Many HAPO Returns

Maternal Glycemia and Neonatal Adiposity: New Insights from the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study

Robert S. Lindsay

Humans have the greatest fat content of any mammalian species at birth (1). It has been known for many years that abnormally high maternal glucose (as is the case when the mother has type 1 or type 2 diabetes during pregnancy) is characteristically associated with increased fat deposition in utero. In pioneering work in the 1950s, Pedersen (2) suggested that in the offspring of mothers with diabetes, excess fetal insulin production was key in promoting fetal overgrowth. Specifically, maternal hyperglycemia led to excess exposure of the fetus to maternal glucose, fetal hyperinsulinemia, and excess growth. The Pedersen hypothesis was later modified by Freinkel and Metzger, who added a potential role of other nutrients to fetal overgrowth in diabetic pregnancy (3); however, the central role of fetal hyperinsulinism and control of maternal glucose remained. The potential clinical importance of maternal glycemia and fetal overgrowth has increased, since it became apparent that exposure to maternal diabetes could exert long-term effects on the offspring, increasing the risk of type 2 diabetes and obesity (4,5).

Gestational diabetes—diabetes with first onset or recognition during pregnancy (6)—has long been a controversial clinical area. Methods of screening for gestational diabetes, the specific tests used, and even the biochemical definition of diabetes during pregnancy have varied between and indeed within countries. Such controversies usually flourish in the absence of high-quality evidence, and in this case, the uncertainties have reflected a lack of large, suitably designed, observational, and randomized control trials. There have been particular problems with the interpretation of previous observational trials as the diagnosis of gestational diabetes itself likely alters medical and particularly obstetric practice, rendering outcomes such as rates of caesarean section difficult to assess (7). Happily, the evidence base has improved hugely in recent years. In 2005, Crowther et al. (8) provided clear evidence that diagnosis of glucose abnormality in pregnancy and management designed to lower blood glucose resulted in modification of birth weight and indeed improvement in perinatal outcomes. More recently, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) investigators have completed an extensive data collection examining the relationship of maternal glucose, measured by a 75-g oral glucose tolerance test, to neonatal outcomes. The HAPO investigators have already demonstrated a continuous graded relationship between maternal glucose and the primary outcomes of the study, including fetal insulin (as assessed by cord C-peptide at birth) and macrosomia (9). In this issue of *Diabetes*, the HAPO investigators examine the relationship of maternal glucose and fetal insulinemia (as defined by umbilical cord C-peptide) to fetal adiposity (10). The investigators show a continuous relationship between maternal glycemia and neonatal adiposity, similar to that described for macrosomia. Further, there is a continuous relationship between neonatal insulin and adiposity either by skinfolds or derived percent body fat at birth.

The investigators are once again to be congratulated on this landmark study. Key strengths of the HAPO study include its large size and the diverse populations studied using a single research protocol. A critical (and difficult to achieve) design feature is that glucose results of the majority of women in the HAPO study remained blinded, reducing the risk of bias arising from changes in clinical behaviors secondary to the perceived risks relating to maternal glycemia (9). Several points emerge. First, it is encouraging, and perhaps even surprising, that maternal glucose measured at a single point in pregnancy is so effective at predicting birth outcomes, as was also the case in the investigators' first publication (9). Second, the current study confirms the relationship of maternal glucose, neonatal insulin, and adiposity and the important role of fetal insulin in growth, suggested by Pedersen. Notably, however, these relationships appear to be present in a graded fashion across the spectrum of maternal glycemia. Thus, maternal glucose appears to be influencing fetal growth, insulin, and adiposity not just when mother's glucose is "high," but in a continuous manner across all levels of glucose. For example, the likelihood of neonatal skinfolds above the 90th percentile increased by almost 40% when maternal fasting glucose at the oral glucose tolerance test was 4.2–4.4 mmol/l compared with $<$4.2 mmol/l. Maternal glucose emerges as a key determinant of growth and adiposity. From a scientific perspective, this suggests that the mechanisms proposed by Pedersen are important in the control of fetal growth and adiposity, not just in overt maternal diabetes but across the normal population, and are potentially a central part of

From the Metabolic Medicine Group, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland.
Corresponding author: Robert S. Lindsay, rsl3c@clinmed.gla.ac.uk.
DOI: 10.2337/db08-1562

See accompanying original article, p. 453.

the way that fetal growth is regulated. One of the interesting implications of this relates to fetal programming. High levels of maternal glucose increase the risk of excess adiposity and abnormal glucose tolerance in maternal type 1 diabetes (11) and type 2 diabetes (4,5) and influence the penetrance of genetic syndromes of diabetes (12). Risks of excess adiposity have in turn been related to fetal hyperinsulinemia (13). Given the HAPO results, it is reasonable to wonder how far into the range of maternal glucose such programming effects might occur and more provocatively whether clinical management affects them. Similarly, our high fat content at birth and the difference in fat between ourselves and our closest evolutionary relatives suggest that relatively high neonatal fat content has been advantageous to us in our recent evolutionary history (1). It is suggested that part of this advantage may be explained by the increased metabolic demands inherent in the relatively large human brain at birth (1). What then is optimal fatness at birth for short- and long-term outcomes? Follow-up of children in the HAPO cohort will be critical.

Finally, it is hoped and expected that the detailed analysis of the HAPO study will support international agreement on a single definition of gestational diabetes. Future publications of the HAPO group should allow definition of the relative roles of fasting, 1- and 2-h glucose in prediction of adverse outcomes, and interaction with these and other risk factors. The process of achieving consensus will be challenged by the continuous relationships with outcomes. Nevertheless, the considerable strengths of the HAPO study should allow the investigators and the clinical community the best available opportunity to define the level of glycemia at which diagnosis and intervention may improve outcomes for mother and child.

ACKNOWLEDGMENTS

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

REFERENCES

1. Kuzawa CW: Adipose tissue in human infancy and childhood: an evolutionary perspective. *Am J Phys Anthropol* Suppl. 27:177–209, 1998
2. Pedersen J: Weight and length at birth in infants of diabetic mothers. *Acta Endocrinologica* 16:330–342, 1954
3. Freinkel N: Banting Lecture 1980: Of pregnancy and progeny. *Diabetes* 29:1023–1035, 1980
4. Pettitt DJ, Aleck KA, Baird HR, Carraher MJ, Bennett PH, Knowler WC: Congenital susceptibility to NIDDM: role of intrauterine environment. *Diabetes* 37:622–628, 1988
5. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC: Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. *N Engl J Med* 308:242–245, 1983
6. World Health Organization: *Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications*. Geneva, World Health Org., 1999 (WHO/NCD/NCS/99.2)
7. Naylor CD, Sermer M, Chen E, Sykora K: Cesarean delivery in relation to birth weight and gestational glucose tolerance: pathophysiology or practice style? Toronto Trihospital Gestational Diabetes Investigators. *JAMA* 275:1165–1170, 1996
8. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS: Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med* 352:2477–2486, 2005
9. Metzger BE, Lowe LP, Dyer AR, Trimble ER, Chaovarindr U, Coustan DR, Hadden DR, McCance DR, Hod M, McIntyre HD, Oats JJ, Persson B, Rogers MS, Sacks DA: Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med* 358:1991–2002, 2008
10. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Cooperative Research Group: Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: associations with neonatal anthropometrics. *Diabetes* 58: 453–459, 2009
11. Clausen TD, Mathiesen ER, Hansen T, Pedersen O, Jensen DM, Lauenborg J, Damm P: High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care* 31:340–346, 2008
12. Stride A, Shepherd M, Frayling TM, Bulman MP, Ellard S, Hattersley AT: Intrauterine hyperglycemia is associated with an earlier diagnosis of diabetes in HNF-1alpha gene mutation carriers. *Diabetes Care* 25:2287–2291, 2002
13. Weiss PA, Scholz HS, Haas J, Tamussino KF, Seissler J, Borkenstein MH: Long-term follow-up of infants of mothers with type 1 diabetes: evidence for hereditary and nonhereditary transmission of diabetes and precursors. *Diabetes Care* 23:905–911, 2000