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Abstract

Objective: This study investigates the association between a prior history of pregnancy complications and cardiovascular disease (CVD) among Kentucky women aged ≥ 50 years.

Methods: Data were analyzed from participants ($n = 3909$) in the Kentucky Women's Health Registry (2006–2008). Primary outcomes were self-reported prevalence of CVD, including angina, heart attack, heart failure, and arrhythmia. Pregnancy complications used as predictors were preterm labor, preeclampsia, gestational diabetes mellitus (GDM), and third trimester bleeding. Logistic regression analyses were conducted to determine associations between prevalence of CVD and pregnancy complications, controlling for age, education, and smoking status.

Results: Overall, 199 (5.1%) women reported angina, 79 (2.0%) reported heart attack, 44 (1.1%) reported heart failure, and 642 (16.4%) reported arrhythmia. One pregnancy complication was reported by 614 (15.7%) women, and two or more complications were reported by 130 (3.3%) women. In regression models adjusting for age, education, and smoking, compared to women who were never pregnant, women with no pregnancy complications had a similar risk of reporting heart attack (odds ratio [OR] 1.2, 95% confidence interval [CI] 0.5–2.7), but women with one pregnancy complication (OR 2.5, 95% CI 1.03–6.0) and two or more complications (OR 4.2, 95% CI 1.4–10.6) had an increased risk. Similar results were seen for angina and arrhythmia, but not heart failure.

Conclusions: Women who experience pregnancy complications are more likely to report prevalent CVD (including angina, heart attack, and arrhythmia), suggesting a link between adverse pregnancy events and CVD. Pregnancy complications may serve as signals for future CVD, presenting an opportunity for early intervention and prevention.

Introduction

CARDIOVASCULAR DISEASE (CVD) has been the leading cause of death for Americans almost every year since 1900. Nearly 37% of deaths among women in the United States are attributed to CVD.¹ The American Heart Association (AHA) recognizes that the most effective prevention strategy for CVD among women is for physicians to instill an awareness of the risk factors for women by acknowledging gender differences in the signs for CVD. Research demonstrates a relationship between adverse pregnancy events and adverse fetal outcomes.^{1–3} Less is known about pregnancy complications and their relation to future poor health outcomes for the mother, especially CVD.

Some studies indicate a relationship between adverse pregnancy outcomes and an increased risk for vascular and

metabolic disease for the mother, and the complications have appeared to have an additive effect.⁴ It is suggested that this relationship between pregnancy complications and an increased risk for CVD exists because adverse pregnancy events and vascular disease share common disease mechanisms, such as the inflammatory response and metabolic syndrome.^{4,5} The importance of this research area is that the maternal vascular risks associated with pregnancy events could potentially be modified and treated.^{6–8}

The purpose of this study is to assess the association between a history of pregnancy complications (preterm labor, preeclampsia, gestational diabetes mellitus [GDM], and bleeding during the third trimester) and the presence of CVD (angina, heart attack, heart failure, irregular heartbeat, or arrhythmia) in a sample of Kentucky women aged ≥ 50 years. The research questions asked in this study are: Is there an

association between a history of adverse pregnancy events and prevalence of CVD? Is there a relationship between specific pregnancy complications and CVD? Is there a dose-response relationship between the number of pregnancy complications and the risk of CVD?

Materials and Methods

This analysis is cross-sectional and uses data from the 2006–2008 Kentucky Women's Health Registry (KWHR). The KWHR is a nonrandomized sample of women who volunteer to participate. The survey includes questions about demographics, health history, mental health, and physical health. The KWHR is distributed among Kentucky women (aged 18–89) through the mail and internet. The Center for the Advancement of Women's Health provided 3 years of deidentified data for Kentucky women ≥ 50 years of age. This study was approved by the University of Kentucky Institutional Review Board.

Study sample and exclusion criteria

The total sample size for women aged ≥ 50 4193. Women were excluded if they had incomplete data because of not answering the question or if they selected Choose not to answer as their response. Of the 4193 women, 27 were excluded because of inconsistent data (such as reporting a pregnancy complication yet also reporting never being pregnant), 14 did not report CVD outcomes, 225 did not list an education level, and 18 did not indicate their smoking status. The remaining women included in our study had complete data ($n = 3909$, 93.2% of all eligible).

Pregnancy status

Women were categorized as having experienced a pregnancy with the survey question: How many times have you been pregnant? All women who answered one or more were considered to have experienced pregnancy; women who reported zero were categorized as never experiencing a pregnancy. The study did not differentiate between women with full-term pregnancies and women who did not carry full-term (from spontaneous or induced abortions).

Adverse pregnancy events

To assess history of pregnancy complications, the survey asked: During your pregnancies, did you experience any of the following (CHOOSE ALL THAT APPLY): preterm labor, preeclampsia, gestational diabetes, bleeding during third trimester, none, and Choose not to answer.

Additional explanations of these terms in the survey were as follows: "preterm labor defined as contractions and changes in your cervix between your 20th and 36th week of pregnancy, may lead to preterm birth; preeclampsia defined as high blood pressure during pregnancy; gestational diabetes defined as high blood sugar during pregnancy."

Cardiovascular disease

CVD was ascertained via self-report using the question: Have you ever had any of the following? CHOOSE ALL THAT APPLY: angina, heart attack, heart failure, irregular heart beat or arrhythmia, mitral valve prolapsed, rheumatic

fever, heart murmur, aortic aneurysm, peripheral vascular disease or claudication, congenital (present at birth) heart disease, other.

The CVD outcomes chosen for analysis in the study were angina, heart attack, heart failure, and irregular heartbeat or arrhythmia. The CVD outcomes were included based on their prevalence in the study sample ($>1\%$) and their being characteristic of adult-onset CVD.

Statistical analysis

All simple demographic statistics for this study (mean age, age categories, education, gravidity, and smoking status) were calculated as counts and percentages using frequency codes in the statistical software.

The pregnancy complication variable in the analysis was created based on whether or not a participant experienced a pregnancy, no pregnancy complications (did not report any of the adverse events), one pregnancy complication, or two or more pregnancy complications. The age categories included women aged 50–59 years, 60–69 years, and 70+ years. The education variable was categorized, in years of education, as ≤ 12 years, 13–16 years, and ≥ 17 years. Smoking status was classified as current, former, or never smoker. The study population was 95.2% white and 2.5% black, with the rest Asian, American Indian, or other, and 0.4% self-identified as Hispanic ethnicity. Because of the small proportion of non-white women in the survey, race/ethnicity was not used in the analysis.

Logistic regression analysis determined the association between pregnancy complications and CVD outcomes, controlling for age, education, and smoking status.

$$\text{logit}(p) = \ln \frac{p}{(1-p)} = \alpha + \beta_{(1)}x_1 + \beta_{(2)}x_2 + \beta_{(3)}x_3$$

where p = probability of experiencing a CVD outcome according to pregnancy status and complication, x_1 = age category, x_2 = education status, and x_3 = smoking status. The statistical software used in the study was SAS 9.2 (SAS Institute, Cary, NC).

Results

Table 1 presents the descriptive statistics of the sample stratified according to pregnancy status. The majority of women experienced a pregnancy without complications (64.3%), 15.5% never experienced a pregnancy, 15.7% experienced one complication during pregnancy, and 4.3% of the women experienced two or more complications during pregnancy. The mean age of the sample is 59.8 (± 7.6) years. Among the entire study sample, 38.4% had 17 years or more of education. Most of the women in study sample had 2–3 pregnancies (52.3%). The majority of the women never smoked (59.7%). Among current smokers, 8.8% experienced one pregnancy complication, and 15.4% had two or more pregnancy complications.

Table 2 displays, among women who were ever pregnant, those with a reported history of adverse pregnancy events by age category, education, gravidity, and smoking status. The most frequently occurring pregnancy complication was preterm labor (9.8%). In general, pregnancy complications were reported more frequently among younger women, current

TABLE 1. AGE, EDUCATION LEVEL, GRAVIDITY, AND SMOKING STATUS BY HISTORY OF PREGNANCY COMPLICATIONS
DATA AMONG WOMEN IN THE KENTUCKY WOMEN'S HEALTH REGISTRY

	All n = 3909	Never experienced a pregnancy n = 607/3909 15.5%	No complications during a pregnancy n = 2558/3909 65.4%	Experienced 1 complication during pregnancy n = 614/3909 15.7%	Experienced 2 or more complications during pregnancy n = 130/3909 3.3%
Mean age (SD)	59.8 (7.4)	58.3 (6.4)	60.3 (7.5)	59.4 (7.5)	58.3 (6.7)
Age categories					
50–59 years	59.3% ^a	68.0%	55.7%	63.7%	69.3%
60–69 years	30.6%	26.7%	33.1%	25.9%	23.1%
70+ years	10.1%	5.3%	11.3%	10.4%	7.7%
Education					
≤12 years	33.6%	20.6%	36.4%	34.2%	38.5%
13–16	27.9%	25.4%	27.4%	32.1%	29.2%
17+	38.4%	54.0%	36.2%	33.7%	32.3%
Number of pregnancies					
0	15.5%	100%	NA	NA	NA
1	13.0%	NA	16.7%	12.5%	4.6%
2–3	52.3%	NA	63.7%	55.9%	53.9%
4+	19.2%	NA	19.6%	31.6%	41.5%
Smoking status					
Current	8.0%	7.4%	7.5%	8.8%	16.9%
Former	32.3%	32.3%	32.1%	32.4%	34.6%
Never	59.7%	60.3%	60.4%	58.8%	48.5%

^aPercentages represent the proportion of women in each column with this characteristic.

NA, not applicable; SD, standard deviation.

smokers, and women reporting more pregnancies. Table 3 shows reported prevalent CVD among survey participants. In general, CVD was more common among older women, current or former smokers, less educated women, and women reporting more pregnancies.

Table 4 displays the percentage of CVD events among women who reported pregnancy complications. More pregnancy

complications were associated with a higher prevalence of reported CVD. A history of GDM was associated with the highest reporting of angina (11.6%) and arrhythmia (28.1%), and third trimester bleeding was associated with the highest reporting of heart attack (5.1%) and heart failure (2.6%).

Table 5 displays results of the logistic regression models predicting CVD. The odds of reporting angina, heart attack,

TABLE 2. PROPORTION OF WOMEN WITH REPORTED HISTORY OF ADVERSE PREGNANCY EVENTS
AMONG WOMEN IN THE KENTUCKY WOMEN'S HEALTH REGISTRY

	n	Preterm labor n = 324/3302 9.8%	Preeclampsia n = 222/3302 6.7%	Gestational diabetes n = 146/3302 4.4%	3rd trimester bleeding n = 195/3302 5.9%
Mean age (SD)		59.6 (7.4)	58.1 (6.1)	57.1 (5.5)	61.0 (8.2)
Age categories					
50–59 years	1905	10.7% ^a	8.1%	6.0%	5.6%
60–69 years	1035	8.5%	4.8%	2.6%	5.5%
70+ years	362	9.12%	4.7%	1.1%	8.6%
Education					
≤12 years	1190	10.4%	5.1%	4.0%	7.0%
13–16 years	937	10.9%	7.9%	4.6%	5.9%
17+ years	1175	8.3%	7.4%	4.8%	4.9%
Number of pregnancies					
1	509	5.3%	7.7%	2.0%	2.8%
2–3	2043	8.8%	5.5%	4.3%	5.3%
4+	750	15.6%	9.3%	6.5%	9.7%
Smoking status					
Current	269	14.1%	6.7%	4.8%	11.5%
Former	1065	9.7%	6.4%	5.4%	6.3%
Never	1968	9.3%	6.9%	3.9%	4.9%

Includes only women who reported at least one pregnancy.

^aPercentage listed is of the total in each row (e.g., of the 269 current smokers, 38 [14.1%] reported preterm labor).

TABLE 3. REPORTED CARDIOVASCULAR DISEASE AMONG WOMEN IN THE KENTUCKY WOMEN'S HEALTH REGISTRY

	n	Angina n = 199/3909 5.1%	Heart attack n = 79/3909 2.0%	Heart failure n = 44/3909 1.1%	Arrhythmia n = 642/3909 16.4%
Mean age (SD)		60.5 (7.6)	65.0 (8.7)	66.1 (9.9)	60.5 (7.5)
Age categories					
50–59 years	2318	5.0% ^a	1.0%	0.7%	15.6%
60–69 years	1197	4.9%	2.8%	1.2%	17.2%
70+ years	394	6.3%	5.3%	3.8%	18.5%
Education					
≤12 years	1315	6.5%	2.5%	2.1%	15.7%
13–16 years	1091	5.7%	1.8%	0.6%	19.3%
17+ years	1503	3.5%	1.7%	0.7%	15.0%
Gravidity					
0	607	4.0%	1.2%	1.0%	14.2%
1	509	5.1%	1.8%	0.8%	15.7%
2–3	2043	4.5%	1.9%	1.1%	16.4%
4+	750	7.6%	3.3%	1.6%	18.9%
Smoking status					
Current	314	9.2%	3.2%	1.9%	17.5%
Former	1261	5.8%	2.6%	1.4%	16.3%
Never	2334	4.2%	1.5%	0.9%	16.4%

^aPercentage listed is of the total in each row (e.g., of the 314 current smokers, 29 [9.2%] reported angina).

and arrhythmia were increased among women who had two or more complications during pregnancy; no increase, however, was seen for heart failure. Women who reported no pregnancy complications were similar to never pregnant women for all CVD outcomes.

Figures 1, 2, 3, and 4 represent the adjusted odds ratios (ORs) for prevalent CVD (angina, heart attack, heart failure, and arrhythmia) for each pregnancy complication adjusting for age, education, and smoking status. The reference is never pregnant women. The presence of any pregnancy complication was associated with an increased risk for angina, heart attack, and arrhythmia but not for heart failure. Figure 5 represents the odds of CVD for women with complications during their pregnancy, using women who were pregnant but without pregnancy complications as the reference group. Again, for CVD outcomes other than heart failure, there was an increased risk associated with a history of one pregnancy complication, with additional

risk seen among women reporting two or more pregnancy complications.

Discussion

These results suggest that women who experience adverse pregnancy events of preterm labor, preeclampsia, GDM, or bleeding during the third trimester may be at increased risk for developing subsequent CVD. The results also demonstrate that the women with no pregnancy complications resemble the reference group of never pregnant women, suggesting the observed finding is not merely related to pregnancy. In addition, an increased number of complications are related to increased odds for CVD, indicating a dose-response between number of pregnancy complications and CVD outcomes.

The results of this study are consistent with other findings in this field.^{4–7} Preeclampsia has been most consistently

TABLE 4. PROPORTION OF WOMEN WITH REPORTED CARDIOVASCULAR DISEASE STRATIFIED BY PREGNANCY COMPLICATION HISTORY AMONG WOMEN IN THE KENTUCKY WOMEN'S HEALTH REGISTRY

	n	Angina n = 199/3909 5.1%	Heart attack n = 79/3909 2.0%	Heart failure n = 44/3909 1.1%	Arrhythmia n = 642/3909 16.4%
Pregnancy history					
Never	607	4.0% ^a	1.2%	1.0%	14.2%
No complications	2558	4.4%	1.8%	1.1%	15.1%
One complication	614	7.2%	3.2%	1.1%	21.8%
Two or more complications	130	13.9%	5.4%	1.5%	26.9%
Pregnancy complication					
Preterm labor	324	8.3%	3.1%	1.2%	21.3%
Preeclampsia	222	9.5%	4.1%	0.5%	22.1%
Gestational diabetes	146	11.6%	3.4%	0.7%	28.1%
3rd trimester bleeding	195	8.7%	5.1%	2.6%	25.6%

^aPercentage listed is of the total in each row (e.g., of the 324 women with preterm labor, 27 [8.3%] reported angina).

TABLE 5. ADJUSTED ODDS RATIO OF CARDIOVASCULAR DISEASE EVENTS ASSOCIATED WITH ADVERSE PREGNANCY EVENTS EXPERIENCED BY WOMEN IN THE KENTUCKY WOMEN'S HEALTH REGISTRY

	Angina n = 199/3909 5.1%	Heart attack n = 79/3909 2.0%	Heart failure n = 44/3909 1.1%	Arrhythmia n = 642/3909 16.4%
Pregnancy history				
Never	Reference	Reference	Reference	Reference
No complications	1.0 (0.6-1.6)	1.2 (0.5-2.7)	0.7 (0.3-1.9)	1.0 (0.8-1.4)
One complication	1.7 (0.98-2.7)	2.5 (1.03-6.0)	0.8 (0.3-2.5)	1.6 (1.2-2.2)
Two or more complications	3.2 (1.7-6.2)	4.2 (1.4-10.6)	1.0 (0.2-5.31)	2.2 (1.4-3.5)
Age categories				
50-59 years	Reference	Reference	Reference	Reference
60-69 years	1.1 (0.8-1.5)	3.0 (1.8-5.1)	1.9 (0.9-3.9)	1.2 (0.9-1.4)
70+ years	1.3 (0.8-2.1)	5.6 (3.0-10.5)	5.6 (2.7-12.0)	1.3 (0.9-1.7)
Education				
17+ years	Reference	Reference	Reference	Reference
13-16 years	1.5 (1.1-2.3)	1.1 (0.6-1.9)	1.0 (0.4-2.7)	1.3 (1.2-1.6)
≤12 years	1.7 (1.2-2.5)	1.1 (0.7-2.0)	2.6 (1.2-5.6)	1.0 (0.8-1.2)
Smoking status				
Never	Reference	Reference	Reference	Reference
Former	1.4 (0.9-1.9)	1.6 (1.0-2.6)	1.4 (0.7-2.6)	0.9 (0.8-1.2)
Current	2.0 (1.3-3.1)	2.3 (1.1-4.9)	2.2 (0.9-5.6)	1.1 (0.8-1.4)

Multivariate models adjusted for pregnancy history, age, education, and smoking status.

linked to future CVD.⁹⁻¹⁵ Preeclampsia complicates 2%–4% of pregnancies and is identified by the new onset of hypertension and proteinuria.¹⁶ This is among the leading causes of maternal and perinatal morbidity and mortality in Europe and North America.^{5,7,9} A history of preeclampsia could possibly double the woman's risk for early cardiac, cerebrovascular, and peripheral arterial disease.^{13-15,17-21} Atherosclerosis and preeclampsia both have impaired endothelial and vascular function, which would provide the mechanistic linkage between the perinatal complication and CVD later in life.^{16,19}

GDM complicates approximately 4% of all pregnancies that occur in the United States.²² Pregnancy alters the metabolic state, subsequently altering glucose metabolism, which results in a continuum of glucose tolerance potentially associated with a continuum risk for later CVD.²³ Epidemiological studies suggest poor outcomes among infants born to mothers with GDM and support the belief that some adult-onset diseases have their origin in fetal life.²⁴ Women

who suffer GDM are also at an increased risk of developing diabetes and CVD postpregnancy.²⁵ Bentley-Lewis²² suggests that certain biochemical parameters, such as inflammation, are responsible for CVD among women with GDM. For example, one study suggests that a high proportion of women with GDM will develop type 2 diabetes within 2–5 years, which subsequently increases the woman's risk for CVD.²⁶ McCormack et al.²⁷ found a significant association between late gestational bleeding and preeclampsia, GDM, and preterm birth, as well as such poor fetal outcomes as low birth weight and low Apgar scores. To our knowledge, however, little is known about third trimester bleeding and subsequent maternal CVD.

The main limitations of the study are related to the study sample and the validity of the answers they provided. The study used self-reported survey responses, and medical records were not used to validate respondents' answers. The survey respondents did not consent to a medical record review, nor would a review have been feasible, given that

FIG. 1. Odds of angina, comparing women who experienced a pregnancy without complications and women who experienced pregnancy with complications (adjusted for age, education, and smoking status).

FIG. 2. Odds of heart attack, comparing women who experienced a pregnancy without complications and women who experienced pregnancy with complications (adjusted for age, education, and smoking status).

FIG. 3. Odds of heart failure, comparing women who experienced a pregnancy without complications and women who experienced pregnancy with complications (adjusted for age, education, and smoking status).

women came from every county in the state and may have multiple healthcare providers. The questions used in the survey, however, are similar to those used in other national surveys, such as the Behavioral Risk Factors Surveillance Survey (BRFSS) and the National Health Interview Survey (NHIS). Recall bias may also be present. For example, women in the 50–59 age category reported a greater proportion of adverse pregnancy events compared to women who were aged ≥ 60 . This may have been related to what younger women could better remember or the information they received from their doctors, which may have changed over time. Additionally, diagnostic criteria for both pregnancy complications and cardiovascular outcomes may also have changed over time. This was a convenience sample of motivated women who were more likely to be health conscientious compared to women who did not participate in the study. This sample was relatively well educated, had a small proportion of smokers and a small proportion of reported CVD, and was racially homogeneous. This study was also limited by the questions available on the questionnaire. Some relevant issues that were not included in the survey questions are non-proteinuric hypertensive pregnancies and intrauterine growth restriction complications.

The demographics of the sample do not reflect other study samples of Kentucky women. For example, Kentucky BRFSS

FIG. 4. Odds of arrhythmia, comparing women who experienced a pregnancy without complications and women who experienced pregnancy with complications (adjusted for age, education, and smoking status).

FIG. 5. Odds of cardiovascular disease, comparing women who experienced one pregnancy complication and women who experienced two or more pregnancy complications (adjusted for age, education, and smoking status). Reference group is ever pregnant women without pregnancy complications.

data from 2008 show that 24.3% of Kentucky women currently smoke²⁸ compared to our study, where 8% of women currently smoke. Although this study sample differs from other Kentucky study samples, the expected signals of increased CVD prevalence among current and former smokers and increased age are still displayed. This offers internal validity because what is normally expected to contribute to the outcome is still seen in our results. The prevalence of CVD in this sample is probably much lower than what one would see in a representative population. Even with these limitations, the relation between adverse pregnancy events and subsequent CVD is consistent and suggests that this type of methodology provides a convenient way to examine this problem in a real-world population.

Conclusions

This study demonstrated an association between a history of adverse pregnancy events and prevalence of CVD among Kentucky women aged ≥ 50 years. There is a dose-response relationship between the number of pregnancy complications and CVD. The more pregnancy complications experienced among women who had ever been pregnant, the greater the risk for CVD. Never being pregnant did not appear to be protective against CVD. Women who suffer complications during pregnancy may be experiencing an early manifestation of CVD, suggesting that these events can serve as a marker of future CVD events, which offers an early opportunity for intervention. Knowing that pregnancy complications can potentially serve as a signal for a predisposition to CVD, women and their physicians should use these pregnancy events as a physiological stress test to better quantify CVD risk and dictate improved prevention strategies.

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