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Preconception Blood Pressure Levels and Reproductive Outcomes in a Prospective Cohort of Women Attempting Pregnancy

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Abstract

Elevated blood pressure in young adulthood is an early risk marker for cardiovascular disease. Despite a strong biologic rationale, little research has evaluated whether incremental increases in preconception blood pressure have early consequences for reproductive health. We evaluated preconception blood pressure and fecundability, pregnancy loss and live birth in the Effects of Aspirin on Gestational and Reproduction trial (2007–2011), a randomized clinical trial of aspirin and reproductive outcomes among 1228 women attempting pregnancy with a history of pregnancy loss. Systolic and diastolic blood pressure were measured during preconception in the first observed menstrual cycle and in early pregnancy, and used to derive mean arterial pressure. Fecundability was assessed as number of menstrual cycles until pregnancy, determined through human chorionic gonadotropin testing. Pregnancy loss included both human chorionic gonadotropin-detected and clinical losses. Analyses adjusted for treatment assignment, age, body mass index, race, marital status, smoking, parity and time since last loss. Mean preconception systolic and diastolic blood pressure were 111.6 (SD 12.1) and 72.5 (SD 9.4) mmHg. Risk of pregnancy loss increased 18% per 10 mmHg increase in diastolic blood pressure (95% CI 1.03, 1.36) and 17% per 10 mmHg increase in mean arterial pressure (95% CI 1.02, 1.35) in adjusted analyses. Findings were similar for early pregnancy blood pressure. Preconception blood pressure was not related to fecundability or live birth in adjusted analyses. Findings suggest preconception

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blood pressure among healthy women is associated with pregnancy loss, and lifestyle interventions targeting blood pressure among young women may favorably impact reproductive health.

Keywords

reproduction; women's health; pregnancy loss; fecundability; blood pressure

Introduction

Subfecundity is a key health concern among young adults, with approximately 6–15% of couples attempting pregnancy in the United States experiencing infertility[1–3] and, of those who become pregnant, 20–30% experiencing a pregnancy loss.[4, 5] Women with a personal history of adverse reproductive events, such as pregnancy loss and preterm birth, are at greater risk for cardiovascular disease later in life,[6, 7] raising the hypothesis that early-stage cardiovascular dysregulation is initiated very early in life and may be associated with adverse reproductive events.

Elevated blood pressure levels in young adulthood, particularly diastolic blood pressure (DBP), are associated with a greater risk of developing cardiovascular disease.[8, 9] Although genetics play a role in inter-individual variation in blood pressure, many lifestyle and environmental factors influence risk of hypertension, potentially through multiple pathways including inflammation, oxidative stress and endothelial dysfunction.[10] These same pathways have been associated with adverse reproductive events, through effects on key reproductive processes such as ovulation, implantation and vascularization of the placenta.[11–14]

Despite a strong rationale for a shared pathology for elevated blood pressure and adverse reproductive events,[8, 9] prior research on preconception hypertension and reproductive outcomes is sparse and inconclusive.[15, 16] To our knowledge, preconception blood pressure, a relatively easy and non-invasive measure of cardiovascular disease risk, has not been studied in relation to reproductive health among women without pre-existing cardiovascular disease. To address this research gap, we evaluated the association of preconception and early pregnancy blood pressure with fecundability, pregnancy loss, and live birth in a prospective time-to-pregnancy and pregnancy outcomes cohort.

Methods

Consistent with National Institutes of Health policy, our data can be made available to other researchers. For details, please see http://grants.nih.gov/grants/policy/data_sharing/ for the National Institutes of Health data sharing policy.

Study Design

This preconception prospective cohort study is set in the Effects of Aspirin on Gestation and Reproduction (EAGeR) trial, a randomized clinical trial of low-dose aspirin and reproductive outcomes conducted from 2007–2011. As previously described,[17] participants were recruited from six clinical sites across the United States. At the beginning of the first

menstrual cycle of follow-up, participants were assigned to either daily 81 milligrams aspirin plus folic acid or placebo plus folic acid, which participants continued to take for up to 6 months of attempting pregnancy and throughout pregnancy if pregnancy was achieved. Women were eligible if they were actively trying to conceive and had experienced 1–2 prior pregnancy losses and up to two prior live births. Additional inclusion criteria were age 18–40 years, regular menstrual cycles of 21–42 days, no history of infertility, no major medical problems for which they were currently being treated by a physician (including hypertension and polycystic ovarian syndrome [PCOS]), no known contraindication to aspirin, and no indication for anticoagulant treatment.

During the preconception enrollment visit, participants completed demographic and medical history questionnaires, provided blood and urine samples and had anthropomorphic measures taken. Follow-up continued for up to 6 cycles of attempting pregnancy and throughout pregnancy for those who became pregnant. The institutional review boards at all participating institutions approved the study protocol, and all participants provided informed consent prior to data collection. All study procedures were carried out in accordance to institutional guidelines and in adherence with the principles of the Declaration of Helsinki. The EAGeR trial is registered at ClinicalTrials.gov (no. NCT00467363).

Preconception blood pressure was measured at enrollment by trained study staff with a sphygmomanometer. Cuff size (small, adult or large) was determined by arm circumference. Three sequential blood pressure measures were averaged to produce summary systolic blood pressure (SBP) and DBP measures. Mean arterial pressure (MAP) was calculated from SBP and DBP measures using the following formula: MAP=DBP+(1/3*[SBP-DBP]). Blood pressure measures were also captured during regularly scheduled prenatal care visits at 4, 8, 12, 16, 20, 28 and 36 weeks gestation. We evaluated blood pressure at 4 weeks gestation only, as later measures were scheduled to occur after the majority of losses had taken place. Blood pressure was modeled continuously in units of 10 millimeters of mercury (mmHg).

Pregnancy status was assessed via presence of human chorionic gonadotropin (hCG). Women performed at-home and in-clinic hCG tests at the end of each cycle (Quidel Quickvue, Quidel Corporation, San Diego, CA, sensitive to 25 mIU/ml hCG). In addition, β-hCG was measured in first-morning urines from the last 10 days of the first two menstrual cycles during follow-up and on all end of cycle visits to detect pregnancy (catalogue no. 4221-16, Diagnostic Automation Inc., Calabasas, CA and catalogue no. R1S0011R, BioVendor, Asheville, NC).

Fecundability, the menstrual cycle-specific probability of pregnancy, was assessed as time-to-pregnancy, the number of menstrual cycles from the beginning of follow-up to either positive hCG test or censoring. Of the 431 participants who did not become pregnant, 318 were censored at the end of follow-up and 113 prior to the end of follow-up (median 3, interquartile range [IQR] 1–4 cycles).

Assessment of pregnancy loss included both hCG-detected losses and clinically recognized losses. hCG-detected losses were identified either by a positive urine pregnancy test at the clinic followed by absence of clinical signs of pregnancy, or by testing of beta-hCG in urine

samples collected at home on the last 10 days of each woman's first and second cycle of study participation and on spot urine samples collected at all post-cycle visits. Clinical losses were identified for participants who had a clinically confirmed pregnancy on ultrasound at approximately 6.5 weeks (determined when ultrasound confirmed a gestational sac, molar pregnancy, ectopic pregnancy or blighted ovum), but later experienced a participant- or clinician-observed loss. Live births included births of a living infant, with complete follow-up data on 1088 participants.

At baseline, participants self-reported age, race (white vs. non-white), marital status (married, living as married, other), cigarette smoking (any vs. none), parity (any previous live birth vs. none), time from last pregnancy to enrollment (≤4, 5–8, 9–12, and >12 months), number of prior pregnancy losses (1 vs. 2), and number of cycles attempting pregnancy prior to enrollment. Height and weight at enrollment were used to calculate body mass index (BMI).

Statistical analyses

Descriptive statistics were summarized as frequencies and percents, means and standard deviations (SDs) or medians and IQRs. A total of 97 participants were missing information on number of cycles attempting pregnancy before study entry, 8 were missing blood pressure measures, 14 were missing BMI and 19 were missing time since last pregnancy loss. We addressed missingness through multiple imputation, using chained equations to generate 20 datasets.[18]

Fecundability was assessed with a discrete-time survival model, and accounted for left-truncation (cycles attempting pregnancy prior to enrollment) and right censoring. Right censoring was assumed to be non-informative conditional on all variables included in the model. Pregnancy loss was assessed using log-binomial models, weighted by the inverse of probability of pregnancy to account for exclusion of participants who did not become pregnant. Risk of live birth was assessed using log-binomial models. Models were adjusted for treatment assignment, age, BMI, race, marital status, cigarette smoking, parity and time from last pregnancy loss to enrollment. We additionally investigated the impact of no pregnancy as a competing risk for pregnancy loss and live birth by modeling both the cause specific and sub-distribution hazards for pregnancy loss and live birth.[19] Cause-specific hazards can be interpreted as the instantaneous risk of pregnancy loss and live birth per change in blood pressure, but assume that those with competing risks (eg. not achieving pregnancy) will still experience the event of interest (eg. pregnancy loss). Sub-distribution hazards can similarly be interpreted as the instantaneous risk of pregnancy loss and live birth, but appropriately allow competing events to remove at risk women from the sample.

To further explore the relationship between blood pressure and pregnancy loss, we conducted several secondary analyses. First, we evaluated hypertension following thresholds from the 2017 guidelines from the American College of Cardiology and the American Heart Association[20] (SBP ≥130 or DBP ≥80 mmHg for hypertension stage I and SBP ≥140 or DBP ≥90 for hypertension stage II as compared to normal blood pressure <120 and <80 mmHg). Second, we investigated differences by pregnancy loss type (hCG-detected losses versus clinical losses). Third, we evaluated the association of early pregnancy blood pressure

with clinical loss for comparison to our findings for preconception blood pressure. Finally, because inflammation and platelet activation are pathways through which blood pressure may be associated with reproductive outcomes, we evaluated randomization to low-dose aspirin (LDA) as a potential effect modifier of the association between blood pressure and reproductive outcomes. All analyses were conducted in SAS 9.4 (Cary, NC) and figures were produced in R (Vienna, Austria).

Results

Among the 1228 women enrolled in the EAGeR trial, mean age was 28.7 (SD 4.8) years and 95% were white (Table 1). The majority were married (92%), had at least some college education (86%) and had a household income greater than $40,000/year (67%). Mean BMI was 26.3 (SD 6.5) kg/m^2. All women had experienced a prior loss (67% with one and 33% with two losses) and 53% were parous. At baseline, mean SBP was 111.6 (SD 12.1) mmHg and mean DBP was 72.5 (SD 9.4) mmHg (Figure S1, please see http://hyper.ahajournals.org). Mean MAP was 85.5 (SD 9.6) mmHg. A total of 307 (25.2%) met criteria for hypertension stage I and 53 (4.3%) for hypertension stage II.

Fecundability

A total of 797 (64.9%) participants achieved pregnancy. Mean SBP and DBP were 111.1 (SD 11.8) and 72.1 (SD 9.1) among those who achieved pregnancy and 112.6 (SD 12.8) and 73.2 (SD 9.7) among those who did not achieve pregnancy, respectively. In unadjusted models, higher levels of all blood pressure measures were associated with lower odds of fecundability (fecundability odds ratio [FOR] 0.90, 95% confidence interval [CI] 0.83, 0.98 per 10 mmHg MAP) (Table 2). After adjustment, associations were attenuated (FOR 0.98, 95% CI 0.90, 1.08 per 10 mmHg MAP). Adjusting for all covariates except BMI produced effect estimates similar to unadjusted models (FOR 0.92, 95% CI 0.84, 1.00 per 10 mmHg MAP), suggesting that BMI was a key explanatory factor in the unadjusted association of blood pressure with fecundability. Findings were similar for the group assigned to LDA and placebo (Table 3).

Pregnancy loss

Of the 797 participants who achieved pregnancy, 188 experienced a loss (23.6%), with 55 hCG-detected losses and 133 clinically-recognized losses. Mean SBP and DBP were 112.3 (SD 12.3) and 73.5 (SD 9.2) among those who experienced a loss and 110.7 (SD 11.6) and 71.6 (SD 9.1) among those who had a live birth. In unadjusted models, an increase in all blood pressure measures was associated with a greater risk of pregnancy loss (relative risk [RR] 1.21, 95% CI 1.07, 1.37 per 10 mmHg MAP) (Table 2). After adjustment, the associations remained (RR 1.17, 95% CI 1.02, 1.35 per 10 mmHg MAP). In an alternate competing risks analysis, cause-specific and subdistribution hazards of pregnancy loss were similar to the main findings, with a 10 mmHg increase in MAP associated with a 14% (95% CI 0.96, 1.35) greater risk of pregnancy loss (Table 4).

In a secondary analysis, women with blood pressure levels above the threshold for stage I and stage II hypertension had a 15% (95% CI 0.86, 1.55) and 18% (95% CI 0.65, 2.16)

greater risk of pregnancy loss as compared to women with normal blood pressure. However, as anticipated, small group sizes contributed to imprecise estimates (Table S1, please see http://hyper.ahajournals.org).

DBP and MAP had a similar pattern of association with both hCG-detected and clinical loss (RR 1.14, 95% CI 0.86, 1.52 for hCG-detected and RR 1.20, 95% CI 1.01, 1.42 for clinical loss per 10 mmHg MAP) (Table S2, please see http://hyper.ahajournals.org). We additionally evaluated the association of blood pressure measured in very early pregnancy at a median of 4.4 weeks' gestation (IQR 4.1 to 7.9, range 2.0–20.0 weeks' gestation) with clinical loss. Preconception and very early pregnancy blood pressure were moderately correlated (r=0.49 and r=0.53 for SBP and DBP) and mean change in SBP and DBP from preconception to early pregnancy was 0.45 (SD 11.7) and 1.39 (SD 9.37) mmHg, respectively. Overall, early-pregnancy blood pressure measures showed a similar pattern of association with clinical loss as compared to preconception blood pressure measures (RR 1.18, 95% CI 1.00, 1.38 per 10 mmHg MAP in early pregnancy) (Table S2, please see http://hyper.ahajournals.org).

Finally, we observed a marginally stronger association of preconception DBP and MAP with risk of pregnancy loss in the placebo group (RR 1.27, 95% CI 1.06, 1.53 per 10 mmHg MAP) as compared to the LDA group (RR 1.07, 95% CI 0.88, 1.30 per 10 mmHg MAP) in adjusted analyses (p-interaction=0.08; Table 3).

Live birth

Of the 1,088 participants with complete follow-up, 597 (55.9%) achieved a pregnancy ending in a live birth over the 6 menstrual cycles of observation. In unadjusted models, higher blood pressure measures were associated with lower risk of live birth (RR 0.91, 95% CI 0.86, 0.96 per 10 mmHg MAP) (Table 2). After adjustment, associations were attenuated (RR 0.96, 95% CI 0.90, 1.02 per 10 mmHg MAP). In a secondary competing risks analysis, cause-specific and subdistribution hazard ratios were similar to the main findings, with a 10 mmHg increase in MAP associated with an 8% lower risk of live birth (95% CI 0.84, 1.01 for subdistribution hazard) (Table 4).

We observed a marginally stronger association of preconception DBP and MAP with risk of live birth in the placebo group (RR 0.92, 95% CI 0.84, 1.00 per 10 mmHg MAP) as compared to the LDA group (RR 0.99, 95% CI 0.92, 1.07 per 10 mmHg MAP) in adjusted analyses (p-interaction=0.07; Table 3).

Discussion

The findings from this study are novel in suggesting that both preconception and very early pregnancy blood pressure levels are prospectively associated with risk of pregnancy loss among healthy women with 1–2 prior pregnancy losses. We observed that a 10 mmHg increase in preconception DBP and MAP were associated with a 17% and 18% increase in risk of pregnancy loss, respectively. Findings were consistent across type of pregnancy loss (hCG-detected and clinical losses) and were persistent into very early pregnancy. We observed no clear associations of preconception blood pressure with fecundability after adjustment for BMI, suggesting that pathways related to BMI, which is strongly related to

fecundability,[21] may explain the marginal association of blood pressure with fecundability. These findings suggest that screening and lifestyle interventions targeting maintenance of healthy blood pressure levels among reproductive-aged women may have additional important short-term benefits on reproductive health.

Few prior studies have evaluated the association of preconception hypertension with pregnancy loss. In a prospective cohort of 2,940 women attempting pregnancy in Anhui, China, women with self-reported hypertension during preconception had a greater risk of pregnancy loss (RR 2.27, 95% CI 1.27, 4.04).[15] However, in a matched case-control study among 550 women in Hamadan Province, Iran, a trend was observed between high blood pressure and lower risk of pregnancy loss (odds ratio [OR] 0.42, 95% CI 0.15, 1.16).[16] Prior research has been limited by reliance on health care records or self-reported hypertension, and including only those with diagnosed hypertension. Similar to the study in Anhui, we observed that higher blood pressure was associated with a greater risk of pregnancy loss, although our population was largely normotensive. As hypertension is less common among young adults, with stage II hypertension affecting approximately 11% of women ages 24 to 32,[22] differences in blood pressure at sub-clinical levels may constitute a significant portion of risk related to blood pressure in this group and therefore warrants further exploration. Interestingly, DBP was more strongly associated with pregnancy loss than SBP, a finding similar to research on cardiovascular disease endpoints. For example, the Framingham Heart Study found that DBP is a stronger predictor of coronary heart disease than SBP among adults age 20–49 (hazard ratio [HR] 1.34, 95% CI 1.18, 1.51 DBP and HR 1.14, 95% CI 1.06, 1.24 SBP per 10 mmHg).[9] Our findings suggest that incrementally higher DBP among young women may be additionally associated with more proximal pathophysiologic processes contributing to risk of pregnancy loss.

Although the etiology of pregnancy loss is often unknown, factors related to key reproductive processes, including ovulation and quality of the oocyte, implantation and decidualization of the endometrium, and vascularization of the placenta, may alter risk of pregnancy loss.[23] Our observation of the association of higher blood pressure with higher risk of pregnancy loss among women with a history of loss would support the idea that one or more of these processes may be adversely impacted by higher blood pressure, or that the biochemical milieu associated with higher blood pressure contributes to harming these processes. Indeed, the inflammation, oxidative stress, and endothelial dysfunction that partly underlie development of essential hypertension[24] have also been implicated in pregnancy loss.[11–14] Additionally, thrombotic factors such as enhanced platelet activation associated with increased production of pro-inflammatory cytokines and endothelial dysfunction in essential hypertension[25] have been found to be greater among women with pregnancy loss, suggesting that an abnormal thrombotic response may be associated with risk of pregnancy loss.[26] Pregnancy loss and other adverse reproductive outcomes may serve as sensitive markers of early-stage progression towards cardiometabolic disease in young adults, and further elucidating the cardiometabolic risk factors for pregnancy loss may help identify early intervention strategies, such as regular physical activity[27] and following a Dietary Approaches to Stop Hypertension [DASH]-type diet,[28] that may be dually associated with a reduction in risk of adverse reproductive outcomes and later development of cardiometabolic disease. Additional research is needed among women with clinically-defined hypertension

and at risk for pregnancy loss to determine whether antihypertensive pharmacologic interventions may be safe and effective in preventing recurrent pregnancy loss.

We did not have sufficient data to evaluate the association of blood pressure with pregnancy loss by type of loss, including loss due to aneuploidy, although it is likely blood pressure may differentially effect losses due to different underlying biologic mechanisms.[29] This remains an important point for further research in understanding the mechanisms and risk factors for differing causes of pregnancy loss; however, the estimates for overall loss observed in our study have utility in clinical practice where loss type is frequently unobserved.

Our study has several strengths and limitations. First, the EAGeR trial is unique in having preconception measures of blood pressure as well as a gold-standard prospective assessment of fecundability and pregnancy loss, including hCG-detected losses. However, although our study is prospective, we cannot extrapolate whether the association between DBP and pregnancy loss is causal and/or due to common causes. Additionally, as the study is a prospective cohort, differential loss to follow-up is a potential source of bias; however, the similarity of findings between the secondary hazard analyses and our main analyses suggest that this is unlikely to be a major concern. A unique feature of this study was the randomization to low-dose aspirin. Our observation that the associations between preconception blood pressure and both pregnancy loss and live birth were partially attenuated in the group assigned to LDA may suggest that a pathway responsive to the anti-coagulant and anti-inflammatory properties of aspirin partly underlies the relationship between blood pressure and pregnancy loss. However, because we were not adequately powered to observe interactions with LDA, we cannot make unequivocal conclusions. That the associations of DBP and MAP with pregnancy loss and live birth are particularly strong in the placebo group does support the overall findings for an association of preconception blood pressure with pregnancy loss in the general population. However, because our cohort had a history of 1–2 prior pregnancy losses, findings should be generalized with caution to those with no history of pregnancy loss. Additionally, our study population was largely white, were mostly moderate- to high-income and had no preexisting major medical conditions, and future research is needed to confirm whether these findings are generalizable across race/ethnicity and socioeconomic status, and to those with preexisting medical complications such as hypertension and polycystic ovary syndrome.

Perspectives

While we observed that preconception DBP and MAP were associated with elevated risk of pregnancy loss, our findings do not establish causality and additional research is needed exploring the physiology underlying this association to suggest potential routes for intervention. Our findings do suggest that preconception blood pressure is a marker for increased risk of pregnancy loss independent of age, body mass index and other risk factors, and adds to the evidence base suggesting early markers of cardiometabolic risk may be associated with adverse reproductive events. Our findings are particularly important as they describe risk among women with a history of pregnancy loss, who are at higher risk of experiencing a future loss[30] and for whom preventing pregnancy loss is an increased

concern. Future research is needed to confirm these findings and explore the potential underlying etiologies of this relationship, with the goal of identifying physiologic pathways amenable to intervention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty and Significance

1) What Is New

- Elevations in preconception blood pressure predicted risk of pregnancy loss among healthy young women with a history of pregnancy loss
- No significant associations were found for preconception blood pressure and fecundability or probability of live birth

2) What is Relevant?

- Although additional research is needed, these findings suggest that intervening on elevations in blood pressure during preconception may reduce risk of pregnancy loss, a particular concern among women with a history of pregnancy loss
- Behavioral interventions, such as increasing physical activity and following a DASH-type diet, may have a dual benefit among reproductive-aged women in both favorably impacting reproductive health and reducing future risk of cardiovascular disease

3) Summary

Our findings among healthy women with a history of pregnancy loss currently attempting pregnancy suggest that increases in preconception diastolic blood pressure and mean arterial pressure are associated with a greater risk of pregnancy loss. This elevation in risk of pregnancy loss was observed in a largely normotensive cohort, and adds evidence to the importance of maintaining healthy blood pressure levels during early adulthood.

Table 1

Study participant characteristics at baseline: EAGeR Trial (n=1228)

Characteristic	No. (%)
Age (years; mean, SD)	28.7 (4.8)
Race/ethnicity	
Non-Latina white	1162 (94.6)
Other	66 (5.4)
Education	
<high school	25 (2.0)
High school	145 (11.8)
>high school	1057 (86.2)
Income	
<$40,000	406 (33.1)
$40,000–<$100,000	330 (26.9)
≥$100,000	491 (40.0)
Marital status	
Married	1124 (91.5)
Live with partner	74 (6.0)
Other	30 (2.4)
Smoking	
Yes	57 (4.6)
No	1171 (95.4)
BMI (kg/m^2; mean, SD)	26.3 (6.5)
Parous	
Yes	651 (53.0)
No	577 (47.0)
Number of previous losses	
1	825 (67.2)
2	403 (32.8)
Time from last pregnancy to loss	
<5 months	647 (53.5)
5–8 months	214 (17.7)
9–<12 months	107 (8.9)
≥12 months	241 (19.9)
Treatment assignment	
Low-dose aspirin	615 (50.1)
Placebo	613 (49.9)

Table 2

Preconception blood pressure and fecundability, pregnancy loss and live birth

Variable	Fecundability	Pregnancy loss*	Live birth
	FOR (95% CI)	RR (95% CI)	RR (95% CI)
Systolic blood pressure (10 mmHg)			
Unadjusted	**0.93 (0.87–0.99)**	**1.11 (1.01–1.22)**	**0.95 (0.91–0.99)**
Adjusted†	0.99 (0.92–1.06)	1.08 (0.97–1.20)	0.98 (0.93–1.02)
Diastolic blood pressure (10 mmHg)			
Unadjusted	**0.91 (0.84–0.99)**	**1.22 (1.08–1.39)**	**0.91 (0.86–0.96)**
Adjusted†	0.99 (0.90–1.08)	**1.18 (1.03–1.36)**	0.96 (0.90–1.01)
Mean arterial pressure (10 mmHg)			
Unadjusted	**0.90 (0.83–0.98)**	**1.21 (1.07–1.37)**	**0.91 (0.86–0.96)**
Adjusted†	0.98 (0.90–1.08)	**1.17 (1.02–1.35)**	0.96 (0.90–1.02)

*Weighted by probability of pregnancy (predictors: systolic blood pressure, diastolic blood pressure, study group, age, BMI, race [white vs. non-white], marital status [married, living as married, other], cigarette smoking, parity, study site, number of prior losses and time from last pregnancy loss to enrollment [≤4 months, 5–8 months, 9–12 months, >12 months])

†Adjusted for treatment assignment, age, BMI, race (white vs. non-white), marital status (married, living as married, other), cigarette smoking, parity and time from last pregnancy loss to enrollment (≤4 months, 5–8 months, 9–12 months, >12 months)

Table 3

Preconception blood pressure and fecundability, pregnancy loss and live birth by assignment to placebo or low-dose aspirin

Variable	Fecundability		Pregnancy loss*		Live birth	
	Placebo group	LDA group	Placebo group	LDA group	Placebo group	LDA group
	FOR (95% CI)	FOR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Systolic blood pressure (10 mmHg)						
Unadjusted	0.97 (0.89–1.07)	**0.89 (0.81–0.97)**	**1.13 (0.99–1.30)**	1.09 (0.94–1.25)	0.95 (0.89–1.02)	**0.94 (0.88–1.00)**
Adjusted†	1.04 (0.94–1.15)	0.94 (0.86–1.04)	1.10 (0.95–1.28)	1.05 (0.91–1.22)	0.98 (0.92–1.05)	0.97 (0.92–1.03)
Diastolic blood pressure (10 mmHg)						
Unadjusted	0.89 (0.79–1.00)	0.92 (0.82–1.04)	**1.37 (1.16–1.61)**	1.06 (0.87–1.28)‖	**0.85 (0.79–0.92)**	0.96 (0.89–1.04)‖
Adjusted†	0.97 (0.86–1.10)	1.00 (0.88–1.14)	**1.31 (1.09–1.57)**	1.05 (0.86–1.28)≠	**0.89 (0.82–0.97)**	1.01 (0.94–1.10)‖
Mean arterial pressure (10 mmHg)						
Unadjusted	0.92 (0.82–1.03)	0.89 (0.79–1.00)	**1.31 (1.12–1.55)**	1.09 (0.90–1.32)	**0.88 (0.81–0.95)**	0.94 (0.88–1.02)
Adjusted†	1.00 (0.88–1.13)	0.97 (0.85–1.10)	**1.27 (1.06–1.53)**	1.07 (0.88–1.30)	**0.92 (0.84–1.00)**	0.99 (0.92–1.07)

*Weighted by probability of pregnancy (predictors: systolic blood pressure, diastolic blood pressure, study group, age, BMI, race [white vs. non-white], marital status [married, living as married, other], cigarette smoking, parity, study site, number of prior losses and time from last pregnancy loss to enrollment [≤4 months, 5–8 months, 9–12 months, >12 months])

†Adjusted for treatment assignment, age, BMI, race (white vs. non-white), marital status (married, living as married, other), cigarette smoking, parity and time from last pregnancy loss to enrollment (≤4 months, 5–8 months, 9–12 months, >12 months)

≠Interaction $P<0.1$

‖Interaction $P<0.05$

Table 4

Preconception blood pressure and pregnancy loss and live birth; Competing risks analysis

Variable	Cause specific hazards		Subdistribution hazards	
	Pregnancy Loss	Live birth	Pregnancy Loss	Live birth
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Systolic blood pressure (10 mmHg)				
Unadjusted	1.08 (0.96–1.21)	0.98 (0.92–1.05)	1.07 (0.95–1.20)	**0.91 (0.86–0.98)**
Adjusted *	1.09 (0.95–1.24)	0.99 (0.92–1.07)	1.08 (0.95–1.24)	0.95 (0.88–1.02)
Diastolic blood pressure (10 mmHg)				
Unadjusted	1.17 (1.00–1.36)	0.96 (0.88–1.04)	1.15 (0.99–1.34)	**0.86 (0.79–0.94)**
Adjusted *	1.16 (0.98–1.37)	0.96 (0.88–1.06)	1.14 (0.97–1.35)	0.93 (0.84–1.02)
Mean arterial pressure (10 mmHg)				
Unadjusted	1.15 (0.99–1.34)	0.96 (0.89–1.05)	1.13 (0.97–1.32)	**0.87 (0.80–0.94)**
Adjusted *	1.15 (0.98–1.36)	0.97 (0.88–1.07)	1.14 (0.96–1.35)	0.92 (0.84–1.01)

* Adjusted for treatment assignment, age, BMI, race (white vs. non-white), marital status (married, living as married, other), cigarette smoking, parity and time from last pregnancy loss to enrollment (≤4 months, 5–8 months, 9–12 months, >12 months)