Breathing Life Into the Lifecourse Approach
Pregnancy History and Cardiovascular Disease in Women


The lifecourse approach to epidemiology has broadened our understanding of chronic disease as a developmental process that evolves over the entire lifespan. Subclinical syndromes at an early phase in life may offer insights into later health that are not presently recognized. For example, a woman’s reproductive history is an often overlooked predictor of later chronic disease. Increasing evidence suggests that pregnancy complications unmask predisposition to cardiovascular disease and may serve as cardiovascular risk markers particular to women. Because cardiovascular disease is the leading cause of death among women, an understanding of the ways in which pregnancy complications presage risk, or possibly alter risk, can further the understanding of cardiovascular disease mechanisms.

In 2002, Sattar and Greer suggested that pregnancy constitutes a physiological “stress test” that reveals latent chronic disease (Figure, A). The authors highlighted the implications for future maternal cardiovascular risk of 4 common pregnancy complications: gestational diabetes, hypertensive disorders, low birthweight delivery (<2500 g), and preterm delivery (<37 weeks). For brevity, we refer here to this group of syndromes as “complicated pregnancies,” recognizing that less prevalent pregnancy complications may also predict cardiovascular risk. As a group, these complicated pregnancies are characterized by inflammation, vasculopathy, altered angiogenesis, thrombosis, and insulin resistance: pathophysiologic processes common to coronary heart disease and stroke. Our intent is to update the growing literature, outline research needs, and question whether it is time to incorporate pregnancy history into cardiovascular risk assessment.

Gestational Diabetes
Gestational diabetes (GDM) affects as many as 5% of pregnancies. Since the 1980s, it has been clear that GDM has major implications for the mother beyond pregnancy: roughly half of women with previous GDM will develop type 2 diabetes (T2DM) within 10 years. The Fifth International Workshop-Conference on Gestational Diabetes and the American Diabetes Association recommended enhanced glucose testing schedules for women with a GDM history. Despite these recommendations, rates of T2DM screening remain low in women with a history of GDM. A GDM diagnosis may also provide a window of opportunity for diabetes prevention, because risk for T2DM may be lowered with a lifestyle modification or medication. Such preventive interventions may also avert cardiovascular disease, as suggested by a finding of 70% higher risk of cardiovascular disease among women with a GDM history. The increased risk is attributable largely to T2DM but may also stem from abnormal vascular function among women with GDM who have not developed T2DM.

Preeclampsia
Preeclampsia is a hypertensive disorder of pregnancy that affects ≈5% of pregnancies. Former preeclamptic patients have ~4-fold higher incidence of hypertension and twice the risks of heart disease, stroke, and venous thromboembolism. Recurrent preeclampsia has been associated with end-stage renal disease and hypothyroidism. Preeclampsia has been associated with insulin resistance, endothelial dysfunction, and antiangiogenic factors in maternal circulation; these and other cardiovascular risk factors may predate preeclamptic pregnancies and simply persist postpartum. On the other hand, preeclampsia itself may be a risk factor for future cardiovascular disease, through persistent subclinical systemic vascular damage or endothelial dysfunction occurring in women who were healthy before the onset of preeclampsia; however, definitive evidence for this hypothesis is lacking.

Preterm Delivery
Preterm delivery (<37 weeks of gestation) accounts for >12% of deliveries in the United States and 5% to 9% of deliveries elsewhere in the developed world. Mothers who have delivered preterm infants have at least double the risk of cardiovascular disease. The strength and nature of the association of preterm delivery with future cardiovascular risk likely depends on whether the preterm birth was medically indicated or spontaneous, as well as any precipitating complications. The main indications for medically indicated preterm births are preeclampsia and fetal growth restriction. It is not clear how much of the association of preterm delivery
with cardiovascular risk is driven by preeclampsia as the indication for early delivery. The combination of preterm delivery and preeclampsia is particularly predictive of future risk of cardiovascular disease, with 7-fold higher risks for women with preterm preeclamptic pregnancies compared with normotensive term deliveries.\textsuperscript{18}

Spontaneous preterm birth has a clinical profile reminiscent of cardiovascular risk. Women with a history of spontaneous preterm delivery have higher inflammatory levels, larger waist circumference, and dyslipidemia years after delivery.\textsuperscript{22} The extent to which spontaneous preterm birth predicts cardiovascular events is presently unknown but is suggested by the 3-fold increased risk of cardiovascular mortality observed among women with a history of nonpreeclamptic preterm deliveries, a high proportion of which are likely spontaneous.\textsuperscript{18}

**Neonatal Birthweight**

Neonatal birthweight predicts maternal lifespan.\textsuperscript{23–27} Maternal cardiovascular mortality drops by 25\% per standard deviation higher birthweight.\textsuperscript{25} Low birthweight (<2500 g) infants comprise \(\approx\)8\% of births; their mothers have double the risk of cardiovascular mortality of mothers of normal birthweight infants (3500 g).\textsuperscript{23–26} Low neonatal birth weight usually results from intrauterine growth restriction or from preterm birth, resulting in a neonate appropriate for gestational age but smaller than term. Because these reasons for low birthweight differ in their pathogenesis, their links to cardiovascular risk prediction may differ as well.

By the age of menopause, we estimate that at least 20\% of all women will have had a pregnancy complicated by diabetes, preeclampsia, a low birthweight infant, or preterm delivery. This figure is undoubtedly higher for black women, who are 50\% to 100\% more likely than white mothers to have poor pregnancy outcomes\textsuperscript{28} and 30\% more likely to die from cardiovascular disease than white women.\textsuperscript{29}

A full understanding of the utility of pregnancy history for cardiovascular disease prevention requires multidisciplinary efforts from epidemiologists, basic researchers, and patient-oriented researchers. Clinically, we need to integrate the pregnancy care delivered by obstetricians and nurse midwives with primary care performed by internists. Although electronic medical records should aid in this integration, alterations in beliefs regarding the utility of reproductive events in predicting cardiovascular disease may require changes in provider training.

Several steps are prompted by the emerging data linking complicated pregnancies with cardiovascular risk. To maximize the utility of the pregnancy history, we need to:

1. Fully characterize the trajectories that lead from complicated pregnancies to cardiovascular events for different populations of women. It will be important to determine the extent to which these overlapping pregnancy complications predict cardiovascular risk independent of each other. For example, to what extent does a history of preterm birth predict future cardiovascular disease risk after accounting for preeclampsia? We also
need to identify the particular definitions and combinations of pregnancy complications that are the most sensitive and specific for predicting cardiovascular disease in maturity. For example, is cardiovascular risk best, and most simply, predicted by the history of any of these 4 complications, or is it more effective to capture the joint occurrence of particular complications, such as preterm preeclampsia? The answers to these questions require large longitudinal data sets that include data on pregnancy complications, cardiovascular risk factors, lifestyle risk factors, and cardiovascular events.

2. Determine the time course from complicated pregnancies to the first emergence of cardiovascular risk factors to develop screening schedules for women with and without particular pregnancy complications. We already have screening recommendations for women with a history of gestational diabetes; should we develop similar guidelines for lipid screening for women who have delivered preterm? Directed research to determine the predictive value of pregnancy complications will enable the development of such recommendations.

3. Determine the independent contribution of complicated pregnancies to cardiovascular disease risk, above and beyond the suite of cardiovascular risk factors that are screened as routine preventive care. Would pregnancy history add to the prognostic value of cardiovascular risk scoring systems such as the Framingham or Reynolds scores?

4. Develop partnerships between researchers, clinicians, and information systems managers to link prenatal to primary care records, so that women’s primary care providers are alerted to the pregnancy history of their parous patients.

5. Promote truly translational research to establish experimental animal models to determine whether pregnancy complications may exacerbate underlying endothelial dysfunction leading to novel organ damage in the mother, increasing her risk of future disease, or whether complications are simply markers of latent disease risk.

6. Foster obstetric and internal medicine cross-training: include obstetric rotations or electives in internal medicine residencies and continue to require internal medicine rotations in obstetric training.

The stress test of pregnancy provides glimpses into the otherwise silent early adult years in which chronic disease trajectories are set, yielding important prognostic data at an early life phase when targeted prevention is more timely and effective. Researchers need to elucidate the specific pathways through which complicated pregnancies predict and/or cause cardiovascular disease and need to explore the utility of detailed pregnancy history as an essential part of women’s clinical history. We have the opportunity to change disease trajectories before they emerge as chronic disease at menopause (Figure, B). It is time to breathe life into the lifecourse approach by applying our growing knowledge of the importance of pregnancy history to prevent and better treat cardiovascular disease in women.

Acknowledgments

We thank Dr Susan Mason and Eileen Hibert for assistance in estimating the lifetime prevalence of complicated pregnancies and to Michael Cichanowski for preparing the figure.

Sources of Funding

This research was supported by a pilot grant from Harvard Catalyst/ The Harvard Clinical and Translational Science Center (National Institutes of Health grant 1 UL1 TR002578-02 and financial contributions from participating institutions). E.W.S. was funded by NHLBI grant K24HL096141. The funding body had no input or influence on the contents of this article.

Disclosures

S.A.K. is a co-inventor on patents related to the use of angiogenic proteins in pre-eclampsia diagnosis/prediction. These patents have been licensed to several companies. S.A.K. is a consultant to Abbott Diagnostics, Beckman Coulter, Roche and Johnson & Johnson that are developing angiogenic factor assays.

References


