

# An ounce of prevention...

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A number of factors have contributed to the estimated 16% prevalence of gestational diabetes mellitus (GDM) in diverse populations around the world.<sup>1</sup> As of 2014, 39% of the world's adults were overweight, and 13% were obese.<sup>2</sup> In the United States in that same year, 70% of adults were overweight or obese<sup>3</sup>; 40% were obese, and 10% had a body mass index of  $>40$  kg/m<sup>2</sup> (class 3 obesity).<sup>4</sup> Among adolescent girls aged 12–19 years, 21% were obese and 8% were extremely obese ( $\geq 120\%$  of the 95th percentile for age).<sup>5</sup> This epidemic of overweight and obesity has been associated with a simultaneous increased prevalence of type 2 diabetes mellitus.<sup>6</sup> Various conditions associated with insulin resistance have also become more common in the United States<sup>7</sup> and presumably throughout the world. In some populations, child-bearing has been postponed well into adulthood so that increasing maternal age is also likely a contributor.<sup>8</sup> Furthermore, there is credible evidence in some ethnic groups that exposure to maternal hyperglycemia while in utero places the offspring at increased risk for childhood and adult obesity and type 2 diabetes mellitus later in life.<sup>9,10</sup> This would suggest the potential for a runaway “feedback loop” with more GDM predisposing the offspring to obesity and insulin resistance, leading to more GDM in each successive generation.

Observational studies have demonstrated a continuous relationship between maternal oral glucose tolerance test (OGTT) glucose levels and various adverse pregnancy outcomes in the offspring, such as macrosomia and hyperinsulinemia with associated neonatal adiposity.<sup>11</sup> Adverse outcomes in the mother such as increasing cesarean delivery rates and hypertensive disorders of pregnancy have also been documented.<sup>11</sup> Randomized controlled trials (RCTs) have demonstrated that identification and treatment of even mild degrees of glucose intolerance can decrease the likelihood of adverse pregnancy outcomes.<sup>12,13</sup> The International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria for the diagnosis of GDM,<sup>14</sup> the only thresholds that are based on pregnancy outcomes, are being adopted increasingly around the world.<sup>15,16</sup> They use a 75-g, 2-hr OGTT rather than the traditional (in the United States) 100-g, 3-hr OGTT and require only 1 (or more)

elevated value(s) to diagnose GDM. Pregnant women meeting the IADPSG criteria, but not the traditional GDM criteria, have been shown to be at significantly increased risk of adverse outcomes.<sup>17</sup> The use of these criteria will allow more at-risk gravid women to receive interventions that, it is hoped, will prevent some of the adverse outcomes and dampen the aforementioned cycle of mother-to-child transmission. However, use of the IADPSG criteria will further increase the proportion of gravid women with GDM who require such interventions, placing added stress on already limited healthcare resources. For these reasons, novel approaches to prevention of GDM, and innovative models for lower resource use in treatment when GDM is present, are critically important.

The RCT by Wang et al<sup>18</sup> published in this issue of the Journal tests an approach to the prevention of GDM in high-risk women in Beijing. One-half of 300 overweight or obese gravid women were assigned randomly to a supervised fairly intensive exercise program throughout the second and third trimesters; the other one-half of the women received routine prenatal care. RCTs are extremely labor intensive for the investigators and, in this case, for the subjects as well. The recruitment rate of 44% of eligible participants is extremely impressive for a study that involved overweight or obese, presumably sedentary, individuals committing to a supervised 30-minute stationary cycle exercise session 3 times weekly for approximately 23 weeks! Only 25% of each group (exercise and control) dropped out over the course of the trial, and 90% of those in the exercise group who continued attended  $\geq 80\%$  of scheduled sessions. The study used the IADPSG criteria for GDM that used a 75-g 2-hr OGTT, which were adopted in China in August 2014. In the control group 41% of the women experienced GDM. This very high rate may be attributed to the high-risk nature of the subjects (all overweight or obese) as well as the use of the less stringent IADPSG diagnostic criteria. The rate of GDM was decreased by almost one-half to 22% in the group that was assigned to the exercise regimen. Such a reduction in GDM is a remarkable achievement and offers great promise as an approach to ameliorating the increasing GDM epidemic described earlier.

Metaanalyses of RCTs of exercise to prevent or treat GDM have reported mixed results<sup>19,20</sup>; in the current RCT, an important feature appears to be the early institution of regular exercise at the beginning of the second trimester. The exercising group gained significantly less weight than the control group during the second trimester (4.1 vs 5.9 kg). As the authors point out, the lack of weight gain difference between groups in the third trimester could be at least partially related to the fact that 40% of the women in the control group were diagnosed with GDM and that the interventions applied in these pregnancies might have limited their third-trimester weight gain.<sup>21</sup> The third-trimester weight gain in the 2 groups was so similar (4.6 kg in each group) that this

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explanation may not be adequate to explain the phenomenon. The finding that reductions in weight gain (compared with control group) were limited to the second trimester supports the role of early institution of the intervention.

Some important questions remain to be answered about the generalizability of this strategy to other populations. Are there ethnic differences in the impact of exercise on carbohydrate metabolism? Similar trials in other ethnic groups will be helpful. It seems likely that there will be varying degrees of willingness or resistance to this approach in different populations and cultures. Will it be feasible to convince overweight and obese gravid women in other settings and circumstances to participate in a similar exercise regimen from early pregnancy? Although direct supervision of the exercise sessions was critical to the study design, such an approach may be quite costly and limit the applicability in underfunded healthcare systems. Will an exercise prescription be followed under nonexperimental, less closely supervised, conditions? It also remains to be determined whether other forms of exercise may be similarly effective in settings where the availability of cycle ergometry exercise equipment is limited. If most of these questions can be answered affirmatively, there will be a relatively low-tech intervention that can help to interrupt the cycle of ever increasing GDM.

This report raises other intriguing possibilities. Women with a history of GDM are at increased risk for the development of type 2 diabetes mellitus as the years go by. In the Diabetes Prevention Program RCT, when women with a history of GDM who met the criteria for prediabetes were assigned randomly to lifestyle intervention, metformin or usual care, those in the control group experienced type 2 diabetes mellitus at a rate of 15% per year, although the rate in the 2 treatment groups was halved.<sup>22</sup> This suggests potential long-term benefits to the program of exercise during pregnancy. Introducing sedentary overweight and obese women to a regimen of exercise performed at least 3 times weekly during pregnancy might influence them to continue in this healthy lifestyle subsequently. Will the decrease in weight gain over the course of pregnancy be carried over and result in less retained weight over time? A decision analysis demonstrated that the IADPSG recommendations for diagnosing GDM would be cost-effective only if women with GDM received intensive counseling and care after delivery to prevent type 2 diabetes mellitus.<sup>23</sup> If gravid women are willing to follow an intervention such as this and if it is effective in other populations, this could be an effective way to introduce overweight and obese women who are at risk for type 2 diabetes mellitus to the kind of lifestyle intervention needed for primary prevention! ■

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