Considerations in the Management of Gestational Diabetes Mellitus: "You Are What Your Mother Ate!"

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Diabetes Care 2016;39:13–15 | DOI: 10.2337/dci15-0030

It is clear that there remains a global crisis in the development and consequences of chronic diseases such as obesity and type 2 diabetes. These conditions lead to complications that increase morbidity and mortality, such as heart disease, stroke, amputations, and kidney disease. We have learned a great deal about the pathogenesis of these disorders and also about both treatment and preventive interventions. Clearly, there remains considerable progress to be made specifically in addressing these conditions and, more importantly, in preventing these conditions in resource-poor areas.

Over the recent past, there has been a startling new set of observations on the genesis of these conditions. There are data that certain processes observed in utero and in early childhood can certainly affect the risk of developing chronic diseases at a later age (1–3). This clearly provides a great opportunity to interdict on these pathophysiological processes when they may have the greatest effect. As such, there is a growing interest in learning more about epigenetic phenomena and how these events that can be observed in prenatal and early postnatal life can modulate the risk for the development of chronic diseases (i.e., obesity and type 2 diabetes) in adolescence and early adulthood.

In this regard, it is of great interest to study a metabolic environment that may play a great role in later issues affecting human health. Specifically, given the importance of the maternal environment and the potential impact that gestational diabetes mellitus (GDM) may have, we devote a special section in this issue of *Diabetes Care* to articles related to GDM. The topics covered in this special section include evaluation of dietary factors, intervention strategies to prevent and treat GDM, and appropriate screening and diagnostic testing. As is the case with most topics, new data are presented that address specific areas, while at the same time, data are presented that set the stage for the next logical step in addressing scientific and clinical questions.

In the late 1950s and early 1960s, glucose levels in pregnancy that predicted the development of type 2 diabetes in the mother and the incidental observation of an increased perinatal mortality rate focused attention on this occasionally observed but hitherto little considered problem (4,5). Since then, knowledge has increased dramatically, and differences of opinion and controversy have increased exponentially. The link between maternal glucose levels and adverse pregnancy outcomes exhibits a continuum of risk (6). This continuum also applies to the progression of women with hyperglycemia in pregnancy to postpartum type 2 diabetes (7). Although an increased perinatal mortality rate is now not considered a major problem for women in the developed world, it still exists and fetal morbidity is still present. Much recent concern and research have focused on the adverse effects of intrauterine programming and the expression of epigenetic changes in adult life (2,3,8), which has generated the interest in providing a special section in *Diabetes Care*.

Given that there is no apparent threshold level but a continuum of risk for all adverse events related to the maternal glucose levels, how diagnostic levels and treatment targets have been derived is a matter of consensus. For evidence related to the diagnostic levels, we are indebted to the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (9), and for consensus, to the recommendations of the International Association of the Diabetes and Pregnancy Study Groups (10), subsequently endorsed by the World Health Organization (WHO) (11). WHO, in addition to the diagnostic criteria, has also changed the terminology. All women with an abnormal result at any stage of pregnancy will be classified as having hyperglycemia in pregnancy and then subdivided into having either diabetes in pregnancy or GDM.

Few clinicians would dispute that dietary factors are crucial to the development

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See accompanying articles, pp. 16, 24, 31, 39, 43, 50, 53, 55, 61, and 65.

of both type 2 diabetes and diabetes in pregnancy. Few clinicians would dispute that dietary advice and manipulation are key components of the treatment paradigm. However, evidence for these clinical realities is difficult to obtain. Four of the articles in the special section relate to dietary studies. The systematic review by Schoenaker et al. (12), focused on observational studies, highlighted the lack of specific information available and hence the difficulty in providing evidence-based dietary advice. The Finnish Gestational Diabetes Prevention Study (RADIEL) (13) reported a positive outcome for the prevention of GDM in high-risk women by lifestyle interventions, including diet and exercise. However, this positive outcome needs to be interpreted with caution. The results were only marginally significant, after adjustment for multiple factors, and the control group was more historical rather than an alternative active intervention. Nonetheless, this is important information to have in our goal to reduce GDM development.

Many studies have focused on the potential advantages of diets using foods with a low–glycemic index (GI). However, a large study where a low-GI diet was compared with a higher-fiber diet in normal pregnancies did not show positive advantages (14). Specifically, Markovic et al. (15) examined the effects of a low-GI diet compared with a higher-fiber diet on pregnancy outcomes for women at high risk of GDM. No significant differences were noted. It is possible that the diet of women in pregnancy is generally less than optimal and studies in pregnancy, where there is a control group receiving some diet-altering advice and a similar number of clinic visits, are unlikely to demonstrate an advantage under what could be considered normal clinical care.

Several learned societies (16,17) have advocated a low-carbohydrate diet for the treatment of women with GDM, but this concept has been challenged by Hernandez et al. (18) in a tightly controlled pilot study reported in this issue of *Diabetes Care*. They hypothesized that the standard low-carbohydrate/high-fat diet for women with insulin resistance may have unintended consequences for infant health. The higher-carbohydrate and hence lower-fat diet may reduce maternal insulin resistance. What is the effect long term of a low-carbohydrate diet? The article by Bao et al. (19), also featured in this issue, found that a lower-carbohydrate diet with a higher intake of protein and fat from animal sources increased the risk of developing type 2 diabetes. Thus, perhaps the diet that is most suitable for the treatment of women with GDM may not be the optimal long-term diet. Clearly, this area of research as related to the translational message is a work in progress!

The heterozygous form of maturity-onset diabetes of youth, in any of its increasingly recognized variants, is a glucose abnormality that may first be incidentally detected by routine glucose testing in pregnancy. Given that women with maturity-onset diabetes of youth may be potentially overtreated in pregnancy to the detriment of the fetus, then at least awareness of this possible diagnosis should be considered. The incidence, variable in different populations, may be about 1% of women with GDM and perhaps 0.1% of the overall population. The article by Rudland et al. (20) suggested that a clinical algorithm that may help "screen" these women and certainly deserves further evaluation in a wider population.

A letter from McIntyre et al. (21) raises important issues and concerns about the early diagnosis of GDM in pregnancy. Early testing of women with acknowledged risk factors is encouraged, but the WHO criteria indicates that any woman with a fasting glucose $\geq$5.1 mmol/L at any time during pregnancy should be considered to have hyperglycemia in pregnancy. As the fasting glucose will normally fall in the initial stages of pregnancy, it is possible that women with a marginally elevated result may be overdiagnosed. As an alternative, an early HbA_{1c} measurement has some advantages but has less-than-optimal correlation with the results of the glucose tolerance test (GTT). Which "gold standard" is correct? As the nonpregnant world transitions to the use of HbA_{1c} for the diagnosis of diabetes, there is clearly a need for a major clinical trial to compare these two tests in early pregnancy—perhaps HAPO II?

A large population-based study from Alberta, Canada, by Donovan et al. (22) demonstrated a more than 90% compliance with testing for GDM, predominantly, in the first stage, by a glucose challenge test (GCT). Although the GCT is no longer recommended by WHO, it was encouraging to see in their health system arrangement that, of those women who were positive, more than 90% of women completed their GTT. This is in contrast to another area of Canada (23) where only about a third of women progressed to the GTT. However, one of the concerns about the GCT is that it delays definitive testing. In the article by Donovan et al. (22), the delay was acknowledged, but with an appropriate threshold for diagnosis this delay could be deemed acceptable. Perhaps before the GCT is abandoned, an appropriate trial of outcomes and perhaps consideration of health economics should be undertaken.

The prospective study of De Souza et al. (24) found that ultrasound determined that abdominal total and visceral fat rather than subcutaneous fat were associated with GDM and various degrees of glucose abnormalities in the later weeks of pregnancy. In the final article featured in the special section, Ferrara et al. (25) suggested strategies to use after the GDM pregnancy is completed. Interventions to adjust diet and lifestyle were effective for at least 6 months and then the effectiveness began to diminish. Again, perhaps it is a work in progress.

If high compliance with a GCT and the definitive GTT can be achieved, then a clinical trial to compare this historical means of testing with the WHO recommendations could be justified. In certain health service arrangements, health economic data may facilitate this particular discussion. Clearly the rationale of early testing of pregnant women needs further consideration. While primarily introduced to define undiagnosed type 2 diabetes, it is having the unintended consequences of possibly diagnosing women with GDM who may have normal results at other times during the pregnancy. A clinical outcomes study using glucose levels and HbA_{1c} in the early weeks of pregnancy is urgently required.

The articles featured in the special section in this issue of *Diabetes Care* demonstrate the range of the clinical and scientific work being presented to the field and provide a good overview of the depth and breadth of what is happening related to diabetes and pregnancy. These studies solve some issues regarding treatment but, importantly, raise critical questions for further consideration.

Diets to achieve the best outcomes during pregnancy are likely to be different from diets advised for the best long-term general health outcomes. Another unanswered question is the long-term consequences in adolescence and early adulthood from the dietary intake during pregnancy in general, and GDM in particular. It is our aspiration to continue being the premium forum where these topics can be presented and considered. Until then, it may be important to continue to understand what has recently been restated, that "you are what your mother ate!" (26,27).

Acknowledgments. W.T.C. is supported in part by National Institutes of Health (NIH) grant 1U54-GM-104940, which funds the Louisiana Clinical and Translational Science Center, and NIH grant P50-AT-002776.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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