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Cardiovascular disease family history and risk of pregnancy loss

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ABSTRACT

Purpose: To determine whether family history of cardiovascular disease (CVD) is a risk factor for pregnancy loss, given potential shared etiology, including vascular mechanisms involved in reproduction and placentation.
Methods: In a prospective study, first-degree family histories were self-reported before pregnancy among women with 1–2 previous losses. Women were followed for up to 6 menstrual cycles while attempting pregnancy and through pregnancy. Pregnancies were ascertained by urinary human chorionic gonadotropin and confirmed by ultrasound. Risk ratios and 95% confidence intervals for pregnancy loss were estimated using weighted Poisson regression models with robust standard errors adjusted for covariates including prepregnancy body mass index and sociodemographics.
Results: Of 1228 women enrolled, 742 had a clinically confirmed pregnancy, and of these, 18% experienced a clinical pregnancy loss. Forty six percent of women reported family history of CVD, diabetes, hypertension, or hypercholesterolemia/dyslipidemia. Family history of CVD was not associated with the risk of pregnancy loss overall (1.01; 95% confidence interval: 0.64, 1.59) or among women with 2 previous losses (1.05; 0.51, 2.17). Family history of hypertension was also not associated with pregnancy loss (0.98; 0.65, 1.46).
Conclusions: Family history of CVD is not providing additional information helpful in determining the risk of subsequent pregnancy loss in an at-risk group.

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Introduction

Pregnancy loss is common, with estimates typically ranging from about 15% to 31% [1–5]. Many of these losses are due to problems with implantation and may not be clinically apparent, and the causes of pregnancy loss are myriad and often poorly understood. Pregnancy loss may be due to genetic abnormalities, uterine malformations, hormonal abnormalities, immunologic disorders, and other causes [6], and in many cases, the etiology is never determined. In fact, fifty to seventy-five percent of recurrent losses are idiopathic [7]. Pregnancy loss also has significant emotional impacts on families, and women are often at increased risk of depression and anxiety after a loss [8].

Pregnancy loss has been linked to cardiovascular disease (CVD) [9–14], suggesting that there may be commonalities between the two conditions such as regulation of vascular processes that are also important to placentation and placental development [15]. Family history of CVD captures the genetic contribution of CVD risk including vascular pathways that could be shared with pregnancy loss. However, few studies on pregnancy loss have prospectively captured extensive family history information [16,17]. Although all pregnant women may be interested in their risk of pregnancy loss, women who experience a previous loss may more likely inquire of their clinical provider about the subsequent risk of loss, given its adverse psychological impact, than women who have had successful pregnancies or never previously pregnant [8,18,19]. Our objective, therefore, was to evaluate how family history of CVD including parental history of hypertension is associated with pregnancy loss in a population of women who had experienced previous pregnancy losses.

The authors have no conflicts of interest to disclose.

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Methods

Study design

This was a prospective analysis of observational data from the Effects of Aspirin in Gestation and Reproduction trial which enrolled 1228 women from four university medical centers in the United States (2007–2011). Study design and participant enrollment are described in detail elsewhere including ClinicalTrials.gov (#NCT00467363) [20,21]. Briefly, women with a history of pregnancy loss were randomized to daily low-dose aspirin to evaluate reproductive outcomes. Participants were 18–40 years old, had one or two documented previous pregnancy losses, up to two prior live births, had regular menstrual cycles (i.e., 21–42 days in length), and were attempting pregnancy without the use of fertility treatment. Women with a known history of infertility treatment or presence of major medical disorders were excluded. The institutional review board at each study site and data coordinating center approved the trial protocol. All participants provided written informed consent before enrolling.

Pregnancy loss assessment

Participants were followed for up to six menstrual cycles while attempting pregnancy or throughout their pregnancy for those who became pregnant. The primary outcome of interest was clinical pregnancy loss ($n = 133$). Pregnancy loss was determined by objective criteria as previously described [22,23]. Pregnancy status was determined using daily first-morning urine collection and spot urine clinic pregnancy tests at monthly visits. A human chorionic gonadotropin (hCG)-detected pregnancy was determined from a positive result using a urine pregnancy test (Quidel QuickVue, Quidel Corporation). Free β-hCG was also measured in spot urine samples, collected the last 10 days of each woman's first and second study cycle of participation, to enable a more sensitive detection of very early pregnancy than possible with conventional urine pregnancy testing (catalog No. 4221-16, Diagnostic Automation Inc.; catalog no. RIS0011R, BioVendor). Clinically confirmed pregnancies were identified by either intrauterine gestational sac on ultrasound at 6–7 weeks' gestation, clinical recording of fetal heart tones, or a later-stage confirmation of pregnancy.

Both implantation failures and clinically recognized pregnancy loss were captured. The current analysis investigated clinical losses primarily and all losses secondarily. Implantation failures were defined as either (1) positive urine hCG pregnancy test at home or the clinical site followed by absence of signs of clinical pregnancy at the study ultrasound with or without missed menses or (2) positive hCG from the batched augmented urine testing described previously followed by the absence of a positive pregnancy test at home or in the clinic [22]. Clinically recognized pregnancy losses were defined as a pregnancy loss after ultrasound confirmation and included ectopic pregnancies; pre-embryonic, embryonic, and fetal losses; and stillbirths.

Family history

Family history information was self-reported at baseline by questionnaire. Participants first completed a table on the vital status of all first-degree family members, including causes of death for those who have passed away (i.e., heart disease, cancer, cerebrovascular disease, chronic lower respiratory disease, diabetes, influenza/pneumonia, Alzheimer's, trauma, kidney disease, septicemia or other, specify). They were also asked whether their first-degree family members had been diagnosed with cardiovascular conditions and to specify the type of condition in free text such as heart attack, myocardial infarction, coronary artery disease, coronary heart disease, congestive heart failure, angina, deep vein thrombosis, stroke, aneurysm, ischemic heart disease, or related procedures (e.g., stents, bypass, pacemaker) and provide the age at diagnosis. The participant was also asked to report family history of diabetes, hypertension, and hypercholesterolemia. Family history of CVD was examined independently and in combination with family history of hypertension, hypercholesterolemia, and diabetes. Premature CVD was defined as diagnoses/events before 65 years of age for female relatives and 55 years of age for male relatives. As participants do not have the same number of siblings, parental history was also examined separately. In addition, family history of pregnancy loss among first-degree relatives included mother, sister, half-sister, and daughters, and family history of pregnancy loss expanded to second-degree relatives additionally included both grandmothers and aunts.

Covariates

At a baseline visit before randomization, participants completed questionnaires on demographics, lifestyle habits, medical and reproductive history, and family medical history. Height and weight were measured, and body mass index (BMI, kg/m^2) was calculated. Total cholesterol was measured using the Roche COBAS 6000 chemistry analyzer (Roche Diagnostic, Indianapolis, IN) using a cholesterol oxidase enzymatic determination using serum samples collected at baseline.

Statistical analysis

Descriptive statistics were presented to summarize characteristics between women with family history of CVD/hypertension and without. Fisher's exact test and Student's *t*-test were used to test differences between groups. As pregnancy loss is contingent on becoming pregnant, inverse probability weights were calculated based on factors associated with pregnancy, including maternal age, race, prepregnancy BMI, income, and education.

Weighted Poisson regression models [24] with robust standard errors were used to estimate risk ratios and 95% confidence intervals for clinical pregnancy loss after adjusting for maternal age and race and in a separate model, additionally prepregnancy BMI, income, education, total cholesterol, C-reactive protein, insulin, and systolic blood pressure. Although these are potential mediators of the association between family history and pregnancy loss (i.e., CRP, SBP), we *a priori* wanted to evaluate this additional model to see if it would have prognostic value against typically collected clinical information. All analyses were conducted for the overall study sample and then stratified by a number of prior pregnancy losses and parity. This stratification was to examine whether having a successful previous pregnancy or conversely experiencing many previous losses would differ in its association with CVD family history. We also repeated our analyses among women ($n = 797$) with any pregnancy loss even if the loss occurred before clinical confirmation and were identified by hCG or home testing alone ($n = 55$). Missing values for covariates were imputed by generating 25 imputed data sets using the Multiple Imputation by Chained Equations algorithm [25] and then aggregated by using the standard combination rules for multiple imputation. Post hoc power calculations were carried out to assess the strength of associations that can be ruled out as compared with typical uses of family history information for traditional CVD risk. Analyses were conducted using SAS version 9.4 (SAS Ins. Inc. Cary, NC).

Results

Seven hundred thirty-two women had a clinically confirmed pregnancy. Among them, 127 (17%) experienced a clinical

pregnancy loss. Of these losses, four (3%) were after 20 weeks. The study participants were predominantly white (97%) and over 50% had annual incomes above $75,000 (Table 1). Forty two percent of the women were nulliparous and all women experienced 1 or 2 previous losses. Thirty three percent suffered more than 1 previous loss and most women (84%) experienced a recent loss (i.e., within a year). Approximately 16% of women reported a family history of CVD and 24%, a family history of hypertension. Family history of CVD versus no family history of CVD was associated with higher levels of total cholesterol (172.0 ± 28.5 vs. 164.7 ± 28.4 mg per dL, $P = .01$).

Familial history of CVD was not associated with clinical pregnancy loss in unadjusted or adjusted models (Table 2). When analyses were repeated with all pregnancy losses including nonclinical implantation failures (188 losses of 797 hCG pregnancies), findings remained similar. In addition, family history of premature CVD, diabetes, hypertension, or cholesterol was not associated with pregnancy loss. The combination of any family history of CVD-related conditions (i.e., heart disease, diabetes, hypertension, or cholesterol) was also not associated with pregnancy loss (risk ratio 1.06; 0.75, 1.50). We performed secondary analyses to examine whether associations differed among women with 2 losses as well as women with no previous live births; results were similar in these subgroups. Further stratifying by family history of pregnancy loss also did not alter results (data not shown).

Given the proportion of pregnancy loss among women without a family history of CVD being 0.15 (=94/605), we had 80% power to detect associations 1.75 or greater, assuming type 1 error of 0.05. Hence, we could not rule out weaker associations.

Discussion

Main findings

Despite the biological plausibility that a familial history of CVD and related comorbidities could be associated with risk of pregnancy loss, we found no evidence of a strong relationship among women who had experienced at least one previous loss in the past. Findings were not altered after stratifying by factors including number of previous losses, primary versus secondary losses, and family history of pregnancy loss, among others. Hence, the link between the two conditions remains uncertain and there was no prognostic value of learning a woman's family history of CVD.

Family history information is routinely collected in medical practice and serves as a convenient method to assess genetic risk. The National Heart Lung and Blood Institute Family Heart Study previously demonstrated that parental coronary heart disease and hypertension can be accurately captured by proxy reports with sensitivities of 85% and 76%, respectively, and specificities above 90% when compared with parental self-report [26]. Although family history also captures inherited risk due to shared lifestyle habits and behaviors, it still represents a good measure of genetic risk. In fact, the predictive ability of family history information for heart disease rivals information from directly measured genes, and genetic risk scores derived from Genome Wide Association Study findings were unable to outperform family history in predication of coronary heart disease [27]. In addition, family history remains associated with subclinical measures of atherosclerosis even after adjustment for personal lifestyle risk factors [28,29]. However,

Table 1
Baseline characteristics by family history of cardiovascular disease

	Total*		Family history of CVD			
			No		Yes	
	N	%/SD	*N*	%/SD	*N*	%/SD
Total	797	(100.0)	669	(100.0)	128	(100.0)
White	769	(96.5)	645	(96.4)	124	(96.9)
Beyond high school education	707	(88.7)	597	(89.2)	110	(85.9)
Annual household income ($US)						
Less than $19,999	54	(6.8)	47	(7.0)	7	(5.5)
$20,000–$39,999	187	(23.5)	163	(24.4)	24	(18.8)
$40,000–$74,999	116	(14.6)	94	(14.1)	22	94
$75,000–$99,999	114	(14.3)	86	(12.9)	28	(21.9)
v$100,000 or over	326	(40.9)	279	(41.7)	47	(36.7)
Number of previous pregnancy losses						
1	524	(65.7)	289	(43.2)	52	(40.6)
2	273	(34.3)	230	(34.4)	43	(33.6)
Nulliparous	341	(42.8)	289	(43.2)	52	(40.6)
Any pregnancy loss	188	(23.6)	154	(23.0)	34	(26.6)
Clinical loss	133	(16.7)	110	(16.4)	23	(18.0)
<1 y from last loss to randomization	662	(83.1)	557	(83.3)	105	(82.0)
Gestational age of last pregnancy loss ≥ 20 wk' gestation	19	(2.4)	16	(2.4)	3	(2.3)
Randomized to treatment (LDA)	412	(51.7)	345	(51.6)	67	(52.3)
Smoking in past year	22	(3.0)	17	(2.8)	5	(4.3)
Family history of:						
CVD	128	(16.1)	0	0	128	(100.0)
Premature CVD	85	(10.7)	0	0	85	(66.4)
Diabetes	133	(16.7)	87	(13.0)	46	(35.9)
Hypertension	188	(23.6)	120	(17.9)	68	(53.1)
Hypercholesterolemia	165	(20.7)	124	(18.5)	41	(32.0)
Family history of any of the above	379	(47.6)	251	(37.5)	128	(100.0)
Pregnancy loss	302	(37.9)	254	(38.0)	48	(37.5)
Maternal age, y	28.7	(4.6)	28.3	(4.5)	30.5	(4.7)
Body mass index, kg/m^2	25.5	(6.1)	25.4	(5.9)	26.4	(7.5)
Total Cholesterol (mg/dL)	165.9	(28.5)	164.7	(28.4)	172.0	(28.5)
C-reactive protein (mg/L)	2.4	(3.9)	2.3	(3.9)	2.7	(4.2)

* Information was missing for BMI ($n = 11$), time from last loss to randomization ($n = 14$), gestational age of last pregnancy loss ($n = 99$). In addition, information was missing for total cholesterol ($n = 12$) and C-reactive protein ($n = 12$).

Table 2
Association between family history and risk of clinical pregnancy loss in the EAGeR trial

	N (losses)	Unadjusted	Age, race adjusted	Fully adjusted*
		RR (95% CI)	RR (95% CI)	RR (95% CI)
Clinical pregnancy loss	742 (133)			
CVD	117 (23)	1.08 (0.69, 1.70)	1.01 (0.64, 1.59)	1.01 (0.64, 1.59)
Premature CVD	79 (11)	0.73 (0.40, 1.35)	0.70 (0.38, 1.30)	0.70 (0.38, 1.30)
Diabetes	123 (20)	0.91 (0.57, 1.46)	0.87 (0.54, 1.40)	0.87 (0.54, 1.40)
Hypertension	169 (32)	1.06 (0.71, 1.57)	0.98 (0.65, 1.46)	0.98 (0.65, 1.46)
Hypercholesterolemia	151 (23)	0.78 (0.49, 1.23)	0.75 (0.47, 1.19)	0.75 (0.47, 1.19)
Any of the above	350 (68)	1.14 (0.81, 1.59)	1.06 (0.75, 1.49)	1.06 (0.75, 1.50)
2 Prior losses	252 (51)			
CVD	40 (9)	1.10 (0.54, 2.24)	1.05 (0.51, 2.16)	1.05 (0.51, 2.17)
Premature CVD	25 (5)	0.88 (0.34, 2.25)	0.86 (0.34, 2.21)	0.86 (0.33, 2.21)
Diabetes	46 (6)	0.64 (0.28, 1.44)	0.63 (0.28, 1.44)	0.63 (0.28, 1.44)
Hypertension	60 (10)	0.84 (0.44, 1.61)	0.75 (0.39, 1.47)	0.74 (0.38, 1.47)
Hypercholesterolemia	49 (9)	0.87 (0.42, 1.78)	0.83 (0.40, 1.72)	0.82 (0.40, 1.72)
Any of the above	118 (24)	1.00 (0.59, 1.69)	0.95 (0.56, 1.63)	0.95 (0.55, 1.65)
Nulliparous	313 (62)			
CVD	45 (12)	1.28 (0.68, 2.42)	1.36 (0.70, 2.65)	1.33 (0.67, 2.61)
Premature CVD	29 (5)	0.82 (0.33, 2.04)	0.84 (0.33, 2.11)	0.80 (0.32, 2.04)
Diabetes	47 (8)	0.78 (0.36, 1.67)	0.77 (0.36, 1.65)	0.77 (0.36, 1.66)
Hypertension	66 (13)	0.96 (0.53, 1.74)	0.95 (0.51, 1.76)	0.95 (0.51, 1.76)
Hypercholesterolemia	77 (12)	0.68 (0.36, 1.29)	0.68 (0.36, 1.31)	0.68 (0.36, 1.30)
Any of the above	147 (30)	0.99 (0.60, 1.61)	0.98 (0.59, 1.63)	0.98 (0.59, 1.62)
All pregnancy losses*	797 (188)			
CVD	128 (34)	1.28 (0.68, 2.42)	1.36 (0.70, 2.65)	1.33 (0.67, 2.61)
Premature CVD	85 (17)	0.82 (0.33, 2.04)	0.84 (0.33, 2.11)	0.80 (0.32, 2.04)
Diabetes	133 (30)	0.78 (0.36, 1.67)	0.77 (0.36, 1.65)	0.77 (0.36, 1.66)
Hypertension	188 (51)	0.96 (0.53, 1.74)	0.95 (0.51, 1.76)	0.95 (0.51, 1.76)
Hypercholesterolemia	165 (37)	1.00 (0.55, 1.82)	1.01 (0.55, 1.87)	1.01 (0.55, 1.87)
Any of the above	379 (97)	0.68 (0.36, 1.29)	0.68 (0.36, 1.31)	0.68 (0.36, 1.30)

* Adjustment for age, race (categorical), BMI categories, income, education, total cholesterol, C-reactive protein, insulin, and systolic blood pressure.

given the age of our participants, family histories may have not been fully realized (i.e., first-degree relatives were still too young to have events because of late age of onset of CVD) and misclassification may have impacted our results.

Two previous retrospective studies using large registry data found that parents of women with previous pregnancy loss are at increased risk of CVD [16,17]. In a Danish study of over 1 million parents, the miscarriage rate of daughters was weakly associated with greater risk of parental CVD events (HR 1.15; 1.09–1.21 for having 3 or more previous miscarriages among daughters) [17]. In a Scottish study, the risk was slightly higher with parents of women who had two miscarriages before their first birth having elevated risk of ischemic heart disease (adjusted HR 1.29; 1.08–1.55) and an even higher risk for parents of women with 3 or more losses (adjusted HR 1.53; 1.11–2.11) [16]. Our analysis using prospective data, however, answers a slightly different question. As the previous studies linked data over time, the parental events occurred after the pregnancy loss suffered by their daughters. Hence, they did not evaluate the usefulness of prospective information on parental CVD risk as a proxy for genetic risk. Most likely, both having few events in young age and weak associations may explain our null findings. In addition, index event bias [30] cannot be ruled out as a reason for null findings as our reference group of women who experienced a previous pregnancy loss may already have elevated family history in comparison to parous women with no history of pregnancy loss.

However, the usefulness of genetic information for predicting pregnancy loss remains of interest as family history information could be useful in prognostic settings against other clinical factors, which we included in our models despite their potential as intermediates (i.e., cholesterol, CRP, and SBP). Genetic studies of pregnancy loss have the added complexity of involving three gene pools; the mother, the father, and the embryo [31]. As we only captured family history from women, this may only represent one part of the picture. A meta-analysis of 428 case-control studies showed that maternal genes related to CVD have been previously implicated in reoccurring pregnancy loss (defined in different studies as ranging from 2 or 3 previous losses), including those involved in pathways of angiogenesis, coagulation, and vascular function [31]. Other genes linked to the immune response and metabolism were also identified [31]. These observations were restricted to genes reproduced across different studies although most genes identified were only found in single studies. Despite the large number of investigations, the authors concluded that none of the genes identified were that strongly credibly linked to pregnancy loss, given the heterogeneity between studies beginning with the selection of cases and controls [31].

In a previous study, 48% of women ($n = 26$) with unexplained recurrent pregnancy loss had a family history of CVD compared with 24% of women with previous normal pregnancy ($n = 34$) [32]. They noted this difference was not significant because of insufficient power [32], but our larger study also did not identify a significant association. Typically, family history is associated with 2–5 times increased risk because of shared genetics and environmental influences [33], hence its clinical utility in medical practice. Our analysis rules out such strong associations as even women who had two previous losses only had a slightly higher prevalence of family history of CVD or hypertension (~3% difference, Table 1). Although we could not rule out weaker associations, more evidence from the previous investigation suggests there may not be a solid link. After evaluating cardiovascular function among women with recurrent pregnancy loss, they found no differences in cardiac output, blood pressure, and other cardiovascular measures [32]. On the other hand, another small study found increased endothelial dysfunction among 29 women with recurrent pregnancy loss compared with 22 women with previous healthy pregnancies by measures of brachial artery reactivity and biochemical measures (e.g., VEGF) [34]. Taken together, the link between CVD risk and pregnancy loss remains unclear.

Our study included a comprehensive family history assessment with prospective follow-up to assess very early losses. All women in our study experienced at least one pregnancy loss. Potentially, family history could make a stronger difference in prediction if there was a comparison group of women with no history of losses and known previous live birth (i.e., the lowest risk group). However, such a comparison might not be the most clinically useful, given the rarity of recurrent pregnancy loss as defined as having 3 or more consecutive losses (1% couples [31]), in the general population. Rather, most couples would want to know after having a single previous loss whether they may have a higher risk of a second or third loss. Nevertheless, participants were predominantly white (95%) and findings may not be generalizable to other races. A larger sample size might have been able to detect any weaker associations. Strengths of our investigation included a comprehensive maternal family history assessment and prospectively ascertained pregnancies with careful assessment of early losses.

Conclusion

Family history of CVD was not associated with a prospective risk of pregnancy loss in a cohort of women with prior pregnancy loss. As we could not rule out such associations for women who never previously had a pregnancy loss, studies capturing incident losses in the future may remain informative.

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