The Predictive Pregnancy

What Complicated Pregnancies Tell Us About Mother’s Future Cardiovascular Risk

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For the first time, the American Heart Association 2011 Guidelines on the Prevention of Cardiovascular Disease in Women named pregnancy complications as risk factors for cardiovascular disease.1 The committee recommended that clinicians query a detailed history of gestational diabetes mellitus, preeclampsia, preterm delivery, or delivery of a small-for-gestational age-neonate as part of routine clinical intake. They urged obstetricians to refer women with complicated pregnancies to primary care or cardiology for monitoring of cardiovascular risk factors. This novel recommendation is based largely on recent discoveries emerging from the big epidemiology of linked national birth and death registry databases in Europe. These studies have shown consistent statistical associations between history of pregnancy complications and significantly increased risk of cardiovascular disease (CVD) in the decades after complex pregnancy.2–9 Yet, based as they are on administrative records, these studies are largely silent on the clinical course from complicated pregnancy to CVD event. What, exactly, is a clinician to do with the knowledge that a history of pregnancy complications doubles CVD risk as a woman matures? To fulfill the promise of the American Heart Association recommendation, we need data to determine appropriate prevention strategies, screening schedules, clinical targets, and treatment regimens for the large proportion of women who bear a telling history of complicated pregnancy.10

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In this issue of Circulation, Fraser and colleagues provide findings that begin to put clinical flesh on the statistical associations between complicated pregnancy and CVD risk.11 In their 18-year follow-up of 3416 women originally enrolled during pregnancy in the Avon Longitudinal Study of Parents and Children (ALSPAC), Fraser and colleagues document that 36% of mothers had index pregnancies complicated by hypertension, gestational diabetes mellitus, preterm delivery, fetal growth restriction, or macrosomia. Because most women bear >1 child, the lifetime prevalence of complicated pregnancy is even higher. With the exception of macrosomia, each of these pregnancy complications has been associated with 50% to 300% elevated risk of CVD; combined pregnancy complications, such as preterm preeclampsia, carry even higher risks of CVD.2–9 The excess CVD risk associated with a history of complicated pregnancy rivals that of cigarette smoking12 and parental history of CVD.13

To describe the emerging CVD risk after complicated pregnancies, Fraser and colleagues examined a set of established individual CVD risk factors, which they also assembled into a Framingham risk score for CVD events. Not surprisingly, the women with glycosuria or diabetes mellitus during pregnancy had higher levels of fasting glucose and insulin many years after the pregnancy; we know from previous studies that nearly 50% of women with a history of gestational diabetes mellitus will develop type 2 diabetes mellitus within 10 years.14 In fact, several organizations have called for an aggressive glucose-screening schedule in the years after a diabetic pregnancy.14,15 Gestational diabetes mellitus is perhaps the poster child for a pregnancy complication that can be used to target early screening and intervention to prevent long-term chronic disease.

Fraser also found that, nearly 2 decades after pregnancy, women with a history of gestational hypertension or preeclampsia had elevated body mass index, waist circumference, and blood pressure compared with women who had had normotensive pregnancies. Both hypertensive pregnancy groups appeared to have elevated levels of C-reactive protein, glucose, proinsulin, low-density lipoprotein, and lower high-density lipoprotein, although these were not always statistically significant, especially in the smaller preeclampsia group. Overall, the 16% of women with a history of hypertensive pregnancy had 30% higher Framingham risk scores than women with normotensive pregnancies—even after adjustment for their prepregnancy body mass index.

The last pregnancy complications that Fraser and colleagues examined were extremes of fetal growth and preterm delivery. Women who had borne small-for-gestational-age infants had elevated blood pressure nearly 20 years later; women who had delivered macrosomic infants had more central adiposity and mild elevations in a range of risk factors, largely explained by their prepregnancy body mass index. Perhaps the most surprising finding, given the evidence from large registry studies that preterm delivery is associated with increased CVD risk,2,4–6 is the lack of association of preterm delivery with elevated CVD risk factors among the 139 ALSPAC participants who had pre-
term births. This may be the result of the modest number of preterm deliveries in the cohort. Alternatively, preterm delivery may be associated with CVD risk through pathways not captured by the conventionally screened CVD risk factors that Fraser tested.

Fraser’s article tells us about the association of pregnancy complications with established CVD risk factors that are screened systematically as women mature, but are rarely tested in young women. Thus, it is not known whether the women with complicated pregnancies had underlying CVD risk before pregnancy. Although the very definitions of preeclampsia and gestational diabetes mellitus require that women return to normal levels of blood pressure and glucose tolerance in the postpartum period, new research suggests that complicated pregnancies may be preceded by a variety of undetected clinical or subclinical CVD risk factors.17 Regardless of the origin of the CVD risk, Fraser’s findings in the 2 decades after pregnancy suggest that pregnancy history may serve as an early stress test revealing CVD risk.18

The ALSPAC cohort is still young—follow-up was to a mean age of 48 years—and CVD risks may or may not continue to diverge for women with and without complicated pregnancies. Further longitudinal research needs to document exactly when and by how much the CVD risk factors diverge after complicated pregnancy. Armed with this information, we can begin to assess the utility and cost-effectiveness of using pregnancy history as an early CVD screen.

By identifying pregnancy risk factors that predict subsequent CVD risk factors, Fraser’s findings suggest that pregnancy complications can predict CVD risk earlier than conventional CVD risk-screening protocols. However, their data cannot answer an equally pressing question: could pregnancy history predict CVD risk better than current screening protocols? At present, global risk scores, such as the Framingham risk score, are less sensitive for women than they are for men, and identify few high-risk women before the age of 70 years.19 The utility of pregnancy history to improve CVD risk prediction can be assessed only in data sets that are large enough and long-running enough to test the extent to which pregnancy history predicts the risk of actual CVD events above and beyond the traditionally screened CVD risk factors that were tested in the paper by Fraser and colleagues. Unfortunately, very few cohorts have collected sufficient detail on pregnancy history to address this question: the addition of pregnancy complication history to longitudinal cohorts and trials should be a high priority.

This emerging literature begs a larger question: are pregnancy complications anything more than useful early markers of subclinical CVD risk before the pregnancy started? Could pregnancy complications actually increase CVD risk by damaging vasculature or altering metabolism? This question requires experimental methods, including the induction of preeclampsia or gestational diabetes mellitus in animal models and examining whether pregnancy complications cause enduring cardiovascular pathology in the surviving mother.20 If so, the prevention of pregnancy complications becomes all the more urgent.

The potential to use pregnancy history to identify young women at increased CVD risk is important. The pregnancy complications that predict CVD risk are widely prevalent, especially among black women who are at elevated CVD risk and are less likely to access preventive health care and CVD screening as they age. Pregnancy complications emerge early enough in a woman’s life course to offer a meaningful runway for primordial CVD prevention by lifestyle intervention. They may be useful for earlier identification of women who would benefit from primary pharmaceutical prevention. If, in fact, pregnancy history tells us about CVD risk above and beyond our conventional risk assessment, then pregnancy history could prove to be a meaningful improvement to current screening protocols. Finally—and most speculatively—if preventing pregnancy complications could alter a woman’s trajectory toward chronic disease, we could simultaneously improve pregnancy outcomes for neonates and reduce CVD risk for their mothers by preventing pregnancy complications to begin with.

There is much more work to be done. For pregnancy history to prove useful in clinical practice, we need evidence that women with particular pregnancy complications will benefit from specific preventive and therapeutic options that we would not otherwise have prescribed. Yet, if this approach survives trials of its practical utility, it could fundamentally alter the way we deliver preventive care. For much of the history of Western medicine, pregnancy was effectively quarantined in a specialty silo apart from all other aspects of health. Fraser’s work contributes to a new paradigm in which we can exploit for women’s clinical benefit the intimate connections between reproductive and cardiovascular health.

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Disclosures

None.

References


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