Balancing Weight and Glucose in Gestational Diabetes Mellitus

The instinctive concern of a pregnant woman for her baby creates a receptive environment for advice, and so it is particularly important that medical recommendations during pregnancy should be factual and reasoned. In this issue of *Diabetes Care*, Black et al. (1) have shown in a group of women who did not have gestational diabetes mellitus (GDM) by traditional thresholds that maternal overweight and obesity accounted for 21.6% of large-for-gestational-age (LGA) infants, and when GDM as defined by the newer American Diabetes Association (ADA) criteria was added into the equation, the combination was responsible for 23.3% of neonatal LGA. This article is a helpful addition to the debate balancing the impact of maternal adiposity or hyperglycemia on the risk of LGA in the baby.

The historical poor outcomes of pregestational diabetes are testimony to the harmful effects of high glucose in early pregnancy as manifest by congenital malformations and in later pregnancy as evidenced by LGA and its consequences. Interestingly, over time with better glucose control the risk for congenital malformations has decreased but not the risk for LGA (2). A proportion of women with no known diabetes have a pancreas that cannot respond to the increased insulin requirements of pregnancy, and they therefore develop GDM. These women have more LGA and shoulder dystocia (3), and there is good evidence that treatment reduces these problems (4).

Overweight mothers also have less favorable outcomes. In population studies, obesity is associated with more LGA, gestational hypertension, preeclampsia, GDM, and extra pounds retained postpartum, whereas excess weight gain during pregnancy is more closely associated with preeclampsia, LGA, and retained weight postpartum (5–7). Women who have bariatric surgery have less LGA infants on subsequent pregnancies, indicating a role for obesity (8). The prospective study of Vinter et al. (9) using nutrition counseling and physical activity in obese pregnant women showed that less weight gain could be achieved but the maternal outcomes (including the risk of GDM) were similar in control and intervention groups, and the birth weights were not significantly different. In fact, the intervention group babies were slightly heavier at 3,742 vs. 3,593 g. Recent meta-analyses showed similar patterns: weight gain in pregnancy can be attenuated by intervention, but birth weight is unchanged (10–12).

Both hyperglycemia and maternal adiposity increase the risk of LGA. Teasing out the relative importance of these components is a challenge. An analysis of the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) observational data by Catalano et al. (13) showed increased adjusted odds ratios (ORs) for LGA derived from maternal GDM as defined by IADPSG (International Association of the Diabetes and Pregnancy Study Groups) criteria (OR 2.58) and maternal obesity (OR 2.07), and these were additive when both risk factors were present (OR 5.35). Prospective studies have indicated that obesity may be more important in driving LGA (14,15)—perhaps mediated by increased lipids (16).

The article of Black et al. is a retrospective analysis of the records of 9,835 women, all of whom had a 75-g oral glucose tolerance test, and excludes those meeting criteria for GDM used in 2005–2010 (1). In this group of women, 60% were overweight and 19% had GDM by IADPSG criteria, and of these 76% were obese. The obese GDM women had a 5.5-fold increased risk of LGA, whereas obesity alone or GDM alone had a 1.7- or 2.0-fold increased risk of LGA, respectively, similar to the HAPO report (13). Overall however, obesity and overweight accounted for 21.6% of LGA, and when GDM was added to obesity or overweight the combination accounted for a total of 23.3% of LGA. Only in this combined group was birth trauma increased, but this did not reach statistical significance. A recent article by Retnakaran et al. (17) showed similar results, with maternal weight and weight gain but not glucose being predictors of LGA, and these metabolic factors only accounted for 26% of LGA. Thus in study populations that include women diagnosed as GDM by the new ADA criteria obesity appears to play a more important role in determining LGA but, all told, three-quarters of LGA remains unexplained by maternal obesity, weight gain, or glucose. This leaves us with some quandaries: *1*) What can we do to lessen LGA, *2*) where do we draw the line to diagnose GDM, and *3*) what is the real cause of most cases of LGA?

Treating hyperglycemia in pregnancy will reduce LGA, and therapy is straightforward. If nutrition/lifestyle intervention is not successful, then insulin or oral hypoglycemic agents can be used. While on a diet, excess weight gain may be attenuated, but with the addition of insulin or sulfonylurea increased weight gain often ensues, perhaps negating some of the benefits of controlling glycemia. Pursuing diet/activity for longer may be advantageous if the elevation of glucose is mild, rather than rushing into therapy with insulin. In obese women, dieting will reduce weight gain and benefit the mother with less preeclampsia, postpartum weight retention, and perhaps GDM, but the evidence for decreasing LGA is not there at present. It may be that as Symonds et al. (18) suggested, food restriction in early pregnancy can actually be a stimulus for more white adipose tissue accumulation in the fetus, and it is of note that nearly all of the dietary intervention studies started before 20 weeks' gestation. Maybe more advantageous would be public awareness of the adverse consequences of obesity for the baby so that the mother's starting body weight might be lowered. Society has successfully got the message out about smoking and alcohol in pregnancy; obesity and pregnancy weight gain should now be the next targets.

The diagnosis of GDM remains controversial, and there is a National Institutes of Health (NIH) Consensus Conference to examine the issue in March. The new ADA criteria will diagnose between 9–25% of the pregnant population with a disease (19), have major implications for the mother in terms of glucose monitoring, may involve diabetes medications, will mean more obstetrical monitoring and

interventions, and a medical label of high risk for the future that will influence the mother's insurance premiums in most U.S. states. All of this is based on an observational study—not an intervention study demonstrating benefit; meanwhile, reports are now showing that at these levels of glycemia that glucose is playing a minimal role in LGA (1,17). Glucose contributes to these adverse outcomes, but it is unlikely that we have to diagnose nearly 20% as the IADPSG criteria suggest in order to get the optimum benefits. Criteria that diagnose and capture a twofold increased risk of LGA with half the frequency of GDM might be a better balance (20). Before increasing the concerns of pregnant women for their infants more reasoned debate is needed: waiting for the Consensus Conference outcome would be a first good step for the U.S. For the rest of the world, the allure of consensus should not lead to medicalization of so many pregnancies for so little benefit to the mother and her child.

Finally, there is the reality that most LGA occurs independent of obesity and hyperglycemia. Many of us have cared for women with type 1 diabetes or GDM who, despite excellent glucose control and scrupulous attention to management, deliver macrosomic infants. Though one explanation may be the raised IGF-1 present in maternal and fetal circulations (21), I suspect things are more complex. Perhaps a metabolomic approach in women with LGA infants may be a lot more fruitful than endlessly debating criteria for GDM. There may be an unrecognized placental hormone with high levels in diabetic or obese women that causes LGA and may even have a role in obesity. Now that would be a good outcome of this debate!

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References

1. Black MH, Sacks DA, Xiang AH, Lawrence JM. The relative contribution of prepregnancy overweight and obesity, gestational weight gain, and IADPSG-defined gestational diabetes mellitus to fetal overgrowth. Diabetes Care 2013;36:56–62
2. Johnstone FD, Lindsay RS, Steel J. Type 1 diabetes and pregnancy: trends in birth weight over 40 years at a single clinic. Obstet Gynecol 2006;107:1297–1302
3. Fadl HE, Ostlund IK, Magnuson AF, Hanson US. Maternal and neonatal outcomes and time trends of gestational diabetes mellitus in Sweden from 1991 to 2003. Diabet Med 2010;27:436–441
4. Horvath K, Koch K, Jeitler K, et al. Effects of treatment in women with gestational diabetes mellitus: systematic review and meta-analysis. BMJ 2010;340:c1395
5. Nohr EA, Vaeth M, Baker JL, Sørensen TIA, Olsen J, Rasmussen KM. Combined associations of prepregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr 2008;87:1750–1759
6. Ludwig DS, Currie J. The association between pregnancy weight gain and birthweight: a within-family comparison. Lancet 2010;376:984–990
7. Cheng YW, Chung JH, Kurbisch-Block I, Inturrisi M, Shafer S, Caughey AB. Gestational weight gain and gestational diabetes mellitus: perinatal outcomes. Obstet Gynecol 2008;112:1015–1022
8. Smith J, Cianflone K, Biron S, et al. Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. J Clin Endocrinol Metab 2009;94:4275–4283
9. Vinter CA, Jensen DM, Ovesen P, Beck-Nielsen H, Jørgensen JS. The LiP (Lifestyle in Pregnancy) study: a randomized controlled trial of lifestyle intervention in 360 obese pregnant women. Diabetes Care 2011;34:2502–2507
10. Thangaratinam S, Rogozinska E, Jolly K, et al. Effects of interventions in pregnancy on maternal weight and obstetric outcomes: meta-analysis of randomised evidence. BMJ 2012;344:e2088
11. Quinlivan JA, Julania S, Lam L. Antenatal dietary interventions in obese pregnant women to restrict gestational weight gain to Institute of Medicine recommendations: a meta-analysis. Obstet Gynecol 2011;118:1395–1401
12. Dodd JM, Grivell RM, Crowther CA, Robinson JS. Antenatal interventions for overweight or obese pregnant women: a systematic review of randomised trials. BJOG 2010;117:1316–1326
13. Catalano PM, McIntyre HD, Cruickshank JK, et al; HAPO Study Cooperative Research Group. The hyperglycemia and adverse pregnancy outcome study: associations of GDM and obesity with pregnancy outcomes. Diabetes Care 2012;35:780–786
14. Ricart W, López J, Mozas J, et al; Spanish Group for the Study of the Impact of Carpenter and Coustan GDM Thresholds. Body mass index has a greater impact on pregnancy outcomes than gestational hyperglycaemia. Diabetologia 2005;48:1736–1742
15. Bo S, Menato G, Signorile A, et al. Obesity or diabetes: what is worse for the mother and for the baby? Diabetes Metab 2003;29:175–178
16. Catalano PM, Hauguel-De Mouzon S. Is it time to revisit the Pedersen hypothesis in the face of the obesity epidemic? Am J Obstet Gynecol 2011;204:479–487
17. Retnakaran R, Ye C, Hanley AJ, et al. Effect of maternal weight, adipokines, glucose intolerance and lipids on infant birth weight among women without gestational diabetes mellitus. CMAJ 2012;184:1353–1360
18. Symonds ME, Pope M, Sharkey D, Budge H. Adipose tissue and fetal programming. Diabetologia 2012;55:1597–1606
19. Sacks DA, Hadden DR, Maresh M, et al.; HAPO Study Cooperative Research Group. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 2012;35:526–528
20. Ryan EA. Diagnosing gestational diabetes. Diabetologia 2011;54:480–486
21. Luo ZC, Nuyt AM, Delvin E, et al. Maternal and fetal IGF-I and IGF-II levels, fetal growth, and gestational diabetes. J Clin Endocrinol Metab 2012;97:1720–1728