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Pregnancy and Subsequent Glucose Intolerance in Women of Childbearing Age:

Heeding the Early Warning Signs for Primary Prevention of Cardiovascular Disease in Women

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The increased physiologic and metabolic demands of pregnancy act as a “stress test” that may reveal underlying subclinical disease or provide insight into future chronic disease. Pregnancy complications, such as gestational diabetes (GD) and hypertensive disorders, are “early warning” signs for chronic disease in women decades before the menopausal transition. More than 50 years ago, O’Sullivan and Mahan¹ developed criteria for the diagnosis of GD, glucose intolerance first recognized during pregnancy, based solely on observed higher rates of progression to diabetes in women many years postdelivery. A history of GD confers a 7-fold higher risk of type 2 diabetes mellitus and 3-fold higher cardiometabolic risk for women. In 2011, the American Heart Association added GD history to its CVD risk assessment for women based on the strong link to overt diabetes.² Until recently, evidence was insufficient to determine whether a history of GD elevated CVD risk independent of its association with overt diabetes and metabolic disease.

In this issue of *JAMA Internal Medicine*, Tobias and colleagues³ present findings from the Nurses’ Health Study (NHS) confirming higher rates of incident CVD (myocardial infarction and stroke) among women with a history of GD who later develop diabetes than among women without GD or diabetes, accounting for self-reported risk factors during a median 25 years of follow-up. Their new finding is the borderline 30% higher relative risk of CVD events in women with a history of GD who did not develop diabetes compared with women without GD or diabetes. After accounting for weight change and lifestyle behaviors, this excess CVD risk was attenuated to a 20% higher risk for these women. However, this was in the context of a low absolute risk, and so the absolute excess risk was also low (0.07/1000 person-years), but represents 26% of overall excess risk associated with GD (0.27/1000 person-years). This evidence shows that a history of GD may increase CVD risk distinct from overt diabetes or differences in lifestyle behaviors. However, neither the NHS nor a recent Canadian study using administrative databases collected biochemical data,

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which precluded evaluation of whether CVD risk varies by degree of insulin resistance, GD severity, or subclinical profiles among women with GD and no diabetes. Moreover, the study may underestimate excess risk by exclusion of higher-risk women with CVD events before NHS baseline that differentially affect women with a history of GD, and misclassification of older women not universally screened for GD. Finally, this evidence generalizes only to women of Northern European ancestry.

Other previous longitudinal biochemical evidence showed that a history of GD may increase risk of atherosclerosis even without impaired glucose tolerance or dyslipidemia before and after pregnancy. In the Coronary Artery Risk Development in Young Adults study,⁴ among women who reported GD and did not develop diabetes or impaired glycemia had greater carotid artery intima media thickness (cIMT) many years postdelivery. In some models, this difference in cIMT could represent 3 to 5 years of greater vascular aging for women with previous GD without metabolic disorders. GD is also associated with higher risk of diabetes across similar degrees of impaired glucose tolerance in midlife. The Diabetes Prevention Program⁵ found a 71% higher relative risk of diabetes among women with previous GD, and excess risk persisted with a 48% higher relative risk of diabetes 10 years later, independent of baseline impaired glucose tolerance. Taken together, the evidence indicates that higher CVD risk with previous GD may extend beyond the usual clinical definitions of metabolic dysfunction outside of pregnancy. Many unanswered questions remain, including questions about excess risk levels by GD severity and race/ethnicity. More robust evidence is needed before appropriate screening measures, including frequency, and timing of risk assessments, can classify CVD risk in women with GD.

Interventions for women with GD focus on modification of dietary intake and physical activity to promote postpartum weight loss. However, a growing body of evidence shows that lactation improves maternal cardiometabolic profiles, and these favorable effects persist postweaning. The NHS previously found associations between lactation and a 23% lower relative incidence of myocardial infarction,⁶ and 14% lower incidence of diabetes, but these analyses did not evaluate women with GD. It is note-worthy that Tobias and colleagues³ did not investigate the impact of lactation history on GD history and development of diabetes related to subsequent CVD events in women. A prospective study⁷ of 1010 women with recent GD found that lactation duration and intensity were independently associated with a graded 36% to 57% lower 2-year relative incidence of type 2 diabetes mellitus after accounting for prepregnancy obesity, GD severity, perinatal outcomes, and postpartum lifestyle behaviors. Because women with GD are more likely to experience adverse perinatal outcomes, they face greater barriers to breastfeeding that may delay onset of lactogenesis and shorten duration. The role of lactation in risk reduction of chronic disease in women, particularly diabetes and CVD after GD pregnancy, remains an important area for future research.

Heart disease is the leading cause of death in women. Current risk prediction models for atherosclerotic CVD risk do not include pregnancy complications because of limited evidence. The contribution of history of GD to CVD risk estimates, particularly for younger women, has rarely been studied. One 18-year follow-up study⁸ from northern Europe reported a borderline significant 26% higher Framingham CVD risk score for GD, but GD

prevalence was very low (0.4% vs 7% in the United States). Long-term studies are needed among the generation of women who were routinely screened for GD during pregnancy to establish and quantify the relationship to concurrent as well as subsequent cardiometabolic diseases and CVD risk later in life. These studies are daunting and time-consuming because of the extended time from GD to CVD events, as well as the lack of systematic biochemical screening of women during the childbearing years.

Glucose intolerance during pregnancy affords an early warning sign of future CVD risk, primarily related to the higher risk of diabetes. Mounting evidence shows that women with a history of GD and no diabetes have higher CVD risk, although to a lesser degree. Nevertheless, GD identifies young women who may benefit from heightened vigilance after pregnancy, but also poses major challenges for existing health care systems in the early prevention of diabetes and CVD in at risk women. The American Diabetes Association⁹ recommends screening within 4 to 12 weeks after delivery via the 2-hour 75-g oral glucose tolerance test, but less than 50% of postpartum women are tested. In 2012, the American College of Obstetricians and Gynecologists and the National Diabetes Education Program jointly issued a call to action¹⁰ for primary care physicians to improve diabetes screening of women with GD before and after pregnancy to reduce the short- and long-term adverse outcomes, although these recommendations are not grounded in high-grade evidence. As evidence accumulates that pregnancy complications predict future CVD risk in women, health care systems might consider greater surveillance and targeted interventions not only during the perinatal and reproductive periods but also in the decades that follow. These strategies include lifestyle behaviors (heart healthy diet, maintenance of a healthy weight, tobacco avoidance, and physical activity) but also priorities for women's postpartum health, including depression treatment, lactation support (in-hospital and postdischarge), good sleep habits, and social policies that support overall maternal health (extended paid maternity leave). This effort will entail coordinated systems to identify, track, monitor, educate, and treat these women before, during, and after pregnancy. Effective interventions for risk reduction will also require increased awareness and engagement of primary care and specialty clinicians, as well as pragmatic research studies within integrated health care systems to evaluate and achieve optimal health for women decades after the diagnosis of GD.

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