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Maternal medicine

Maternal cardiac function in women at high risk for pre-eclampsia treated with 150 mg aspirin or placebo: an observational study

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Objective To compare maternal haemodynamics in women at low and high risk for preterm pre-eclampsia (PE), and between those at high risk who are randomised to aspirin or placebo.

Design Prospective, longitudinal observational study.

Setting Maternity units in six UK hospitals.

Population Women participating in the Aspirin for Prevention of Preterm Pre-eclampsia (ASPRE) trial. The population comprised three groups of women: low risk for preterm PE (n = 1362), high risk for preterm PE treated with aspirin (n = 208) and high risk for preterm PE on placebo (n = 220).

Methods Women had four visits during pregnancy: 11–14, 19–24, 30–34 and 35–37 weeks' gestation. Blood pressure was measured with a device validated for pregnancy, and PE and maternal haemodynamics were assessed with a bioreactance monitor at each visit. A multilevel linear mixed-effects analysis was performed to examine longitudinal changes of maternal haemodynamic variables, controlling for demographic characteristics, past medical history and medication use.

Main outcome measures Longitudinal changes of cardiac output (CO), mean arterial pressure (MAP) and peripheral vascular resistance (PVR).

Results The low-risk group demonstrated the expected changes with an increase in CO and reduction in MAP and PVR, with a quadratic change across gestation. In contrast, the high-risk groups had a declining CO, and higher MAP and PVR during pregnancy. The administration of aspirin did not appear to affect maternal haemodynamics.

Conclusions Women screened as high risk for preterm PE have a pathological cardiac adaptation to pregnancy and the prophylactic use of aspirin (150 mg oral daily from the first trimester) in this group may not alter this haemodynamic profile.

Keywords Aspirin, cardiac function, cardiac output, haemodynamics, peripheral vascular resistance, pre-eclampsia.

Tweetable abstract In women at high risk of pre-eclampsia, prophylactic use of aspirin may not alter the impaired maternal cardiac adaptation.

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Introduction

Women destined to develop preterm pre-eclampsia (PE) are characterised by an unfavourable cardiovascular adaptation in pregnancy, as shown by constricted intravascular volume, with a shift towards low cardiac output (CO), persistently high peripheral vascular resistance (PVR) and increased mean arterial pressure (MAP),[1-5] and cardiac remodelling with left ventricular concentric hypertrophy and diastolic dysfunction.[1,6-8] These changes render these groups susceptible to further cardiovascular decompensation from any additional circulatory insults during pregnancy.

Recently, the Aspirin for Prevention of Preterm Pre-eclampsia (ASPRE) trial established that in women identified by first-trimester screening as being at high risk of developing PE, administration of aspirin (150 mg/day from 11–14 to 36 weeks' gestation) reduces the incidence of early PE and preterm PE by about 90 and 60%, respectively.[9] Outside

pregnancy, aspirin, a non-steroidal anti-inflammatory drug (NSAIDs), is commonly used for secondary prevention of myocardial infarction, stroke,[10] and reduction of mortality after a cardiovascular event;[11] these effects are thought to be mediated through irreversible inhibition of the cyclooxygenase-1 (COX-1) pathway, thereby reducing production of thromboxane A_2 (TXA_2) and platelet aggregation.[12-14] However, NSAIDs also inhibit the COX-2 pathway, resulting in hypertension and exacerbation of pre-existing heart failure;[13] this dose-dependent complication is explained by inhibition of the compensatory vasodilatory prostacyclin (PGI_2) resulting in systemic vasoconstriction15,16 with consequent increase in afterload, reduction in cardiac output (CO) and cardiac contractility[17,18] as well as increase in blood pressure.[19] In women with a diminished cardiac reserve, such as those destined to develop preterm PE, aspirin, through inhibition of PGI_2 synthesis, could potentially result in disruption of the delicate vasoconstrictor/vasodilator balance,[16,20] a hallmark of cardiac adaptation in pregnancy, causing deterioration in circulatory haemodynamics.

The cardiovascular effects of low-dose aspirin in high-risk pregnancies have not been investigated before. Therefore, the primary objective of this study is to compare longitudinally central haemodynamics in women screened as high risk for preterm PE who were randomised to aspirin or placebo. A second objective was to compare longitudinally central haemodynamics in women who screened as low risk with those who as screened high risk for preterm PE.

Methods

Study population

This haemodynamic study was a sub-study of the ASPRE trial. The trial was made up of two parts. First, a routine population of singleton pregnancies at 11–13 weeks' gestation was screened for a combination of maternal risk factors, mean arterial pressure (MAP), uterine-artery pulsatility index and biomarkers to identify a high-risk group for development of preterm PE. Second, the high-risk group was invited to participate in a randomised trial of aspirin (150 mg/day) versus placebo administered from 11 to 14 weeks until 36 weeks of gestation.[9] (Figure 1)

In this study we recruited 428 women at high risk of PE who participated in the randomised trial and 1362 low-risk women (Figure 1). We aimed to recruit about three patients from the low-risk group for each high-risk patient participating in the study. All patients (high and low risk) were recruited from one of six maternity hospitals in the UK between November 2015 and May 2016. Gestational age was determined from measurement of fetal crown–rump length.[21] Patients were not involved in the development of the research. Women participating in this sub-study on maternal haemodynamics provided written informed consent and the study was approved by the NHS Research Ethics Committee (REC reference: 13/LO/1479). The study was supported by a grant from the Fetal Medicine Foundation (Charity No.: 1037116).

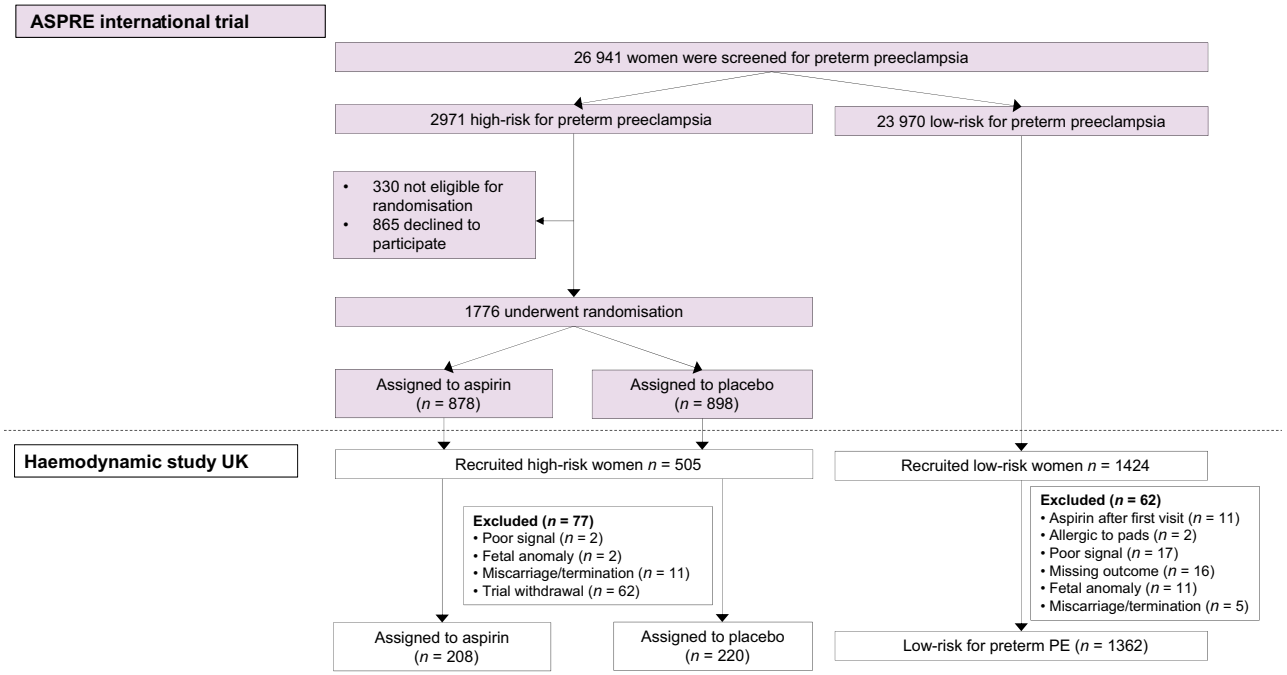

Figure 1. The participants in the ASPRE trial who were recruited for the haemodynamic sub-study.

Maternal factors and pregnancy outcomes

Maternal factors recorded included age, height, weight (at each visit), racial origin (white, black, South Asian, East Asian and mixed), method of conception (spontaneous or use of artificial reproductive technologies), cigarette smoking during pregnancy, medical history (chronic hypertension, asthma, autoimmune disease, diabetes mellitus), medications (antihypertensives, prednisolone, anti-asthmatics, thyroxine), parity and obstetric history (nulliparous, parous with and without previous PE) and compliance with trial drug. Pregnancy outcomes recorded included term and preterm PE, gestational hypertension (GH), gestational diabetes mellitus (GDM), preterm birth, induction of labour, operative deliveries for fetal distress, gestational age at delivery, birthweight percentile and perinatal mortality.

Maternal cardiovascular function

Maternal cardiac function was assessed using a non-invasive, bioreactance method (NICOM, Cheetah Medical Ltd, Maidenhead, Berkshire, UK) validated in both pregnant[22,23] and non-pregnant populations.[24] When an alternating electrical current traverses the thoracic cavity, the bioreactance technology uses the simultaneous relative phase shifts to calculate stroke volume. After 15 minutes of rest, four dual-surface electrodes were applied across the maternal back, and cardiac variables (CO, SV, HR), peripheral vascular resistance (PVR), and mean arterial pressure (MAP) were recorded in a sitting position for 10 minutes at 30-second intervals (20 cycles). The averages of the final 10 cycles of haemodynamic variables were included in the analysis.

Definitions

The definitions of non-proteinuric GH and PE were those of the International Society for the Study of Hypertension in Pregnancy;[25] this is the old definition of this society but it is the one used in ASPRE. Birthweight percentile for gestational age was derived from the Fetal Medicine Foundation reference range.[26]

Inclusion and exclusion criteria

The inclusion criteria were singleton pregnancies recruited into the screening trial (low or high risk for preterm PE) resulting in the birth of normal live births or stillbirths at or after 24 weeks' gestation and attendance for haemodynamic studies for at least three of the four visits. Exclusion criteria were maternal age <18 years, pre-existing maternal cardiac conditions, fetal abnormalities, incomplete follow up and termination of pregnancy or miscarriage following the first visit.

Statistical analysis

Maternal demographic characteristics, medical history and pregnancy outcomes between low-risk women and high-risk groups randomised to aspirin or placebo were recorded. Categorical variables were compared using the Chi-square test or Fisher's exact test. Normality of the distribution of continuous data was assessed with the Kolmogorov–Smirnov test. As the data were not normally distributed, the distribution of maternal weight, CO, SV, MAP and PVR were made Gaussian after $\log_{10}$ transformation. For comparison of continuous data, the Kruskal–Wallis or the one-way ANOVA tests with post-hoc analysis were used for non-normally and normally distributed data, respectively. Data are presented as median (interquartile range) and mean (standard deviation) for non-normally and normally distributed continuous variables, and as n (%) for categorical variables. For the repeated measures analysis of the maternal haemodynamic variables, controlling for demographic characteristics, past medical history, medication use and time (the four visits), a multilevel linear mixed-effects analysis was performed. The fixed-effect component included time (the four visits), treatment (aspirin, placebo), race (white, black, South and East Asian and mixed), maternal age, $\log_{10}$ weight, height, parity and obstetric outcome, spontaneous conception, smoking, family history of PE, medical co-morbidities, medication use and first-order interaction between treatment group and time. 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) (Appendix S1). The anti-log values of the estimated marginal means of each haemodynamic variable at each visit are presented. In addition, the same comparisons were performed between women who developed PE and those who did not in the aspirin and placebo groups (data not shown).

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

Results

Study population

The study population included 1362 and 428 women who screened as low and high risk, respectively. Of the 428 high-risk women, 220 were randomised to placebo and 208 to aspirin. The maternal characteristics and pregnancy outcomes for the three groups at the screening visit are compared in Table 1. Maternal age and the incidence of smoking were similar across the three groups. Comparing low-risk women with the two high-risk groups, the latter were significantly heavier and shorter. In the high-risk groups, there was higher proportion of nulliparous or parous women with previous history of PE, of black racial origin, of chronic hypertension, asthma, diabetes mellitus and treatment with antihypertensives. Regarding pregnancy

Table 1. Demographic and pregnancy characteristics of the study groups

Variable	Low risk (*n* = 1362)	High risk – Placebo (*n* = 220)	High risk – Aspirin (*n* = 208)	Overall *P*-value
Age in years	31.2 (5.1)	31.0 (5.7)	31.5 (5.9)	0.495
Weight at 11–13 weeks, kg	66.8 (60.0–77.0)	70.0 (60.1– 87.5)	75.0 (62.1–87.4)	<0.001
Height, cm	165.2 (6.5)	162.6 (6.4)	163.2 (6.8)	<0.001
Smoking	79 (5.8)	8 (3.6)	9 (4.3)	0.145
Family history of PE	63 (4.6)	30 (13.6)	18 (8.7)	<0.001
Racial origin				
White	1073 (78.8)	128 (58.2)	122 (58.7)	<0.001
Black	146 (10.7)	67 (30.5)	64 (30.8)	<0.001
South Asian	67 (4.9)	18 (8.2)	13 (6.3)	0.064
East Asian	31 (2.3)	3 (1.4)	6 (2.9)	0.836
Mixed	45 (3.3)	4 (1.8)	3 (1.4)	0.074
Nulliparous	645 (47.3)	147 (66.8)	142 (68.3)	<0.001
Previous PE or FGR	52 (3.8)	34 (15.5)	32 (15.4)	<0.001
No previous PE or FGR	665 (48.9)	39 (17.7)	34 (16.3)	<0.001
Medical disorders				
Chronic hypertension	9 (0.7)	16 (7.3)	12 (5.8)	<0.001
Asthma	14 (1.0)	13 (5.9)	12 (5.8)	<0.001
Diabetes mellitus	8 (0.6)	5 (2.3)	1 (0.5)	0.027
Autoimmune disease	10 (0.7)	5 (2.3)	2 (1.0)	0.092
Labetalol	12 (0.8)	44 (20.0)	29 (13.9)	<0.001
Nifedipine / methyldopa	4 (0.3)	7 (3.2)	13 (6.3)	<0.001
Prednisolone	3 (0.2)	0 (0.0)	2 (1.0)	0.397
Compliance to trial drug (%)	—	96.1 (89.8–98.8)	95.7 (87.8–98.7)	0.523
Pre-eclampsia	12 (0.9)	27 (12.2)	15 (7.3)	<0.001
Preterm PE (<37 weeks)	3 (0.2)	8 (3.6)	2 (1.0)	<0.001
Preterm PE (<34 weeks)	0 (0.0)	5 (2.3)	0 (0.0)	<0.001
Term PE (≥37 weeks)	9 (0.7)	19 (8.6)	13 (6.3)	<0.001
Gestational hypertension	16 (1.2)	21 (9.5)	24 (11.5)	0.001
Gestational diabetes	44 (3.2)	18 (8.2)	18 (8.7)	<0.001
Birth <37 weeks' gestation	39 (2.9)	24 (10.9)	23 (11.1)	<0.001
Induction of labour	378 (27.7)	76 (34.5)	77 (37.0)	0.001
Emergency caesarean	183 (13.4)	56 (25.5)	50 (24.0)	<0.001
Operative birth (fetal distress)	141 (10.3)	38 (17.3)	30 (14.4)	0.002
Gestational age at birth, wk	40.0 (39.0–40.9)	39.3 (38.3–40.3)	39.3 (38.3–40.4)	<0.001
Neonatal outcome				
Birthweight percentile	52.7 (24.7–76.4)	26.1 (8.6–62.3)	27.1 (12.2–58.8)	<0.001
Birthweight <10th centile	154 (11.3)	61 (27.7)	46 (22.1)	<0.001
Perinatal mortality	0 (0.0)	4 (1.8)	1 (0.5)	<0.001

Values given as *n* (%), median (interquartile range) or mean (standard deviation).

outcomes, high-risk compared with low-risk women had a higher incidence of PE, GH, GDM, preterm birth, induction of labour, emergency caesarean section, operative birth for presumed fetal distress, perinatal mortality and small-for-gestational-age neonates.

Comparing women allocated to aspirin versus placebo, there was no difference in maternal demographics. The incidence of preterm PE (<34 weeks) was significantly lower in the aspirin group. There was a non-significant trend of lower incidence of both preterm and term PE, emergency caesarean section, operative birth for fetal distress and perinatal mortality in women randomised to aspirin versus placebo.

Multilevel linear mixed-effects models

The fixed effects of the best multilevel models are shown in Figure 1 and Table S2.

Maternal demographic characteristics and medical history

Increasing maternal age was associated with a decrease in $\log_{10}$ CO and HR. Increasing maternal height was associated

with higher log_{10} CO, log_{10} SV and lower HR and log_{10} PVR. Maternal log_{10} weight was associated with higher log_{10} CO, log_{10} SV and HR. Compared wiith white race, South and East Asian race were associated with lower log_{10} CO, log_{10} SV, and higher log_{10} PVR. Compared with white race, black race was associated with lower log_{10} SV, higher HR and lower log_{10} MAP. Smoking was associated with lower log_{10} MAP.

Maternal chronic hypertension, use of labetalol, nifedipine or methyldopa were associated with higher log_{10} PVR, and log_{10} MAP. Use of prednisolone was associated with higher log_{10}CO, log_{10}SV and Log_{10}PVR. The use of aspirin or placebo compared with the low-risk group, was associated with lower log_{10} CO, log_{10} SV, and higher log_{10} PVR and log_{10} MAP.

There was no significant contribution in any of the models from asthma and autoimmune diseases. There was a significant interaction between treatment groups and time for all the cardiac variables, due to the effect of the low-risk group.

Changes with time after controlling for maternal characteristics: aspirin–placebo–low-risk groups

Log_{10} CO in high-risk women from both aspirin and placebo groups demonstrated a steady decline from the first visit onwards (Figure 2, Tables S1 and S3). Low-risk women demonstrated an increase of log_{10} CO until the third visit and a decline thereafter (Figure 2, Tables S1 and S3). Log_{10} SV in both aspirin and placebo groups demonstrated a linear decrease from first to third visit and plateaued from the third to fourth visit, whereas in the low-risk group it increased from the first to second visit, remained stable in the second and third visit, and then declined marginally towards the last visit (Figure 2, Tables S1 and S3). HR in all three groups demonstrated a similar increase with gestation during the first three visits but demonstrated a small decline in the fourth visit (Figure 2, Tables S1 and S3). There was no difference between the three groups in HR across gestation.

Log_{10} MAP in both the aspirin and placebo groups was persistently higher than in low-risk women throughout gestation. All three groups showed a similar linear decrease from first to third visit, followed by an increase towards the fourth visit (Figure 3, Tables S1 and S3). Log_{10} PVR in both the aspirin and placebo groups was higher than in low-risk women throughout gestation (Figure 3, Tables S1 and S3). In the low-risk group, there was a gradual decline with gestation until the third visit, followed by a small increase in the fourth (Figure 3, Tables S1 and S3). In the aspirin and placebo groups, Log_{10} PVR progressively increased with gestation (Figure 3, Tables S1 and S3).

Changes with time after controlling for maternal characteristics for aspirin–placebo (PE and non-PE groups)

There was no significant difference in log10 CO, log10 SV, log10 PVR and HR across gestation between the women who developed PE and those who did not, both in the aspirin and the placebo group (data not shown). Log10 MAP was significantly higher across all four visits in all PE compared with non-PE women (data not shown).

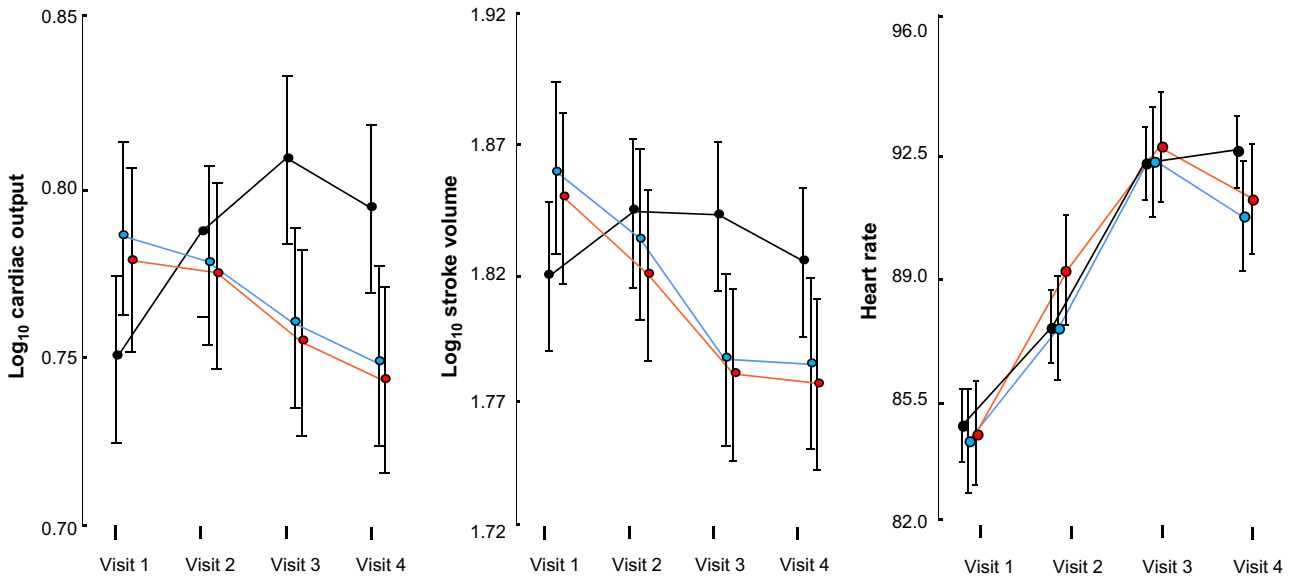

Figure 2. Linear mixed-effects model with estimated marginal means adjusted for prognostic characteristics and 95% confidence intervals for log_{10} cardiac output, log_{10} stroke volume and heart rate in women who screened as low-risk for preterm PE (black line) compared with women who screened as high-risk for preterm PE and who were randomised to aspirin (red line) or placebo (blue line).

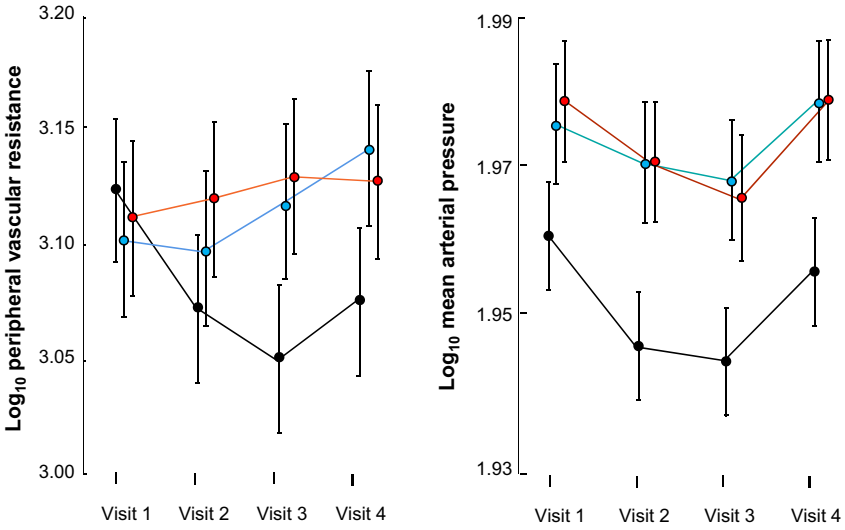

Figure 3. Linear mixed-effects model with estimated marginal means adjusted for prognostic characteristics and 95% confidence intervals for $\log_{10}$ peripheral vascular resistance and $\log_{10}$ mean arterial pressure in women who screened as low-risk for preterm PE (black line) compared with women who screened as high-risk for preterm PE and who were randomised to aspirin (red line) or placebo (blue line).

Discussion

Main findings

This study has demonstrated first that women identified by first-trimester screening as being at high-risk for subsequent development of preterm PE, compared with low-risk women, have impaired cardiovascular adaptation with worsening CO and SV and persistently higher PVR and MAP with advancing gestation. Second, aspirin (150 mg/day from 11–14 to 36 weeks' gestation) may not alter the impaired maternal cardiovascular adaptation.

In this study, we adjusted the maternal haemodynamic variables to maternal height and weight in the linear mixed model, rather than using an indexed cardiac measure.

This is because there remains a controversy concerning the poor correlation between cardiac output and body surface area,[27] especially in the pregnant state.[28] Furthermore, because the commonest formula used for body surface area has been estimated by examining only nine subjects and the assumptions were made based on the relation between height and weight,[29] this may not be valid in pregnancy. As maternal weight increases with advancing gestation, it is unclear which body surface area is to be used, and whether a strict proportionality exists between weight gain in pregnancy and surface area.[28] Finally, with advancing gestation, the increase in maternal weight is also a risk factor for development of pregnancy complications. There is a risk that with indexed values, we could be normalising the cardiac variables in women who are transitioning to a disease state in parallel with weight gain.

Strengths and limitations

This was a large longitudinal study comparing haemodynamic changes in pregnancy between high- and low-risk women for preterm PE identified in the first-trimester by multi-marker screening, and is the first study to compare haemodynamics in high-risk women randomised to aspirin or placebo. Additional strengths were, first, that the dose of aspirin at 150 mg/day would have to a great extent avoided the problem of aspirin resistance reported with lower doses of the drug,[30] and, second, that compliance with medication in both arms of the trial was >95%.

A limitation was that the study was not powered to examine haemodynamic differences between women who developed PE compared with those who did not.

Interpretation

In everyday life the balance between COX-1 and COX-2 activity, and hence the TxA_2 to PGI_2 ratio, is important in maintaining the homeostasis of the coagulation pathway.[13] Such an imbalance was caused iatrogenically during the 1990s with the introduction of COX-2 selective inhibitors for treatment of chronic inflammatory diseases which led to an increase in cardiovascular risk.31,32 Aspirin can inhibit both COX-1 and COX-2 enzymes,[10] albeit with 10–100 times more affinity to COX-1,[32,33] but chronic administration of aspirin can result in inhibition of both COX-1 and COX-2 activity, and hence both TxA_2 and PGI_2. Aspirin doses in excess of 160 mg for 3 days can cause a 40% reduction in PGI_2,[34] but even at a dose as low as 30 mg/day, PGI_2 has been shown to fall by 20% within 4 days of treatment.[35] The finding that aspirin attenuates the

antihypertensive effects of enalapril in patients with heart failure[36] may be the result of a negative effect on the vasodilatory function of PGI_2. These concerns regarding the inadvertent COX-2 inhibition by aspirin are further compounded by evidence that the common use of aspirin in cardioprotection (75 mg/day) has deleterious vasoconstrictor effects in New York Heart Association (NYHA) Class II and III heart failure patients.[15] This negative effect of many NSAIDs is particularly marked in high-risk individuals, such as those with renal and cardiovascular disease.[20] Studies reported that administration of NSAIDs in patients with chronic heart failure caused significant decrease in CO and increase in PVR.[37,38]

This delicate vasoconstrictor/vasodilator balance has particular relevance to our cohort at high-risk of PE because their cardiovascular systems are under the strain of pregnancy-related volume overload. As shown in our study, these women do not demonstrate a normal cardiovascular adaptation in pregnancy; compared with the low-risk cohort, they have static or declining CO and SV, and higher MAP and PVR throughout pregnancy. It is likely that the high-risk group represents women with impaired cardiovascular reserve pre-existing pregnancy, and they are at higher risk not only of preterm PE but also of cardiovascular disease later in their lives. An alternative explanation is that women in the high-risk group have impaired placentation which does not trigger an adequate physiological adaptation to pregnancy.

Pregnancies destined to develop PE have been shown to undergo cardiac remodelling such as left ventricular concentric hypertrophy and diastolic dysfunction,[1,7,8] adaptive changes comparable to that observed in patients with heart failure. Furthermore, 4 years after delivery, women with pregnancies complicated by PE continued to exhibit structural heart alterations consistent with Stage B heart failure.[39]

Although there is consensus that low-dose aspirin at a dose of up to 150 mg/day appears to be safe in pregnancy,[40] no previous studies have examined the maternal cardiovascular effects of this drug. In healthy, non-pregnant subjects, a single dose of 100 mg aspirin achieves an almost complete suppression of COX (95 ± 4% inhibition), indicating its supramaximal dose for antiplatelet effect.[35] Because there is a paucity of data on pharmacokinetics of aspirin in pregnancy, we cannot be certain about the systemic bioavailability of aspirin administered orally in the pregnant state. It was our concern that prolonged aspirin at a dose of 150 mg/day to the high-risk cohort, with potentially diminished cardiac reserve, could upset the thrombotic equilibrium, leading to exacerbation of the vasoconstrictive state and worsening of maternal haemodynamics. Our finding that in the high-risk group use of aspirin did not attenuate the CO or worsen the PVR longitudinally, is reassuring because the results imply that the integrity of the vasoconstrictor/vasodilator prostaglandin balance was not disturbed.

Conclusion

Our study shows that women screened as high-risk for preterm PE exhibit pathological cardiovascular adaptation with worsening CO and static PVR throughout pregnancy when compared with low-risk women. This pathological haemodynamic profile is not altered by 150 mg oral aspirin administered daily from the first trimester.

Disclosure of interests

The authors report no conflict of interests. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

HL, LP and KN conceptualised and planned the study. HL and PJ collected the data for the study. NK, HL and AB analysed the data for the study. HL, AB, LP, KN and NK contributed to writing and editing the final manuscript.

Details of ethics approval

This study was approved on 23 October 2015 by NHS Research Ethics Committee (REC reference: 13/LO/1479).

Funding

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Multilevel linear mixed-effects models for maternal haemodynamic variables: estimated marginal means with 95% confidence interval: anti-log values.

Table S2. Multilevel linear mixed-effects models for maternal haemodynamic variables: fixed effects.

Table S3. Comparisons of the estimated marginal means of the mixed effect models between four visits in the placebo, aspirin and low-risk groups: *P*-values.

Appendix S1. Multilevel linear mixed-effects models. ■

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