Adverse Pregnancy Outcomes Are Associated with Reduced Coronary Flow Reserve in Women With Signs and Symptoms of Ischemia Without Obstructive Coronary Artery Disease: A Report from the Women's Ischemia Syndrome Evaluation-Coronary Vascular Dysfunction Study

Ki Park, MD,[1,*] Odayme Quesada, MD,[2,*] Galen Cook-Wiens, MS,[3] Janet Wei, MD,[2] Margo Minissian, PhD,[2] Eileen M. Handberg, PhD,[1] C. Noel Bairey Merz, MD, FAHA, FACC,[2] and Carl J. Pepine, MD[1]

Abstract

Background: We assessed history of adverse pregnancy outcomes (APOs) and coronary microvascular dysfunction (CMD) in the Women's Ischemia Syndrome Evaluation—Coronary Vascular Dysfunction (WISE-CVD) cohort of women with signs and symptoms of ischemia without obstructive coronary artery disease (CAD). We hypothesized that women with CMD with symptoms and signs of ischemia, without obstructive CAD, are more likely to have a history of APO.

Materials and Methods: WISE-CVD recruited women with suspected ischemia found to have no obstructive CAD ($n = 324$). A subset of these women underwent coronary reactivity testing, including coronary flow reserve (CFR) ($n = 185$). Relationship between history of any APO and CMD was assessed by multivariable linear regression analyses. APOs included any of the following: hypertension during pregnancy, preeclampsia, eclampsia, gestational diabetes, or intrauterine growth restriction (low-birth-weight child).

Results: Overall, 79/324 (24%) women reported at least one APO. Women with APOs were younger (52 vs. 56 years, $p = 0.001$), were more likely obese (body mass index 32 vs. 29 kg/m^2, $p = 0.004$), and had a history of hypertension (56% vs 36%, $p = 0.002$), but otherwise had no additional differences in cardiac risk variables versus women without APOs. Among the subgroup who underwent invasive CFR testing ($n = 185$), those with an APO had lower CFR (2.53 vs. 2.76, $p = 0.016$) versus those without APO.

Conclusions: History of APOs in women with signs and symptoms of ischemia without obstructive CAD is associated with lower CFR indicative of CMD. Whether common pathways involving diffuse microvascular dysfunction may account for this suggested association remains unclear. Further investigation is needed to expand on these exploratory findings.

Keywords: hypertension, pregnancy, cardiovascular disease prevention, coronary flow reserve

Introduction

CARDIOVASCULAR DISEASE REMAINS the leading cause of death in women in the United States. Although some progress has been made in advancement of symptom recog-nition and timely treatment of cardiac symptoms in women, recognition of unique nontraditional cardiovascular risk factors has been lagging. In particular, there is a growing degree of evidence that women who have suffered adverse pregnancy outcomes (APOs) such as preeclampsia and low

---

[1]Division of Cardiology, Department of Medicine, University of Florida, Gainesville, Florida.
[2]Barbra Streisand Women's Heart Center, Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California.
[3]Biostatistics and Bioinformatics Core, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, California.
*These authors contributed equally to this article.

birth weight are at an elevated risk for adverse cardiovascular outcomes later in life.[1] However, the specific mechanisms for this increased risk remain unclear. Abnormalities in vascular function, which may manifest early within the placenta during pregnancy (or perhaps even before implantation), may play a role. Whether a history of an APO is associated with abnormalities in coronary vascular function is unknown. We assessed history of APOs and coronary microvascular dysfunction (CMD) in the Women's Ischemia Syndrome Evaluation—Coronary Vascular Dysfunction (WISE-CVD) cohort of women with signs and symptoms of ischemia without obstructive coronary artery disease (CAD) (URL: www.clinicaltrials.gov. Unique identifier: NCT00832702). Many of these women have been found to have CMD, assessed, in part, by invasive coronary reactivity testing (CRT), which has been associated with adverse cardiovascular outcomes.[2]

We hypothesized that women with symptoms and signs of ischemia, without obstructive CAD, and history of APO are more likely to have CMD.

Methods and Statistical Analysis

We assessed for an association between APOs and abnormal vascular function in a population of women who presented with signs and symptoms of cardiac ischemia without obstructive CAD as described in the WISE.[3] CRT studies were performed at Cedars-Sinai Medical Center (Los Angeles, CA), or the University of Florida (Gainesville, FL), between January 2009 and June 2012 where institutional review boards approved the project and all participants provided written informed consent. Inclusion criteria included symptomatic women with angina or angina equivalent and age ≥18 years of age without obstructive CAD at coronary angiography (performed within the previous 24 months). Primary exclusion criterion included obstructive CAD defined as ≥50% luminal diameter stenosis in ≥1 epicardial coronary artery.

All women underwent baseline evaluation, including collection of demographic variables, risk factors, medical history, medication use, symptom history, physical examination, and labs. Body mass index was calculated as kg/m^2. WISE-CVD women with self-reported pregnancy history available ($n = 324$) were included for analysis of APO prevalence and, among those, women with clinically indicated CRT ($n = 185$, 57%) were included in the APO and CRT analyses. A history of self-reported APO was defined as having any of the following: hypertension during pregnancy, preeclampsia, eclampsia, gestational diabetes, or intrauterine growth restriction (low-birth-weight child). CRT assessment was conducted as per previously published protocols, including coronary flow reserve (CFR) response to adenosine, coronary blood flow change (ΔCBF) and diameter response (ΔACH) to acetylcholine, and nitroglycerin response (ΔNTG).[2]

For baseline demographics, either chi-squared test or Fisher's exact test was used for categorical variables. Summaries for baseline variables reported as mean ± standard deviation and median (range) for variables were provided with t-tests or Wilcoxon rank sum tests with statistical significance defined as p-value ≤0.05. Multiple linear regression analysis with CRT measures as the outcome variables was

performed to assess the relationship with history of APO and to adjust for age and body mass index (BMI), and history of hypertension. A log transformation was made to CFR and CBF due to non-normal residual distributions.

CRT and angiography analysis

CRT was interpreted blinded to clinical data by the WISE Coronary Core Laboratory experienced in interpretation of CRT using previously published methods.[4] Four CRT measures were assessed: (1) abnormal endothelial function defined as a change in epicardial coronary artery diameter ≤0% in response to a maximum dose of acetylcholine (ΔACH); (2) abnormal CFR, defined as CFR <2.5 in response to adenosine; (3) abnormal microvascular endothelial dysfunction, defined as an increase in CBF ≤50% in response to acetylcholine (ΔCBF); and (4) abnormal nonendothelial function defined as a change in epicardial coronary artery diameter ≤20% in response to nitroglycerin (ΔNTG). CFR of <2.5 was defined as abnormal in our study based on previously published data from WISE, in which this cutoff was associated with adverse events.[5] CBF was determined as π (coronary artery diameter/2)^2 × (average peak velocity/2). An abnormal CRT was defined as ≥1 abnormal measure.

Coronary atherosclerosis measured by coronary severity score (CSS) was measured according to prior publication.[6] CSS is an angiographic score that assigns points based on percent diameter stenosis within epicardial vessels; higher scores indicate more severe disease.

Results

Among the 324 WISE-CVD women studied, who reported at least one pregnancy and answered at least one question related to APO, nearly one-quarter [79/324 (24%)] reported at least one APO. Pertinent baseline characteristics are summarized in Table 1. Women with APOs were younger (52 vs. 56 years, $p = 0.001$) and more likely obese (body mass index 32 vs. 29 kg/m^2, $p = 0.004$) and more frequently had a history of hypertension (56% vs. 36%, $p = 0.002$), but otherwise were no different in cardiac risk variables than women without APOs. Notably, there were no differences in systolic or diastolic blood pressure, lipid profile, or glucose levels. Two hundred one women underwent some form of CRT to include CBF, ACH response, NTG response, and/or CFR evaluation with the specific numbers of women undergoing each study noted in Table 3. There were no statistical differences between women who underwent CRT and those who did not, Table 2.

Among those who had some form of CRT evaluation, 46 out of 201 (23%) had history of APO. Among those who underwent CRT evaluation with CFR ($n = 185$), similarly, 39/185 (21%) had history of APO. Results of CRT are summarized in Table 3 and demonstrate that, despite a lower burden of coronary atherosclerosis severity, women with APO had a lower CFR (2.53 vs. 2.76, $p = 0.016$) compared to women without APO. There were no statistical differences in measures of ΔCBF, ΔACH, or ΔNTG.

In linear regression analysis, estimated average units of log CFR of those with APO was 0.085 U lower than those without APO, given the same age and BMI (Table 4). When self-reported history of hypertension was added to the model, p-value for association between APO and CFR changed to

TABLE 1. BASELINE CHARACTERISTICS BY ADVERSE PREGNANCY OUTCOME (N=324)

Characteristic	No APO (n=245)	History of APO (n=79)	p
Age	56.3±10.4	51.9±9.1	0.001
BMI	29.3±7.1	32.3±10.1	0.004
BSA	1.8±0.2	1.9±0.3	0.003
Pulse rate	68.0±10.6	69.7±11.0	0.259
Systolic BP	126.4±18.1	128.3±17.6	0.452
Diastolic BP	67.2±11.7	70.0±13.1	0.090
Total cholesterol	181.9±36.3	175.3±36.9	0.307
TRIG	120.4±78.6	130.4±80.8	0.428
HDL	60.0±16.7	57.3±17.8	0.376
LDL	99.1±32.8	93.3±35.8	0.337
Glucose	96.6±26.1	98.7±25.2	0.640
Creatinine	0.78±0.16	0.75±0.17	0.432
History of hypertension (%)	88 (36)	45 (56)	0.002
ACE-I	48 (21)	17 (22)	0.873
ARB	16 (7)	9 (12)	0.228
Beta blocker	72 (31)	30 (38)	0.267
Calcium channel blocker	53 (23)	21 (27)	0.441
Diuretic	31 (13)	14 (18)	0.350
Vasodilator	10 (4)	3 (4)	1.0
Race			0.841
Native American	2 (1)	1 (1)	
Asian/Pacific Islander	6 (2)	3 (4)	
Black/African American	18 (7)	7 (9)	
Hispanic/Latin	22 (9)	6 (8)	
White/Not Hispanic	183 (75)	59 (75)	
Other/specify	14 (6)	2 (3)	

Data values are represented as mean±SD or *n* (%).
ACE-I, ace-inhibitor; APO, adverse pregnancy outcome; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; BSA, body surface area; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation; TRIG, triglycerides.

TABLE 2. BASELINE CHARACTERISTICS BY CORONARY REACTIVITY TESTING (N=324)

Characteristic	No CRT (n=123)	CRT (n=201)	p
Age	56.0±9.3	54.7±10.8	0.262
BMI	29.8±8.3	30.1±7.9	0.725
BSA	1.8±0.3	1.8±0.2	0.870
Pulse rate	67.5±10.5	68.9±10.8	0.282
Systolic BP	129.1±17.8	125.6±18.0	0.102
Diastolic BP	66.8±13.1	68.5±11.5	0.232
Total cholesterol	177.1±37.0	182.5±36.1	0.319
TRIG	134.7±87.1	115.5±73.4	0.110
HDL	57.8±15.8	60.4±17.5	0.315
LDL	94.9±32.5	99.8±33.9	0.336
Glucose	103.7±33.9	93.8±20.1	0.027
Creatinine	0.8±0.2	0.8±0.1	0.765
History of hypertension (%)	50 (41)	83 (41)	1
History of diabetes	16 (13)	23 (12)	0.725
Statins	66 (55)	70 (35)	0.001
ACE-I	24 (21)	41 (21)	1
ARB	7 (6)	18 (9)	0.393
Beta blocker	50 (42)	52 (27)	0.004
Calcium channel blocker	40 (34)	34 (18)	0.001
Diuretic	17 (14)	28 (14)	1
Vasodilator	4 (3)	9 (5)	0.773
Race			0.820
Native American	0	3 (1.5)	
Asian/Pacific Islander	3 (2)	6 (3)	
Black/African American	9 (7)	16 (8)	
Hispanic/Latin	11 (9)	17 (8)	
White/Not Hispanic	92 (75)	150 (75)	
Other/specify	7 (6)	9 (4)	

Data values are represented as mean±SD or *n* (%).
CRT, coronary reactivity testing.

TABLE 3. CORONARY REACTIVITY TESTING AND CORONARY SEVERITY STENOSIS SCORE IN WOMEN
WITH CORONARY FLOW RESERVE PERFORMED

Invasive measures (Definition of Normal)	N	No APO	History of APO	p
CFR (≥2.5)	185	2.76 ± 0.61, n = 146	2.53 ± 0.43, n = 39	0.016
ΔCBF (>50% increase)	152	67.67 ± 91.62, n = 118	46.77 ± 60.30, n = 34	0.475
ΔACH (>0% increase)	165	−1.46 ± 13.44, n = 130	−0.78 ± 16.15, n = 35	0.316
ΔNTG (>20% increase)	165	14.63 ± 13.74, n = 130	12.63 ± 10.92, n = 35	0.428
Coronary severity stenosis score	161	10.2 ± 4.07, n = 128	9.80 ± 4.34, n = 33	0.462

ΔACH, % diameter change in response to acetylcholine; ΔCBF, % coronary blood flow change in response to acetylcholine; CFR, coronary flow reserve in response to adenosine; ΔNTG, % diameter change in response to nitroglycerin.

$p = 0.066$, Table 5. Women with a history of APO showed abnormal ΔCBF with <50% blood flow increase, and both APO and non-APO groups had an abnormal ΔNTG with <20% diameter change as noted in Table 3.

Discussion

Our study demonstrates that a history of APOs in women with signs and symptoms of ischemia without obstructive CAD is associated with lower CFR indicative of CMD. The potential etiology for this suggested association is unclear, but plausible based on common pathways within microvascular dysfunction. Prior data have suggested that a history of APO is associated with long-term increase in cardiovascular risk. Specifically, data support an association between APO conditions such as preeclampsia and gestational diabetes and elevated risk of cardiovascular events. Women with a history of preeclampsia have a fourfold increased risk of developing chronic hypertension, threefold increased risk of developing type-2 diabetes, and a twofold increased risk for ischemic heart disease and stroke.[7–9] Preeclampsia's independent association with cardiovascular death is not limited to the early postpartum period, but is present throughout the woman's lifetime (adjusted hazard ratio 2.14), as demonstrated by long-term follow-up such as the 30-year follow-up of over 14,000 women in the Kaiser Permanente Child Health and Development Studies pregnancy cohort.[10]

As such, in 2011, the American Heart Association added gestational hypertension and preeclampsia to its algorithm for evaluation of cardiovascular risk in women.[11] However, mechanisms to explain such associations have remained unclear.

Our findings may provide some new insight into potential mechanisms leading to increased cardiovascular risk in women with CMD. Our analysis suggests that history of APOs, in women with signs and symptoms of ischemia without obstructive CAD, is associated with lower CFR indicative of CMD; specifically, women with a history of any APO had evidence of lower CFR value compared with those without APO history. CMD has been increasingly recognized as a cause of angina and associated with increase in long-term cardiovascular events. As these women with history of APO age, underlying vascular dysfunction may become evident through symptoms and signs of myocardial ischemia. Common pathways, which overlap between cardiovascular and placental pathogenesis such as alterations in VEGF, which is a proangiogenic growth factor, inflammation, altered vasoconstriction/dilation, and abnormal microvascular function within the placenta and coronary circulation, may play a role.[12] In addition, in our analysis, addition of hypertension history led to a lower p-value association between APO and CFR. This suggests the association of APO and reduced CFR may be mediated, in part, by hypertension, although this concept warrants further study.

Our data suggest that a history of APO may serve as a marker for future risk of CMD, indicative by abnormal CRT. Current guidelines from the American College of Obstetricians and Gynecologists (ACOG) recommend aggressive screening for hypertension and diabetes after a pregnancy complicated by preeclampsia.[13] The implications of our this study support these recommendations. Further knowledge regarding whether risk modification may mitigate the development of adverse cardiovascular events and CMD should be investigated. Our findings suggest that APO and CMD are associated by a common pathway and support the need for additional data to address this knowledge gap.

Limitations

There are several limitations to our study. Notably, the assessment of APO history was by self-report based on self-report questionnaire only obtained as part of the WISE-CVD

TABLE 4. INVASIVE CORONARY REACTIVITY TESTING MEASURES IN WOMEN WITH CORONARY FLOW RESERVE
PERFORMED—MULTIPLE LINEAR REGRESSION ANALYSIS (ADJUSTED FOR HISTORY OF ADVERSE PREGNANCY OUTCOME,
AGE, AND BODY MASS INDEX)

Invasive measures	Age effect per year (p)	BMI effect per unit (p)	APO History effect (p)
log CFR (n = 183)	−0.001 (0.448)	0.001 (0.716)	−0.085 (0.031)
log ΔCBF (n = 151)	−0.007 (0.049)	−0.013 (0.005)	−0.084 (0.343)
ΔACH (n = 164)	−0.162 (0.110)	−0.298 (0.032)	0.342 (0.899)
ΔNTG (n = 164)	−0.234 (0.015)	−0.115 (0.380)	−2.466 (0.335)
Coronary severity stenosis score (n = 160)	0.061 (0.040)	0.031 (0.457)	−0.435 (0.596)

TABLE 5. INVASIVE CORONARY REACTIVITY TESTING MEASURES IN WOMEN WITH CORONARY FLOW RESERVE
PERFORMED—MULTIPLE LINEAR REGRESSION ANALYSIS (ADJUSTED FOR HISTORY OF ADVERSE PREGNANCY OUTCOME,
AGE, BODY MASS INDEX, AND SELF-REPORTED HISTORY OF HYPERTENSION)

Invasive measures	Age effect per year (p)	BMI effect per unit (p)	APO history effect (p)	History of hypertension effect (p)
log CFR ($n=183$)	−0.0006 (0.662)	0.0014 (0.492)	−0.073 (0.066)	−0.057 (0.088)
log ΔCBF ($n=151$)	−0.004 (0.236)	−0.011 (0.016)	−0.044 (0.615)	−0.206 (0.008)
ΔACH ($n=164$)	−0.186 (0.075)	−0.319 (0.024)	−0.181 (0.947)	2.299 (0.327)
ΔNTG ($n=164$)	−0.255 (0.010)	−0.134 (0.310)	−2.946 (0.259)	2.068 (0.354)
Coronary severity stenosis score ($n=160$)	0.044 (0.136)	0.008 (0.849)	−0.880 (0.283)	1.938 (0.005)

study, and thus, further details of APO history could not be obtained. Limitations of history also apply to hypertension and the variable used in this analysis is self-reported history of hypertension. In addition, we studied APO association in this select cohort of women without obstructive CAD, thus, the generalizability of these results to all women is unknown.

Conclusions

These WISE-CVD analyses suggest that a history of APOs in women with signs and symptoms of ischemia without obstructive CAD is associated with lower CFR indicative of CMD. Our findings support the hypothesis that APO history may be associated with CMD. Whether common mechanisms may underlie both conditions remain unclear and requires further investigation. As such, our findings support the need for continued interdisciplinary research collaboration between obstetrics, maternal-fetal medicine, and cardiology.

Author Disclosure Statement

Funding Information

References

1. Park K, Wei J, Minissian M, Bairey Merz CN, Pepine CJ. Adverse pregnancy conditions, infertility, and future cardiovascular risk: Implications for mother and child. Cardiovasc Drugs Ther 2015;29:391–401.
2. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: Results from the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722–725.
3. Bairey Merz CN, Shaw LJ, Reis SE, et al. Insights from the NHLBI-Sponsored Women's Ischemia Syndrome Evaluation (WISE) Study: Part II: Gender differences in presentation, diagnosis, and outcome with regard to gender-based pathophysiology of atherosclerosis and macrovascular and microvascular coronary disease. J Am Coll Cardiol 2006; 47:S21–S29.
4. Wei J, Mehta PK, Johnson BD, et al. Safety of coronary reactivity testing in women with no obstructive coronary artery disease: Results from the NHLBI-sponsored WISE (Women's Ischemia Syndrome Evaluation) study. JACC Cardiovasc Interv 2012;5:646–653.
5. Pepine CJ, Anderson RD, Sharaf BL, et al. Coronary microvascular reactivity to adenosine predicts adverse outcome in women evaluated for suspected ischemia results from the National Heart, Lung and Blood Institute WISE (Women's Ischemia Syndrome Evaluation) study. J Am Coll Cardiol 2010;55:2825–2832.
6. Sharaf B, Wood T, Shaw L, et al. Adverse outcomes among women presenting with signs and symptoms of ischemia and no obstructive coronary artery disease: Findings from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE) angiographic core laboratory. Am Heart J 2013;166:134–141.
7. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Preeclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. BMJ 2007; 335:974.
8. Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and

subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. Hypertension 2009;53:944–951.

9. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: A systematic review and meta-analyses. Am Heart J 2008;156:918–930.

10. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: Prospective evidence from the child health and development studies cohort. Hypertension 2010;56:166–171.

11. Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women—2011 update: A guideline from the American Heart Association. J Am Coll Cardiol 2011;57:1404–1423.

12. Dvorak HF. Vascular permeability factor/vascular endothelial growth factor: A critical cytokine in tumor angiogenesis and a potential target for diagnosis and therapy. J Clin Oncol 2002;20:4368–4380.

13. Committee on Practice B-O. Practice bulletin no. 137: Gestational diabetes mellitus. Obstetr Gynecol 2013;122: 406–416.

Address correspondence to:
C. Noel Bairey Merz, MD, FAHA, FACC
Barbra Streisand Women's Heart Center
Smidt Heart Institute
Cedars-Sinai Medical Center
127 S. San Vicente Boulevard, Suite A3206
Los Angeles, CA 90048

E-mail: noel.baireymerz@cshs.org