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Commentary

Pregnancy Is a Screening Test for Later Life Cardiovascular Disease: Now What? Research Recommendations

James M. Roberts, MD [a,*], Janet M. Catov, PhD, MS [a,b]

[a] *University of Pittsburgh Magee-Womens Research Institute, Department of Obstetrics Gynecology, Epidemiology and Clinical and Translational Research, Pittsburgh, Pennsylvania*
[b] *University of Pittsburgh Magee-Womens Research Institute the Obstetrics & Gynecology and Epidemiology Departments, Pittsburgh, Pennsylvania*

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Introduction

Several months ago, we wrote a commentary describing pregnancy as a screening test for later life cardiovascular diseases in mothers (Roberts & Hubel, 2010). We emphasized the well-established relationship of preeclampsia and gestational diabetes with later life cardiovascular disease and carbohydrate intolerance, respectively. We also pointed out the less well-established relationships of preterm birth, other pregnancy disorders associated with abnormal placental implantation, and even pregnancy itself with later life heart disease. We further considered the purported protective effect of breastfeeding to reduce cardiovascular disease. In the presentation, we complained that the 2007 American Heart Association's "Evidence Based Guidelines for Cardiovascular Disease Prevention in Women" (Mosca et al., 2007) did not include a pregnancy history as a part of the evaluation of cardiovascular risk for women. We are happy to point out that the new 2011 guidelines from the American Heart Association do include a recommendation to obtain a pregnancy history and also consider both preeclampsia and gestational diabetes as risk factors for later life maternal cardiovascular disease (Mosca et al., 2011).

The question that now arises is how are we to use this information? For gestational diabetes, we need to determine the most cost-effective follow-up to at least identify and perhaps prevent diabetes in later life. For preeclampsia (and by extension other relevant pregnancy disorders), the answer is not at all obvious. Once the pregnancy history of preeclampsia is determined, what is next? Little information is available to guide actions for clinicians. What testing should be done? When should this be done? Is there information to justify testing women with a history of preeclampsia earlier in life than is currently recommended for all women? In this presentation, we attempt to determine the gaps in knowledge that preclude rational decision making. Further, we ask if the information regarding the risk association with pregnancy outcomes can be extended by gathering information in more detail or by association with other risk factors or by laboratory testing. Finally, we outline research needed to guide the rational use of this information.

What to Do with the Information Gained by Pregnancy History?

On the basis of what is currently known, it seems reasonable to emphasize lifestyle modification for women with preeclampsia and gestational diabetes to reduce other coincident risk factors, including smoking, obesity, and sedentary lifestyle. Beyond this, there is little to guide the care provider on how to use the information. If we begin by considering gestational diabetes, the evidence of later life association with diabetes outside of pregnancy is incontrovertible. Consequently, for many years it has been recommended that women with gestational diabetes be tested 6 to 10 weeks after pregnancy for carbohydrate intolerance (Bellamy, Casas, Hingorani, & Williams, 2009). This screening is rarely done and there is no evidence of cost benefit for this approach, if it were introduced. A disconnect between obstetric care and adult preventive care also impedes implementation and evaluation of this recommended screening. In addition, there is no information to guide recommendations for frequency or duration of follow-up. Nor has the impact of this intervention been addressed for cost benefit. This area needs to be addressed specifically.

The situation with preeclampsia is even less well studied, with little evidence-based information to guide recommendations to determine who should be referred for evaluation, when, how often the evaluation should be done, and what should be measured.

* Correspondence to: James M. Roberts, MD, University of Pittsburgh, Magee Womens Research Institute, Obstetrics and Gynecology and Epidemiology, 204 Craft Avenue A311B, Pittsburgh, PA 15213. Phone: +1 412 641 1427; fax: +1 412 641 1503.
E-mail address: jroberts@mwri.magee.edu (J.M. Roberts).

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What Information is Needed?

We present in Figure 1 a brief pregnancy history form that we suggest would be useful. In prior studies with a more complex questionnaire, it is evident that women reliably report their pregnancy events many years after pregnancy (Tomeo et al., 1999). However, validation and refinement of proposed pregnancy history questions are needed.

It would be helpful if the cardiovascular risk associated with preeclampsia could be "fine-tuned." Meta-analyses have identified a doubling of the risk for cardiovascular disease for all women with preeclampsia (Bellamy, Casas, Hingorani, & Williams, 2007). We also know that, in certain subtypes of preeclampsia, the risk of later life cardiovascular disease is much higher. Women with recurrent preeclampsia have an approximately 3- to 5-fold increase of later life cardiovascular death (Funai et al., 2005). Preeclampsia usually occurs after 37 weeks gestation but in the 5% to 10% of preeclamptic women who deliver before 34 weeks gestation, the cardiovascular risk is much greater. In a recent U.S. study of the Kaiser Permanente population, 14,000 women who had preeclampsia before 34 weeks gestation were followed for a median of 37 years. There was an almost 10-fold increased risk for later life cardiovascular death (Mongraw-Chaffin, Cirillo, & Cohn, 2010). Based on these striking differences from other variants of preeclampsia, there is rationale to stratify assessment strategies based on these two clinical findings that can easily and accurately be assessed by history. Other clinical features of preeclampsia that might be useful for stratification of risk include the severity of preeclampsia or the association with or without small-for-gestational-age infants. Evidence regarding the modification of risk by race would also be useful. However, currently no sufficient data exist to test whether these interactions modify risk.

Preeclampsia is generally associated with profound modification of lipids, insulin sensitivity, oxidative stress, and inflammation (Roberts & Hubel, 2009). However, a characteristic of preeclampsia is a wide variation of laboratory findings with quite abnormal results for some women, whereas other women have results in the normal range. Does the magnitude of abnormality correlate with later life risk? Abnormal metabolic or cardiovascular functional changes might also be exploited with postpartum examination of women who have had preeclampsia. Because not all women who have had preeclampsia develop cardiovascular disease, is it possible that women with the most abnormal findings in the year or so postpartum are the group with the greatest long-range risk?

Another question relevant to identifying subsets of women with preeclampsia who might be at increased risk is whether the coincidence of preeclampsia with known risk factors increases risk. We know, for example, that obesity increases the risk for preeclampsia and for later life cardiovascular disease, but is the combination of preeclampsia and obesity nonadditive, additive, or synergistic? This question leads to another area that must be clarified. Although preeclampsia is more common in women

Pregnancy History

1. How many pregnancies have you had?	
2. How many miscarriages?	
3. After how many pregnancies did you breastfeed?	
a. How many months after each pregnancy?	
b. Did you supplement with formula?	☐Yes ☐No
1) How old was the baby (months) when you started formula?	
4. Were any of your babies born early (more than 3 weeks before your due date)?	☐Yes ☐No
a. How many?	
b. Did this occur spontaneously or were you delivered early because you were ill?	☐Yes ☐No
5. Did you have preeclampsia in any of your pregnancies?	☐Yes ☐No
a. Which pregnancy?	
b. How many times?	
c. Were you delivered early because you had preeclampsia?	☐Yes ☐No
1) How many weeks before your due date were you delivered?	
6. Did you have high blood pressure in any pregnancy?	☐Yes ☐No
a. Did you have protein in your urine in that pregnancy?	☐Yes ☐No
7. Did you have gestational diabetes?	☐Yes ☐No
a. Were you treated with insulin?	☐Yes ☐No
b. Were you treated with blood sugar lowering pills?	☐Yes ☐No
8. What was the weight of your babies?	
Baby #1 _____ lbs _____ ounces	
Baby #2 _____ lbs _____ ounces	
Baby #3 _____ lbs _____ ounces	
Baby #4 _____ lbs _____ ounces	
Baby #5 _____ lbs _____ ounces	
Baby #6 _____ lbs _____ ounces	

Figure 1. Suggested brief pregnancy history form.

with cardiovascular risk factors, is it possible that it adds nothing to recognizing risk of cardiovascular disease? Will the currently recommended approach for the assessment of cardiovascular risk factors in women identify all of the coincident risk factors of preeclampsia and cardiovascular disease (Berg, Atkins, & Force, 2008)? If so, does testing for these factors earlier in life in women with a history of preeclampsia have a cost–benefit value?

A difficult question that must be addressed is the possibility that preeclampsia causes later life cardiovascular disease. This has not been the favored hypothesis for several reasons. First, any purported effect of preeclampsia would seem to also imply a similar but less severe effect of normal pregnancy, which is more similar physiologically to preeclampsia than to the nonpregnant state (Roberts & Hubel, 2009). The HUNT study in Norway provides some support for this concept. In this study blood samples were available before and after 2,964 normal or 261 hypertensive (168 preeclamptic and 93 gestational hypertensive) pregnancies. Preeclamptic women had an excess of metabolic and cardiovascular difference relative to women who had normal pregnancies. However, depending on the abnormality, 40% to 70% of these findings were present before pregnancy (Romundstad, Magnussen, Smith, & Vatten, 2010). This indicates that the majority of, but perhaps not all, differences are coincident for preeclampsia and later life cardiovascular disease, but does not exclude a role of preeclampsia in a portion of these differences. Also, because the control group for studying cardiovascular risk in preeclampsia usually consists of women with normal pregnancy outcomes, is it possible that normal pregnancy has a protective effect on the cardiovascular system? There are data to suggest this is true and the concept warrants further investigation (Lawlor et al., 2003).

Research Deficits

The multiple unanswered questions discussed indicate numerous deficits in the knowledge necessary for utilization of information gained by pregnancy history. There are other deficits. The American Heart Association guidelines acquire information about problems of pregnancy other than preeclampsia and gestational diabetes, but only these two pregnancy problems are considered as risk factors. Although not as well-established as preeclampsia, there is epidemiological evidence indicating a substantial risk of cardiovascular disease in women who have delivered preterm infants (Catov, Wu, et al., 2010; Irgens, Reisaeter, Irgens, & Lie, 2001; Lykke et al., 2009). In a large, Norwegian, database study in which both conditions were related to cardiovascular disease a median of fourteen years after a first pregnancy, the risk associated with preterm birth (2.96; 95% confidence interval, 2.12–4.11) without preeclampsia was intermediate between preeclampsia occurring at term or preterm (Irgens et al., 2001). In keeping with this relationship, there is evidence of dyslipidemia in women who have delivered preterm before, during, and after the index pregnancy (Catov et al., 2011; Catov, Ness, et al., 2010; Catov, Parks, & Roberts, 2010). In the United States, preterm birth is substantially more common than preeclampsia (approximately 10% vs. 4%) and warrants further documentation as a cardiovascular risk factor.

There seems to be a relationship between abnormal implantation, abnormal endothelial function, and the metabolic syndrome. Women with preeclampsia or recurrent abortion have abnormal endothelial function years after the abnormal pregnancy (Agatisa et al., 2004; Germain et al., 2007). Thus, it is unlikely that only the pathophysiology of preeclampsia leads to cardiovascular disease in later life (because there is no maternal syndrome with recurrent abortion), but rather indicates that an underlying condition predisposes to the implantation disease and cardiovascular dysfunction. Women with polycystic ovarian syndrome characterized by oligo-ovulation, obesity, and insulin resistance have increased occurrences of preeclampsia and preterm birth during pregnancy (Roos et al., 2011). There are more preterm births in second "normal pregnancies" of women with early onset of preeclampsia in their first pregnancy (Lain, Krohn, & Roberts, 2005). It should not be surprising that these disorders in large populations demonstrate excess risk of cardiovascular disease in later life that increases with the severity and number of pregnancy disorders (Ray, 2006). This relationship should be explored.

Our suggested pregnancy questionnaire requests information about breastfeeding. An emerging literature indicates a reduction in cardiovascular deaths among women who have breastfed that is more evident with increasing duration and intensity of breastfeeding, an area well worth exploring for the benefit of mother and baby (Gunderson, 2009; Schwarz et al., 2009). To date, data are limited, because they are obtained from studies not designed to address this important interaction.

Although the relationship of preeclampsia with cardiovascular disease has been studied extensively, there remain large gaps in our knowledge. The metabolic syndrome is more common 1 year (Smith et al., 2009) and several years (Forest et al., 2005) postpartum and cardiovascular events usually are evident 25 to 30 years after preeclampsia. However, there are no longitudinal preeclampsia follow-up studies; thus, we have no knowledge of the natural history of the progression. We are not even certain if metabolic changes demonstrated postpartum persist, that the women with the metabolic abnormality are the same women with cardiovascular disease in later life. An important point for consideration would be at what age (or time after pregnancy) do the number of formerly preeclamptic women manifest a frequency of laboratory abnormalities sufficient to justify screening? There are also very few studies that include prepregnancy and postpregnancy data, and even fewer that are complemented by data gathered during pregnancy. Such studies would help to determine whether pregnancy and preeclampsia merely unmask cardiovascular disease or actually cause or accelerate cardiovascular dysfunction; perhaps the answer is a combination of these effects.

Finally, mechanistic studies are lacking. What is it about pregnancy that unmasks cardiovascular disease? Several animal studies indicate that endothelial function is more sensitive to insults in pregnancy. Endotoxin (Faas, Schuiling, Baller, Visscher, & Bakker, 1994), interleukin-6 (Orshal & Khalil, 2004), tumor necrosis factor-alpha (Giardina, Green, Cockrell, Granger, & Khalil, 2002), and homocysteine (Powers, Gandley, Lykins, & Roberts, 2004) alter vascular function during pregnancy at dosages that have no or minimal effect in nonpregnant animals. Some of the physiological changes of pregnancy—insulin resistance and increased inflammation—may also be relevant, but have not been tested.

Animal modeling for preeclampsia is improving but is still problematic (Orshal & Khalil, 2004). Many perturbations of pregnant animals mimic the clinical findings of preeclampsia (gestational hypertension, proteinuria, and growth-restricted

infants). Some of these models have been studied extensively (LaMarca et al., 2008) and may provide insights into the mechanisms of preeclampsia. However, these models suffer from the axiom, "Just because people who are shot die does not imply that everyone who dies is shot." It is likely that each of these animal models tests one of many pathways to preeclampsia. Recognizing this limitation, such work is nonetheless useful for approaching mechanisms and, in appropriately chosen models, might test the causal relationship of preeclampsia to later life cardiovascular disease.

Research Opportunities

The appreciation of the relationship of preeclampsia to cardiovascular disease provides opportunities to expand the recognition of women at risk for later life cardiovascular disease beyond just those identified by this and similar pregnancy abnormalities. It is also possible that understanding preeclampsia might increase our understanding of the pathophysiology of cardiovascular disease in women.

Preeclampsia explains a relatively small proportion of cardiovascular disease in women. The addition of a predictive role for other pregnancy conditions provides a small increment. However, is it possible that even normal pregnancy might provide insights into later life cardiovascular risk? It is evident that the differences between normal pregnancy and nonpregnant physiology are more striking than the difference between pregnancy physiology and preeclampsia pathophysiology. This is evident for metabolic, inflammatory, and cardiovascular changes (Roberts & Hubel, 2009). It is also evident that there is actually a large overlap between specific metabolic and inflammatory abnormalities with and without preeclampsia. We and others have shown differences between cardiovascular and metabolic findings in women with or without preeclampsia in pregnancies at least a year earlier (Evans et al., 2011). In preliminary studies, it seems that these differences are more striking in subsequent pregnancies even without the development of preeclampsia. Could these findings guide the recognition of cardiovascular disease risk in women with apparently normal pregnancies? Is it possible that the response to pregnancy stressors unmasks cardiovascular disease risk in women without pregnancy abnormalities?

It remains to be established whether all risk for cardiovascular disease with preeclampsia is explained by the coincidence of risk factors. This should be examined epidemiologically. If all of the risk cannot be explained, there are two interpretations. In addition to the possible role of preeclampsia as a causal factor, is it also possible that the two disorders share currently unknown risk factor(s)? This raises the interesting possibility that risk factors identified for preeclampsia might inform additional risk factors for cardiovascular disease.

One of the unique features of pregnancy is the placenta, a complex and functional organ that is the site of intensive maternal fetal interactions. Materials produced by the placenta are proposed as the cause of preeclampsia, because it is with delivery of the placenta that preeclampsia begins to abate. Increasingly, sophisticated studies of the placenta indicate striking differences between the placenta in preeclamptic and normal pregnancies. Is it possible that these differences could be exploited to identify cardiovascular targets or signals that might be similar with preeclampsia and cardiovascular disease?

Research Recommendations

General

1. Validation of a questionnaire to obtain necessary pregnancy history.

Gestational Diabetes

1. We should determine the optimal time and frequency for carbohydrate tolerance testing after pregnancy to achieve a cost-effective testing schedule.
2. Investigations of lifestyle interventions in this high-risk group to reduce the development of later life diabetes are needed.

Preeclampsia

1. Studies should be done to stratify the risk of cardiovascular disease in subsets of formerly preeclamptic women.
   a. Differences in later life risk based on other clinical presentations of preeclampsia (with or without a growth-restricted infant (intrauterine growth retardation or severe versus mild) should be determined.
   b. Studies of whether laboratory findings (e.g., the metabolic syndrome) or cardiovascular findings during or after pregnancy can define a group with increased risk are needed.
   c. In women with preexisting cardiovascular risk factors, is cardiovascular risk additive, synergistic, or unchanged?
   d. Early onset (<34 weeks gestation) and recurrent (more than one pregnancy) already define a high-risk groups that should be exploited when information for how and when to test previously preeclamptic women have been acquired.
2. We should strive to determine how preeclampsia increases the risk of cardiovascular disease.
   a. Is all of the risk or preeclampsia explained by known and shared cardiovascular risks?
      i. If so, we should determine whether testing at an age earlier than current recommendations is cost-risk beneficial.
   b. Attempts should be made to determine whether preeclampsia "causes" cardiovascular disease.
      ii. This could be approached by cardiovascular and metabolic assessment of women before, during, and after pregnancy.
      iii. Animal studies with reversible models of preeclampsia could be useful.
   c. A search for mechanisms by which preeclampsia increases/unmasks risk for cardiovascular disease, should be performed.
   d. Emerging risk factors identified as relevant to preeclampsia should be tested for relevance to cardiovascular disease and vice versa.
3. Studies are needed to determine the optimal tests and timing of testing for risk of later life cardiovascular disease by longitudinal follow-up of women with prior preeclampsia.

Other Pregnancy Outcomes and Factors

1. Studies of the relationship of having delivered preterm to later life cardiovascular disease should be extended.
2. The quantitative relationship of having delivered a growth-restricted infant or having recurrent abortions to later life cardiovascular disease should be assessed.
3. The effect of breastfeeding to reduce later life cardiovascular disease should be examined in studies designed to address the question of duration and intensity.

Research Strategies

Later Life Outcomes

There are several approaches to obtain the data necessary to answer questions related to outcomes after gestational diabetes, preeclampsia, and other adverse pregnancy outcomes, and other lifestyle factors (pregnancy and postpregnancy weight gain, nursing, etc.). Ideally, a prospective collection of a cohort could be initiated in which all the necessary data could be acquired. This would require collecting data not usually collected and longitudinal follow-up at regular intervals for many (more than 40) years. Although this is an expensive and intensive approach, the National Institutes of Health National Institute for Child Health and Development is currently assembling such a cohort with biological samples collected for studies during pregnancy. This cohort could be followed longitudinally after pregnancy with collection of appropriate data. The National Institutes of Health National Heart, Lung, and Blood Institute has expressed interest in this cohort for longitudinal follow-up. Missing from this cohort are women with preexisting cardiovascular diseases. Such a cohort could be used to assess later life cardiovascular risk with shorter follow-up by assessing surrogate outcomes for cardiovascular disease (metabolic syndrome, endothelial dysfunction, vascular and cardiovascular function, etc.).

Less extensive, but very valuable, would be the addition of a questionnaire such as we have included (Figure 1) as part of all cohort studies of cardiovascular disease in women. Alternatively, existing pregnancy databases from years past could be linked with later life outcomes. It is unlikely that the data necessary to answer all of the questions presented would reside in such databases.

The epidemiological assessment of whether preeclampsia is at least in part causally involved in late life cardiovascular disease requires data on prepregnancy status. Such information is not available in the cohorts we have described. It is nearly impossible to acquire prepregnancy data prospectively from women in developed countries because pregnancy is rarely planned (and, if planned, may provide findings from a group that cannot be generalized). Further, preeclampsia occurs in 3% of low-risk pregnancies. Such data might be obtained in countries in which the majority of women are seen prepregnancy and have a high birth (and perhaps preeclampsia) rates, but again might not be generalizable. Another strategy is to exploit existing databases in which biological data are available across the life cycle in ages relevant to pregnancy. Samples would be available in some women before and also ideally after pregnancy. A weakness of many of these date sources is that the diagnosis of preeclampsia is based on maternal recall, well established to be of limited accuracy. Such data could be enriched by review of hospital records, if available.

Intervention Studies

Because gestational diabetes has been clearly related to later life diabetes and cardiovascular disease, the impact of earlier recognition and treatment of nonpregnant diabetes could be generated from a prospective cohort. It would also seem justified and timely to initiate a trial of behavioral and perhaps pharmacological intervention to delay/prevent the development of diabetes after pregnancy in women with gestational diabetes.

Studies of the effectiveness of approaches to modifying behavior in women with a history of preeclampsia and gestational diabetes are justified; the relationship of obesity, smoking, and activity to cardiovascular disease is clearly established.

More aggressive pharmacological interventions await information about the long-term implications of such treatment. These studies would be made more practical by acquiring demographic, clinical, and biological findings during or after pregnancy that enrich the relationship of preeclampsia to later life cardiovascular disease in individual women beyond a 2-fold increase in risk. (Such information is already available for women with preeclampsia delivering before 34 weeks gestation and with recurrent preeclampsia.)

Studies directed at novel but low risk interventions (increased breast feeding, dietary modification, etc.) to modify surrogate outcomes for late life cardiovascular are timely.

Mechanistic Studies

Studies to determine mechanisms for the effect of preeclampsia (and other adverse pregnancy outcomes) to increase later life cardiovascular disease can use epidemiological, clinical, and fundamental research approaches. The databases described could be used to search for increased cardiovascular risk present in preeclamptic women that is not explained by currently evident coincident risk factors. The presence of residual risk would stimulate a search for novel risk factors. Intensive assessment of metabolic, vascular, and cardiovascular differences between women with and without preeclampsia during and after pregnancy could suggest mechanisms that could be tested by interventions to modify the relevant risk factor.

Animal models of “preeclampsia” in which the interventions leading the “preeclampsia-like” changes are reversible with pregnancy termination might provide useful insights. Do animals with such an intervention have an increased risk of adverse cardiovascular outcomes in follow-up after pregnancy? The assessment of such models superimposed on known preexisting cardiovascular risks could be especially revealing.

Summary

The recognition of the association between pregnancy and later life cardiovascular disease should provide new insights to earlier recognition of cardiovascular risk status for women. To exploit this knowledge several questions, which we hope will be targets for research in the near future, must be answered.

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Author Descriptions

James M. Roberts, MD, is a Senior Scientist at the Magee-Womens Research Institute and a Professor of Obstetrics Gynecology, Epidemiology and Clinical and Translational Research. He has worked for many years as a clinician caring for high-risk women and an investigator studying adverse pregnancy outcomes. Dr. Roberts is also a member of the Women's Health Issues Editorial Board.

Janet M. Catov, PhD, MS, is an Assistant Professor at the University of Pittsburgh in the Obstetrics & Gynecology and Epidemiology Departments, and an Assistant Investigator at the Magee-Womens Research Institute. She is reproductive epidemiologist and has employed several strategies to study the relationship between pregnancy and later life maternal cardiovascular disease risk.