9. Shapiro BT. Promoting wellness or waste? evidence from antidepressant advertising. *Am Econ J Microecon*. 2022;14(2):439-477. doi:10.1257/mic.20190277

10. Carey C, Lieber EM, Miller S. Drug firms' payments and physicians' prescribing behavior in Medicare Part D. *J Public Econ*. 2021;197:104402. doi:10.1016/j.jpubeco.2021.104402

11. Grennan M, Myers K, Swanson A, Chatterji A. No free lunch? welfare analysis of firms selling through expert intermediaries. SSRN. March 20 2021. Accessed January 1, 2023. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3216172 doi:10.2139/ssrn.3216172

12. Starc A, Town RJ. Externalities and benefit design in health insurance. *Rev Econ Stud*. 2020;87(6):2827-2858. doi:10.1093/restud/rdz052

13. Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions of public health, pharmaceuticals, and other medical care to US life expectancy changes, 1990-2015. *Health Aff (Millwood)*. 2020;39(9):1546-1556. doi:10.1377/hlthaff.2020.00284

14. Alpert A, Lakdawalla D, Sood N. *Prescription Drug Advertising and Drug Utilization: The Role of Medicare Part D*. National Bureau of Economic Research; 2015. doi:10.3386/w21714

15. Spatz ID. Better drug ads, fewer side effects. *New York Times*. Posted February 9, 2011. Accessed December 16, 2022. https://www.nytimes.com/2011/02/10/opinion/10spatz.html

Adverse Pregnancy Outcomes—Risk Enhancers Whose Time Has Finally Arrived

Natalie A. Bello, MD, MPH

Heart disease is the leading cause of death globally for both sexes, affecting 1 in 5 women in the United States.[1] Although women have a lower prevalence of obstructive epicardial coronary artery disease compared with men of a similar age, they have higher rates of myocardial ischemia and associated cardiovascular morbidity and mortality.[2] While both sex-based differences due to biological factors such as the timing of menarche and menopause and gender-related differences related to social constructs (eg, delays in time to evaluation of chest pain for women vs men) contribute to these disparities, there is a growing recognition that traditional cardiovascular risk calculators fail to account for sex-specific risk factors such as adverse pregnancy outcomes, which are unique to birthing people who predominantly identify as women. Adverse pregnancy outcomes, including pregnancy-induced hypertensive disorders (preeclampsia and gestational hypertension), preterm birth, and fetal growth restriction, are common manifestations of ischemic placental disease[3] and share a vascular pathophysiologic origin. Along with gestational diabetes, adverse pregnancy outcomes comprise a group of sex-specific cardiovascular risk enhancers associated with a 2- to 4-fold increased risk of future heart disease.[4] Unfortunately, due to a lack of detailed pregnancy history in most existing cohorts and clinical trials of coronary artery disease, to date it has been difficult to examine whether there is a difference in the pathophysiologic development of coronary artery disease in women with a history of adverse pregnancy outcomes compared with those with uncomplicated pregnancies.

Related article page 393

Coronary computed tomography (CT) angiography is a highly accurate, noninvasive diagnostic test that can be used to assess for presence of obstructive epicardial coronary arterial disease with high sensitivity and negative predictive value.[5] While prior strategies of reducing heart disease risk focused on obstructive coronary artery disease burden (defined as stenosis >70%), there is a growing understanding that not only obstructive plaque, but also the presence of any plaque, even noncalcified, is associated with higher risk of cardiovascular morbidity and mortality in a dose-dependent manner (more plaque burden equals greater risk), particularly for women. Similarly, a coronary artery calcium (CAC) score has been shown to be positively correlated with and add incremental value to the assessment of future cardiovascular risk. Compared with a score of 0, even minimal CAC scores are associated with an increased risk of major adverse cardiovascular events.[5,6]

In this issue of *JAMA*, Sederholm Lawesson and colleagues[7] advance knowledge and provide information about the heightened risk of asymptomatic coronary artery disease following individual adverse pregnancy outcomes. Their protocol in the present work from the Swedish Cardiopulmonary Bioimage Study used a single low-dose CT scan to quantify the presence, severity, and extent of atherosclerotic coronary arterial stenoses as well as the presence of noncalcified plaque, and a CAC score. This cross-sectional, population-based cohort study examined 10 528 women with a median age at the time of the scan of 57 years, and in whom imaging was conducted a median of 30 years after their first linked pregnancy in the Swedish National Medical Birth Register. Consistent with other studies, 19% of women had a history of an adverse pregnancy outcome and those individuals also had a higher burden of traditional cardiovascular risk factors, including higher systolic blood pressure and higher prevalence of diabetes, at the time of imaging. The study reported several key findings, including a 3.8% absolute increase in the prevalence of any coronary atherosclerosis in women with a history of adverse pregnancy outcomes compared with those without (32.1% vs 28.3%). The highest increases were seen following a pregnancy affected by preeclampsia (8.0% prevalence increase, 3.1% absolute increase in significant stenosis, 4.2% increase in noncalcified plaque, and 4.1% increase in CAC score >100), with similar findings for gestational hypertension. This translates into an accelerated vascular age, the hypothetical adjustment to chronological age that accounts for the observed severity of coronary artery disease, of 4 to 11 years for women with an exposure to pregnancy-induced hypertensive disorders compared with women without this

history, but not for those with history of gestational diabetes or preterm delivery. The findings after delivery of a small-for-gestational-age infant were mixed.

The authors took their work a step further and examined the burden of CT-diagnosed coronary artery disease in the 83% of women (n = 8334) who had a low predicted 10-year cardiovascular risk (<5%) and would not qualify for aggressive risk factor reduction based on current guidelines. For this Swedish cohort, from a moderate cardiovascular risk region, the SCORE2[8] algorithm was used to provide a low, moderate, or high risk estimate of fatal and nonfatal incident cardiovascular disease. The SCORE2 risk factors include sex, age, smoking status, systolic blood pressure, and total and high-density lipoprotein cholesterol, but unlike the Pooled Cohort Equations,[9] SCORE2 does not consider diabetes, race, or treatment for hypertension, but does incorporate country-specific cardiovascular disease mortality rates by dividing countries in Europe and the Middle East/North Africa into 4 risk regions (low, moderate, high, and very high). For women with a history of preeclampsia who had less than 5% predicted disease risk, their observed burden of significant stenosis (4.5%) was similar to women who had no adverse pregnancy outcome history and intermediate predicted cardiovascular risk (4.8%). Thus, the current risk factor stratification system does an injustice to women with preeclampsia by not accounting for the contribution of preeclampsia as a sex-specific risk factor. This provocative finding confirms what has been shown in 2 prior small studies,[10,11] and effectively suggests that women with a history of preeclampsia could benefit from reclassification to a higher level of risk, although the generalizability of this finding to more racially and ethnically diverse or younger populations is unknown.

Prior attempts at incorporating adverse pregnancy outcomes into cardiovascular disease risk calculators have failed to provide a meaningful shift in disease classification status.[12,13] This may in part be due to the grouping of adverse pregnancy outcomes together as an exposure to enhance power; it is likely that some adverse pregnancy outcomes mediate risk through their association with a heightened burden of traditional risk factors postpregnancy, while other adverse pregnancy outcomes like preeclampsia exert a direct effect on the coronary vessels, among other targets. Clustering vascular and nonvascular adverse pregnancy outcomes together may bias the reclassification schema toward the null, resulting in a smaller effect after accounting for traditional risk factors. Thus, before moving forward to attempt to refine the currently available risk calculators to include all adverse pregnancy outcomes, clinicians must first better understand individual adverse pregnancy outcomes and whether they enhance risk directly or through a shared burden of traditional risk factors. Despite the relatively homogeneous nature of this Scandinavian cohort, one of its great strengths is the population-based study design. Most prior studies examining cardiovascular disease during and after adverse pregnancy outcomes have been retrospective, single-center, cross-sectional analyses examining referred populations of limited size and often lacking adequate control groups. Given the overlap in risk factors for adverse pregnancy outcomes and cardiovascular disease, these studies have not been able to clarify contributing roles of specific adverse pregnancy outcomes in the development of heart disease. The current work is an important step in that direction, demonstrating the independent risk of coronary disease following a hypertensive disorder of pregnancy, while confirming that most of the risk experienced by individuals with a history of other adverse pregnancy outcomes such as gestational diabetes is mediated predominantly by conventional risk factors.

Failure to recognize, prevent, and treat the unique aspects of heart disease in women has resulted in less aggressive lifestyle and medical interventions in women relative to men, leading to potentially avoidable morbidity and mortality.[14] To close the gap between currently delivered and ideal care, and to improve the cardiovascular health of women, clinicians must better understand the unique aspects and mechanistic pathways of heart disease in women. The study by Sederholm Lawesson and colleagues takes us one step closer to parity. While further data accumulate to refine risk calculators and prospectively test whether the addition of adverse pregnancy outcomes to cardiovascular risk stratification is warranted, there are steps that can be taken now to do better by our female patients. Taking a pregnancy history when assessing cardiovascular risk and incorporating adverse pregnancy outcomes, particularly preeclampsia and gestational hypertension, into the risk/benefit discussion around primary preventive strategies and risk factor targets is imperative. Clinicians must also educate birthing people at the time of their pregnancy to understand the impact of an adverse pregnancy outcome on their risk of future heart disease, encourage them to receive timely preventive care focused on risk factor modification, and empower them to share this important medical history with future clinicians if they are not asked about it. There is no time like the present to redouble the efforts to reduce cardiovascular disease in women.

ARTICLE INFORMATION

Author Affiliation: Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California.

Corresponding Author: Natalie A. Bello, MD, MPH, Smidt Heart Institute, Cedars-Sinai Medical Center, 127 S San Vicente Blvd, Ste 3100, Los Angeles, CA 90048 (natalieann.bello@cshs.org).

Conflict of Interest Disclosures: Dr Bello reported receipt of grants from the National Institutes of Health.

REFERENCES

1. Centers for Disease Control and Prevention. CDC WONDER: Multiple Cause of Death Files, 1999-2020. Accessed January 3, 2023. https://wonder.cdc.gov/mcd-icd10.html

2. Aggarwal NR, Patel HN, Mehta LS, et al. Sex differences in ischemic heart disease. *Circ Cardiovasc Qual Outcomes*. 2018;11(2):e004437. doi:10.1161/CIRCOUTCOMES.117.004437

3. Brosens I, Pijnenborg R, Vercruysse L, Romero R. The "great obstetrical syndromes" are associated with disorders of deep placentation. *Am J Obstet Gynecol*. 2011;204(3):193-201. doi:10.1016/j.ajog.2010.08.009

4. Davis MB, Arendt K, Bello NA, et al. Team-based care of women with cardiovascular disease from pre-conception through pregnancy and postpartum. *J Am Coll Cardiol*. 2021;77(14):1763-1777. doi:10.1016/j.jacc.2021.02.033

5. Pontone G, Rossi A, Guglielmo M, et al. Clinical applications of cardiac computed tomography. *Eur Heart J Cardiovasc Imaging*. 2022;23(3):299-314. doi:10.1093/ehjci/jeab293

6. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. *JAMA*. 2012;308(8):788-795. doi:10.1001/jama.2012.9624

7. Sederholm Lawesson S, Swahn E, Pihlsgård M, et al. Association between history of adverse pregnancy outcomes and coronary artery disease assessed by coronary computed tomography angiography. *JAMA*. Published February 7, 2023. doi:10.1001/jama.2022.24093

8. SCORE2 Working Group and ESC Cardiovascular Risk Collaboration. SCORE2 risk prediction algorithms. *Eur Heart J*. 2021;42(25):2439-2454. doi:10.1093/eurheartj/ehab309

9. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk. *J Am Coll Cardiol*. 2014;63(25 pt B):2935-2959. doi:10.1016/j.jacc.2013.11.005

10. Zoet GA, Benschop L, Boersma E, et al. Prevalence of subclinical coronary artery disease assessed by coronary computed tomography angiography in 45- to 55-year-old women with a history of preeclampsia. *Circulation*. 2018;137(8):877-879. doi:10.1161/CIRCULATIONAHA.117.032695

11. Hauge MG, Damm P, Kofoed KF, et al. Early coronary atherosclerosis in women with previous preeclampsia. *J Am Coll Cardiol*. 2022;79(23):2310-2321. doi:10.1016/j.jacc.2022.03.381

12. Søndergaard MM, Hlatky MA, Stefanick ML, et al. Association of adverse pregnancy outcomes with risk of atherosclerotic cardiovascular disease in postmenopausal women. *JAMA Cardiol*. 2020;5(12):1390-1398. doi:10.1001/jamacardio.2020.4097

13. Markovitz AR, Stuart JJ, Horn J, et al. Does pregnancy complication history improve cardiovascular disease risk prediction? *Eur Heart J*. 2019;40(14):1113-1120. doi:10.1093/eurheartj/ehy863

14. Shaw LJ, Pepine CJ, Xie J, et al. Quality and equitable health care gaps for women. *J Am Coll Cardiol*. 2017;70(3):373-388. doi:10.1016/j.jacc.2017.05.051