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Can we improve cardiovascular disease for women using data under our nose? Policy and focus changes needed

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Abstract

Cardiovascular disease (CVD) remains the leading cause of death among women, resulting in 418,665 deaths in 2016, and accounts for 1 in every 4 female deaths in the United States.[1] There are important sex and gender differences in CVD between women and men that contribute to diagnostic, prognostic and treatment uncertainty, resulting in suboptimal CVD care in women. Understanding and addressing these sex and gender differences is an opportunity to improve human health for both women and men. Notably, 86% of US women have at least one pregnancy, and prior work consistently identifies the 1 in 5 pregnancies with adverse pregnancy outcomes (APOs), such as gestational hypertensive disorders including pre-eclampsia, to elevate risk for future CVD in women.[2] In short, a risk predictor readily available in the vast majority of women – literally under our collective nose - might be harnessed for relevant sex-specific atherosclerotic CVD (ASCVD) risk information to address the preventive, diagnostic and treatment gaps that adversely impact women.

Prior work relating APOs to future CVD in women has been limited due to lack of adequate phenotyping for established CVD risk factors, relatively short-term or incomplete follow-up, and lack of accurate APO adjudication. This prior work has not demonstrated sufficiently elevated risk ratios within these limited datasets needed to substantially improve existing CVD risk prediction scores in women.[3] Specifically, because many/most of the APOs include gestational hypertension and preeclampsia, which are strongly linked to hypertension, it has remained unclear if the increased CVD risk is simply due to hypertension versus more unique aspects of APOs. To fill these knowledge gaps, Sondergaard and colleagues present in a very large multiethnic cohort of women more densely phenotyped with longer term follow-up and APO adjudication from the Women's Health Initiative (WHI). They convincingly show that hypertensive disorders of pregnancy and low birth weight independently predict future CVD in women after adjustment for established risk factors and other APOs.

Notably, while the authors conclude that both these APOs should be sufficient risk enhancers to incrementally increase ASCVD risk, recent data from the Nurses' Health Study (NHS) II did not find that adding hypertensive disorders of pregnancy to the ASCVD risk prediction model improved discrimination or risk reclassification.[4] Several noteworthy

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differences between the current cohort and the NHS II most likely accounted for this. In the NHS II, women were surveyed at 3 different time points, and were much younger (mean age at first survey 41.5 yrs) resulting in overall low CVD risk. The WHI recruited women between the ages of 50–79 years at baseline with the APO survey taking place over 20 years subsequent to baseline enrollment. The median age of enrollment was reported as 58 years, leading most of these women answering surveys at 78 years and older. It is quite possible that applying the NHS II index to the ASCVD risk prediction model in this older WHI cohort of women might have found a significant difference in reclassification.

This new study appears to be the largest that adjusts not only for known ASCVD risk factors but also adjusts for other APOs and finds independent associations between hypertensive disorders of pregnancy and low birth weight with late ASCVD. Other strengths include the use of a large and multiethnic cohort. Further, the new study includes the adjudication of APOs, where many large cohort studies are limited by the use of self-report APO adjudication which in older women has low to moderate sensitivity, (although the NHS II composition of nurses would likely improve recall). In our previous systematic review, we found low sensitivity when asking even younger mothers to recall hypertensive pregnancies which would be expected lower predictive values.[5] A limitation of the current analysis is that preeclampsia and gestational hypertension were combined and analyzed as hypertensive disorders of pregnancy because many women reported both. These disorders have been shown to have differences in their associations with CVD, e.g. worse outcomes are consistently reported for preeclampsia compared to gestational hypertension,[3] so future study should be designed to separate them.

These data do not address the persistent query of whether women with APOs have a pre-existing subclinical vascular condition that is simply unmasked during pregnancy that elevates CVD risk, or whether APOs result in de novo damage that results in subsequent CVD. Emerging but limited data suggest that many affected women are not completely healthy prior to pregnancy, with some reports describing pre-conception prevalence of obesity, dyslipidemia, dysglycemia, and even overt hypertension that was previously undiagnosed.[6] Preeclampsia, the most common hypertensive disorders of pregnancy, triggers a cascade of inflammatory, oxidative stress, and lipid peroxidase activity which results in global vascular endothelial dysfunction,[7] and may contribute to the pathophysiology of increased CVD risk. We have reported in a cohort of women with evidence of ischemia and no obstructive coronary disease that women with APOs had abnormally low microvascular coronary flow reserve up to 30 years after the index pregnancy, raising the hypothesis that the APOs may be related to dysfunction of the microvasculature.[8]

Women’s health knowledge, including pregnancy, has been dominantly relegated to the specialty of obstetrics and gynecology with relatively little integration with other medical disciplines and this is particularly true for CVD in women. For example, due to the known black box warning of elevated risk of CVD with menopausal hormone therapy, current guidelines suggest that initiation be limited to years from menopause (chronological age) rather than the actual CVD risk (vascular age).[9] While the 2018 ASCVD cholesterol guidelines recognize hypertension during pregnancy as a *risk enhancing factor*;[10] the Sondergaarg new data suggest that this risk enhancement is independent of blood pressure

and should incorporated into a new ASCVD *risk score* for women. Further, should these ASCVD scores be useful for detection and treatment, it will behoove us to mandate coding of APOs in the electronic medical record, which currently is not done. Specifically, medical and surgical history are mandatory elements in the electronic health record (EHR), while pregnancy history is not. Policy action is needed to: 1) add pregnancy/APO history to medical and surgical history required EHR fields; 2) identify and enter APOs into EHR at time of delivery; 3) access APO EHR history by providers and continuity of care systems over the women's lifecourse; 4) calculate atherosclerotic cardiovascular disease (ASCVD) risk scores adding APO history, in order to improve cardiovascular disease (CVD) in women. Finally, these new data support generation of new hypotheses regarding links between APOs and CVD to be tested for sex-specific mechanistic understanding and novel treatments. This will require prioritization of APO EHR inclusion, entry, and use as well as investigative study of an issue under our nose – pregnancy – to improve human health.

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REFERENCES

1. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation 2020;141(9):e139–e596. doi: 10.1161/cir.0000000000000757 [published Online First: 2020/01/30] [PubMed: 31992061]
2. Rich-Edwards JW, Fraser A, Lawlor DA, et al. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev 2014;36(1):57–70. doi: 10.1093/epirev/mxt006 [published Online First: 2013/09/13] [PubMed: 24025350]
3. Heida KY, Bots ML, de Groot CJ, et al. Cardiovascular risk management after reproductive and pregnancy-related disorders: A Dutch multidisciplinary evidence-based guideline. Eur J Prev Cardiol 2016;23(17):1863–79. doi: 10.1177/2047487316659573 [published Online First: 2016/10/30] [PubMed: 27432836]
4. Stuart JJ, Tanz LJ, Cook NR, et al. Hypertensive Disorders of Pregnancy and 10-Year Cardiovascular Risk Prediction. J Am Coll Cardiol 2018;72(11):1252–63. doi: 10.1016/j.jacc.2018.05.077 [published Online First: 2018/09/08] [PubMed: 30190003]
5. Stuart JJ, Bairey Merz CN, Berga SL, et al. Maternal recall of hypertensive disorders in pregnancy: a systematic review. Journal of women's health (2002) 2013;22(1):37–47. doi: 10.1089/jwh.2012.3740 [published Online First: 2012/12/12]
6. Egeland GM, Klungsoyr K, Oyen N, et al. Preconception Cardiovascular Risk Factor Differences Between Gestational Hypertension and Preeclampsia: Cohort Norway Study. Hypertension 2016;67(6):1173–80. doi: 10.1161/hypertensionaha.116.07099 [published Online First: 2016/04/27] [PubMed: 27113053]
7. Friedman SA, Schiff E, Emeis JJ, et al. Biochemical corroboration of endothelial involvement in severe preeclampsia. American journal of obstetrics and gynecology 1995;172(1 Pt 1):202–3. [published Online First: 1995/01/01] [PubMed: 7847535]

8. Park K, Quesada O, Cook-Wiens G, et al. 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. Journal of women's health (2002) 2019:10.1089/jwh.2019.7925. doi: 10.1089/jwh.2019.7925

9. The 2017 hormone therapy position statement of The North American Menopause Society. Menopause 2017;24(7):728–53. doi: 10.1097/gme.0000000000000921 [published Online First: 2017/06/27] [PubMed: 28650869]

10. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2019;73(24):e285–e350. doi: 10.1016/j.jacc.2018.11.003 [published Online First: 2018/11/14] [PubMed: 30423393]