

Preeclampsia and Later Cardiovascular Disease: A Call to Action

Ann C. Celi, MD, MPH, Janet W. Rich-Edwards, ScD, Ellen W. Seely, MD, Joseph P. Frolkis, MD, PhD, Paula A. Johnson, MD, MPH, and Louise Wilkins-Haug, MD, PhD

There is growing knowledge of the association between preeclampsia and later-life cardiovascular disease [1–9]. This association was highlighted last year by the American Heart Association (AHA) including hypertensive disorders of pregnancy as major risk factors for cardiovascular disease in its guidelines for the prevention of cardiovascular disease in women [1]. Yet hypertensive disorders of pregnancy are viewed by many primary care providers and specialists as obstetric conditions, lying exclusively within the domain of the obstetrician-gynecologist. It is time to sound the call to general internists, obstetrician-gynecologists, and family practitioners to put hypertensive pregnancy on their radar screen.

Overview of Preeclampsia

Preeclampsia is a systemic condition involving a complex cascade of immunologic reaction, complement activation, endothelial dysfunction and dysregulation with thrombosis, well described elsewhere [2]. It affects approximately 5% to 8% of pregnancies and is responsible for approximately 18% of maternal deaths in the United States and 13% worldwide [3]. African-American women and women of lower socioeconomic groups are disproportionately affected [4,5].

Women with preeclampsia deliver preterm 15% of the time [6]. In addition to prematurity, 12% of infants born of preeclamptic pregnancies are small for gestational age (intrauterine growth restriction) [7]. Infants born to mothers with preeclampsia have a risk of mortality 5 times greater than those born to women with normal pregnancies, mostly due to the complications of prematurity [6].

The hypertension of preeclampsia generally resolves after delivery or during the postpartum period. Even if preeclampsia persists into the postpartum period, most women are normotensive by 8 to 12 weeks postpartum. Once the postpartum period is past and immediate medi-

cal issues are resolved, preeclampsia is rarely addressed again by the woman's health care providers, even though patients are at increased risk for both recurrence of preeclampsia in subsequent pregnancies and for cardiovascular disease.

What Is the Risk of Cardiovascular Disease After a Hypertensive Disorder of Pregnancy?

Two meta-analyses of large database studies demonstrate that women with a history of preeclampsia have double the risk of cardiovascular mortality in the decades after pregnancy [8,9]. Women who deliver preterm preeclamptic may be particularly vulnerable, with as high as an estimated 9.5-fold increased risk of cardiovascular disease [10–13]. Some have suggested that the physiologic and metabolic demands of pregnancy may be considered an early "stress test" [14], unmasking underlying endothelial dysfunction or other vascular and metabolic defects [1] that will eventually lead to cardiovascular disease. Alternatively, preeclampsia itself may cause endothelial damage, which may present years later as cardiovascular disease [15]. Despite the unclear etiology, preeclampsia is associated with increased future cardiovascular disease risk, with preterm preeclampsia conferring a much greater risk.

Most of the data associating preeclampsia with cardiovascular morbidity is derived from databases that are only able to follow women into the perimenopausal years; it remains to be seen whether women with a history of preeclampsia continue to bear increased cardiovascular risk as they enter the prime years of cardiovascular event incidence [16].

From the Department of Medicine (Drs. Celi, Rich-Edwards, Seely, Frolkis, and Johnson), and the Department of Obstetrics and Gynecology (Dr. Wilkins-Haug), Brigham and Women's Hospital, Boston, MA.

What is Needed to Address the Health Care Needs of Preeclamptic Women?

Studies with Long-Term Follow-Up

Recently, Fraser et al [17], using a modest-sized prospective cohort, presented provocative data suggesting that preeclampsia is associated with increased calculated 10-year cardiovascular risk using the Framingham Risk Score. Fraser's cohort at this point is too young and too small to have accrued enough cardiovascular events to test whether the addition of preeclampsia to the Framingham Risk Score would increase its power to predict actual cardiovascular events. However, the association of preeclampsia with an 30% higher Framingham Risk Score suggests that preeclampsia may be an early warning of cardiovascular risk, an early signal that precedes the development of hypertension, dyslipidemia, and other established risk factors [18]. Unfortunately, few large longitudinal cohort studies of cardiovascular disease risk factors in women have collected data on history of preeclampsia or other pregnancy complications to test the utility of adding preeclampsia history to cardiovascular risk scoring systems. We need to refocus our research on a woman's reproductive years as a window to her present and future cardiovascular health. This knowledge will better inform clinicians how to incorporate this information into clinical risk scores.

Including Reproductive History as Part of the Routine Visit

Unfortunately, a reproductive history is not well incorporated into the routine annual visit with primary care providers; in addition, if such a history is positive, it is not likely that cardiovascular screening and risk reduction will be carried out [19,20]. Reducing women's cardiovascular risk will require recognition and documentation of preeclampsia as a risk factor by primary care providers. Current data suggest that there is limited recognition of preeclampsia as a risk factor for lifelong cardiovascular disease. In a recent study that surveyed primary care providers at an academic medical center, participants had limited knowledge of preeclampsia as a risk factor. Further, only 5% of general internists asked about preeclampsia in their medical histories and only 9% were providing cardiovascular risk-reduction counseling to women with a history of preeclampsia [20]. A first step to cardiovascular risk reduction following a pregnancy complicated by preeclampsia is inclusion of pregnancy outcomes as a routine component of clinical history by all providers of annual care to women. Elec-

tronically linking obstetrical problem lists to medical problem lists would also be helpful in helping to ensure that follow-up issues are addressed [21].

Cardiovascular Risk Reduction Counseling

Although we do not have data to demonstrate that lifestyle modification will decrease CVD risk in women with prior preeclampsia, extrapolation from studies of other groups at increased risk suggest there will be benefit. Women who develop preeclampsia should receive consistent messages to adopt and maintain a cardioprotective lifestyle. Abundant data suggest that cardiovascular disease is preventable with lifestyle modification. In the Coronary Artery Risk Development in (Young) Adults (CARDIA) study [22], which recruited individuals aged 18 to 32 and followed them for 20 years, maintenance of healthy lifestyle factors (heart-healthy diet, never smoking, modest/no alcohol intake, BMI < 25 kg/m², and regular moderate or vigorous physical activity) was strongly related to having a low cardiovascular disease risk profile in middle age. This association persisted even for those patients with a strong family history of cardiovascular disease. The AHA guidelines for prevention of cardiovascular risk in women include the following lifestyle interventions: avoid exposure to cigarette smoke, engage in regular physical exercise, eat a heart-healthy diet rich in fruits, vegetables, and whole grains, and achieve and maintain an optimal body weight [1]. Further study will be needed to discern how effective a cardioprotective lifestyle is in reducing cardiovascular risk and mortality among former preeclamptic women.

Meeting the Challenge

There is sufficient correlative and prospective data linking preeclampsia and cardiovascular disease to encourage all clinicians to elicit a history of preeclampsia and to include it in patients' problem lists. However, this will be a significant challenge. It is not clear that mothers are able to accurately report their preeclampsia history [23], and most electronic medical records systems do not populate longitudinal medical records with clinical data from pregnancy. We need to improve systems to increase both patient and provider awareness and communication regarding preeclampsia history.

We also need to educate primary care providers to see preeclampsia as a condition that has implications beyond pregnancy. Management of women through their lifespan is a core objective of primary care providers, and the brief time spent incorporating this critical component of

the woman's pregnancy history could, as the data presented above suggest, markedly refine their patients' risk profiles. However, primary care clinicians are already tasked with an overwhelming number of items to cover in a typical 15- or 20-minute visit. Increasingly they are asked to navigate care for cancer survivors, postoperative and postprocedural care, and other areas previously in the domain of subspecialists. An even bigger challenge will be to motivate and enable our patients to adhere to healthy lifestyles. Women raising young children likely have multiple distractions and competing demands, and may put their own needs last [24]. Aggressive education efforts targeting this population may not only lead to improvements in women's health, but parental changes may also increase positive health and lifestyle behaviors in their children [25–27], such as perhaps improved eating habits and engaging in physical activity.

Confronting this compelling data, will we be able to implement the changes needed to improve cardiovascular disease prevention for these patients? Can we develop a streamlined process to make the transition smooth from postpartum care to primary care? Can we begin to understand preeclampsia as a medical condition outside the obstetric silo? Can we make communication between caregivers efficient without overburdening? These questions highlight the need for ongoing dialogue between obstetric and maternal-fetal medicine physicians, primary care internists, and family practitioners. Weaknesses in communication between providers has been reported [28]. Improved systems of communication among care providers that are not overburdensome would be an excellent start to address the needs of these high-risk women. Innovative care models, including postpartum follow-up of women with their infants, may facilitate this. Patient education at the time of visit, followed up and expanded through social media networks and patient advocacy groups, would reinforce messages to engage in heart-healthy practices.

We have sounded the call to recognize preeclampsia for its long-term health consequences. Cardiovascular disease is still the leading cause of death among women. It is time for action, an integrated interdisciplinary approach to women's care that uses her reproductive health as a powerful lens to look at women's longer term health and mortality risk.

Corresponding author: Ann C. Celi, MD, MPH, BWH Division of General Internal Medicine, 75 Francis St., Boston, MA 02115, aceli@partners.org.

References

1. 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. *Circulation* 2011;123:1243–62.
2. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33. January 2002. *Obstet Gynecol* 2002;99:159–67.
3. United Nations Population Fund. Accessed at www.unfpa.org/mothers/facts.htm.
4. Tanaka M, Jaamaa G, Kaiser M, et al. Racial disparity in hypertensive disorders of pregnancy in New York State: a 10-year longitudinal population-based study. *Am J Public Health* 2007;97:163–70.
5. Bryant AS, Worjloh A, Caughey AB, Washington AE. Racial/ethnic disparities in obstetric outcomes and care: prevalence and determinants. *Am J Obstet Gynecol* 2010;202:335–43.
6. Goldenberg RL, Rouse DJ. Prevention of premature birth. *N Engl J Med* 1998;339:313–20.
7. Duley L. The global impact of pre-eclampsia and eclampsia. *Semin Perinatol* 2009;33:130–7.
8. 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.
9. McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J* 2008;156:918–30.
10. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ* 2001;323:1213–7.
11. Smith GCS, Pell JP, Walsh D. Pregnancy complications and maternal risk of ischaemic heart disease: a retrospective cohort study of 129,290 births. *Lancet* 2001;357:2002–6.
12. Lykke JA, Langhoff-Roos J, Sibai BM, et al. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension* 2009;53:944–51.
13. Mongraw-Chaffin ML, Cirillo PM, Cohn BA. Preeclampsia and cardiovascular disease death: prospective evidence from the child health and development studies cohort. *Hypertension* 2010;56:166–71.
14. Sattar N, Greer IA. Pregnancy complications and maternal cardiovascular risk: opportunities for intervention and screening? *BMJ* 2002;325:157–60.
15. Oudejans CB, van Dijk M. Placental gene expression and pre-eclampsia. *Placenta* 2008;29 Suppl A:S78–82.
16. Hastie CE, Smith GC, Mackay DF, Pell JP. Maternal risk of ischaemic heart disease following elective and spontaneous pre-term delivery: retrospective cohort study of 750 350 singleton pregnancies. *Int J Epidemiol* 2011;40:914–9.
17. Fraser A, Nelson SM, Macdonald-Wallis C, et al. Associations of pregnancy complications with calculated cardiovascular disease risk and cardiovascular risk factors in middle age: the Avon Longitudinal Study of Parents and Children.

- Circulation 2012;125:1367–80.
18. Rich-Edwards JW. The predictive pregnancy: what complicated pregnancies tell us about mother's future cardiovascular risk. *Circulation* 2012;125:1336–8.
 19. Nijdam ME, Timmerman MR, Franx A, et al. Cardiovascular risk factor assessment after pre-eclampsia in primary care. *BMC Fam Pract* 2009;10:77.
 20. Young B, Hacker MR, Rana S. Physicians' knowledge of future vascular disease in women with preeclampsia. *Hypertens Pregnancy* 2012;31:50–8.
 21. Rich-Edwards JW, McElrath TF, Karumanchi SA, Seely EW. Breathing life into the lifecourse approach: pregnancy history and cardiovascular disease in women. *Hypertension* 2010;56:331–4.
 22. Liu K, Daviglus ML, Loria CM, et al. Healthy lifestyle through young adulthood and the presence of low cardiovascular disease risk profile in middle age: the Coronary Artery Risk Development in (Young) Adults (CARDIA) study. *Circulation* 2012;125:996–1004.
 23. Stuart JJ, Bairey Merz CN, Berga SL, et al. Maternal recall of hypertensive disorders in pregnancy: a systematic review. *J Womens Health (Larchmt)* 2013;22:37–47.
 24. Mosca L, Mochari H, Christian A, et al. National study of women's awareness, preventive action, and barriers to cardiovascular health. *Circulation* 2006;113:525–34.
 25. Chassin L, Presson C, Rose J, et al. Parental smoking cessation and adolescent smoking. *J Pediatr Psychol* 2002;27:485–96.
 26. Darling N, Cumsille P. Theory, measurement, and methods in the study of family influences on adolescent smoking. *Addiction* 2003;98 Suppl 1:21–36.
 27. West F, Sanders MR, Cleghorn GJ, Davies PS. Randomised clinical trial of a family-based lifestyle intervention for childhood obesity involving parents as the exclusive agents of change. *Behav Res Ther* 2010;48:1170–9.
 28. MacDonald SE, Walker M, Ramshaw H, et al. Hypertensive disorders of pregnancy and long-term risk of hypertension: what do Ontario prenatal care providers know, and what do they communicate? *J Obstet Gynaecol Can* 2007;29:705–10.

Copyright 2013 by Turner White Communications Inc., Wayne, PA. All rights reserved.