Pregestational Diabetes Mellitus and Congenital Heart Defects

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Clinical and epidemiological studies have established a strong link between maternal pregestational diabetes mellitus and an increased risk of CHDs and other adverse pregnancy outcomes. The associations observed between maternal pregestational diabetes mellitus and CHDs are strong (relative risk estimates of ≥4) and evident for type 1 and type 2 diabetes mellitus. Furthermore, the risks of CHDs and other birth defects are known to increase among the offspring of women with diabetes mellitus who have poorer metabolic control and to be attenuated among the offspring of women with pregestational diabetes mellitus who are enrolled in preconception care programs focused on management of pregestational diabetes mellitus. Although the underlying mechanisms for the association of diabetes mellitus with CHDs and other birth defects remain unclear, it is evident that hyperglycemia plays an important role in the development of diabetes mellitus–associated adverse pregnancy outcomes. The extent to which this knowledge has been used to reduce the prevalence of such complications from diabetes mellitus is unclear. There is no evidence in the published literature of recent decreases in the prevalence of CHDs among births in the general population or among births to women with pregestational diabetes mellitus. On the other hand, reports of increasing trends in the prevalence of pregnancies complicated by pregestational diabetes mellitus have raised questions about the potential impact of such trends on the prevalence of diabetes mellitus–associated CHDs.

In this issue of Circulation, Øyen et al describe the results of a large national cohort study in Denmark that examined trends in the prevalence of CHD cases attributable to pregestational diabetes mellitus among 2025727 births from 1998 to 2011, with a low prevalence of exposure to maternal pregestational diabetes mellitus (0.36%) in comparison with that reported in North America (≥1%). The prevalence of births with pregestational diabetes mellitus in this cohort did show an increase over time (from 0.23% in 1978–1986 to 0.42% in 1994–2011), and, in comparison with the overall prevalence of CHD among births to mothers without pregestational diabetes (8/1000), the overall prevalence of CHD among births to mothers with pregestational diabetes mellitus was 4 times greater, which is consistent with previous observations. A troublesome finding in this study was that the high proportion of CHDs attributable to pregestational diabetes mellitus among births to mothers with pregestational diabetes mellitus in 1978 to 1986 (79%) showed only a 6% decline by the end of the study period 1997 to 2011 (74%). This small decline in the attributable fraction of CHDs associated with diabetes mellitus raises questions about the level of awareness about the potential for prevention and limited availability or access to preconception care programs for women.
with pregestational diabetes mellitus. A better understanding of barriers and enabling factors for preconception care, along with the need to understand the barriers to that for a majority of pregnant women with pregestational diabetes mellitus, may enable the development of policies for and allocation of resources to such programs.

The study by Øyen et al.37 has several study design and methodological features that facilitated a comprehensive assessment of questions related to diabetes mellitus and CHDs. First, the large size of the birth cohort study (ie, >2 million births) allowed robust evaluations of associations of a relatively rare exposure (ie, a prevalence of pregnancies complicated by pregestational diabetes mellitus of <1%) with relatively rare outcomes (ie, specific CHD phenotypes with a prevalence of <1% for each specific phenotype). Second, basing the determination of maternal diabetes status on existing records of diagnoses of diabetes mellitus and type of diabetes mellitus allowed for more accurate estimates of prevalence of pregestational diabetes mellitus than in previous large case-control studies where determination of diabetes status was based on self-reports subject to recall error and where prevalence of pregestational diabetes mellitus was probably underestimated. Third, the use of standard nomenclature for CHDs and a hierarchical classification system for CHDs allowed for evaluations of specific phenotypes, and of groupings of CHD phenotypes, as well, based on presumed common developmental origins, enabling meaningful comparisons with reports in the literature. Øyen et al.37 were able to corroborate the strong associations between maternal pregestational diabetes mellitus and CHDs reported in previous case-control studies17,20; that the association of pregestational diabetes mellitus with CHDs is evident for specific CHD phenotypes and grouping of CHD phenotypes; that this association is stronger for certain CHD phenotype groupings (eg, heterotaxia and conotruncal defects) than for others18,20, and that diabetes mellitus is also associated with noncardiac defects. These findings underscore the fact that, today, pregestational diabetes mellitus is an important modifiable risk factor for CHDs, and for other birth defects, as well, in Denmark and probably in many populations around the world experiencing an increasing prevalence of pregnancies complicated by pregestational diabetes mellitus. Øyen et al.37 also corroborated that the risk of CHDs increases with evidence of poor metabolic control or severity of pregestational diabetes mellitus, as suggested by a history of acute pregestational complications, and that the association of CHDs with diabetes mellitus does not vary with type of treatment for diabetes mellitus or type of pregestational diabetes mellitus. These observations highlight the importance of metabolic control as a key element before and early in pregnancy among women with pregestational diabetes mellitus to reduce the prevalence of CHDs and other birth defects associated with pregestational diabetes mellitus. Øyen et al.37 reported weak associations of gestational diabetes mellitus with CHDs, also noted in previous reports, particularly among women with gestational diabetes mellitus and pre-pregnancy obesity. Given that gestational diabetes mellitus represents a diagnosis of diabetes mellitus made during pregnancy after most major CHDs have occurred, it is possible that the observed weak associations with CHDs in this study might have been attributable to residual confounding by undiagnosed pregestational diabetes mellitus. An analysis of these associations stratified by prepregnancy overweight/obesity status would have been elucidating. Also, some information on the prevalence of undiagnosed diabetes mellitus among women of childbearing age in the study cohort or Denmark would have been of interest.

CHDs are common, critical, and costly. Although the causes for many CHDs remain unknown, the study by Øyen et al is a valuable reminder that today the clinical and public health communities, including professional health societies, are faced with a unique opportunity for reducing the public health burden of CHDs through greater and more concerted efforts for improving the management of maternal pregestational diabetes mellitus. Preconception care programs targeting women with pregestational diabetes mellitus have been developed and implemented and found to be effective in reducing the occurrence of adverse outcomes from pregnancies complicated by pregestational diabetes mellitus. An important challenge for the development and sustainment of such programs is securing the commitment and necessary resources in societies with no universal healthcare systems, particularly in communities where poverty and diabetes mellitus are more prevalent and needs are the greatest. In such settings, conversations and concerted efforts involving health professionals, women with pregestational diabetes mellitus, and community leaders or representatives might be helpful in identifying practical approaches for such programs, potential resources for such programs, and mechanisms for obtaining such resources. Effective lifestyle approaches for the prevention or delaying the onset of diabetes mellitus have been identified and need to be incorporated into public education programs more widely to increase awareness about such approaches among women of childbearing age, particularly among women in populations at risk for diabetes mellitus. The potential benefits derived from such efforts will go beyond a reduction in the prevalence of CHDs, because they are likely to include a reduction in the prevalence of a wide range of other adverse pregnancy outcomes and associated health care costs and a greater number of healthier newborns and happier mothers. Without a more proactive and concerted approach, the increasing trends in prevalence of pregnancies complicated by pregestational diabetes mellitus are likely to continue and to exacerbate a widening of health disparities by race/ethnicity and socioeconomic status for women with pregestational diabetes mellitus and their offspring.

Disclosures

None.

References


3. Franklin RC, Jacobs JP, Tchervenkov CI, Béland MJ. Bidirectional cross-map of the Short Lists of the European Paediatric Cardiac Code and
Herz by maternal diabetes mellitus. An international clinical collaboration, lit-


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