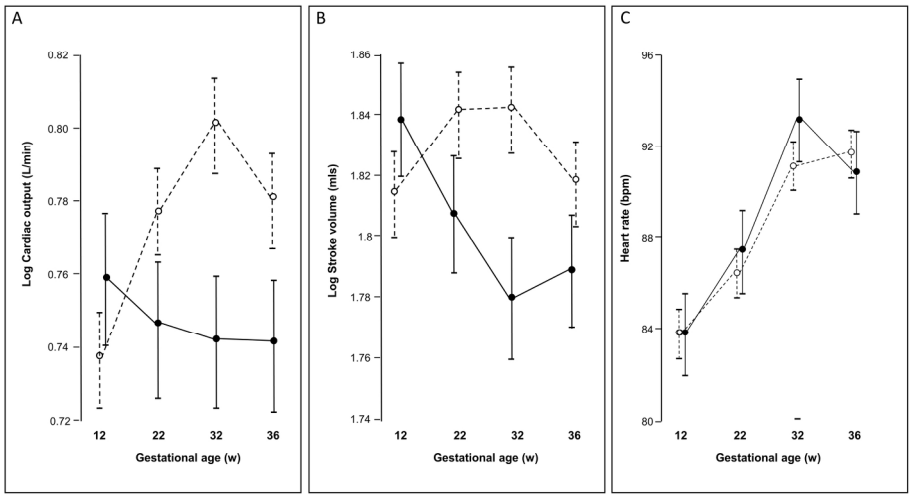

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Figure 4