Insulin Detemir in Pregnancy: A Small but Significant Step Forward?

Pregnancies complicated by diabetes are at increased risk of adverse fetal and maternal outcomes and longer-term health problems in the offspring. Treatments directed at improving glycemic control reduce these risks. However, observational studies show that pregnancies complicated by either type 1 or type 2 diabetes, compared with nondiabetic pregnancies, still have more adverse outcomes, including increased perinatal mortality (1,2).

The recent Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study (3) has established a continuum of risk between glycemic levels obtained during a glucose tolerance test and a variety of adverse fetal and maternal outcomes. Two large randomized controlled trials (4,5) of women with gestational diabetes mellitus, variously diagnosed, have demonstrated that treating and reducing glucose levels during pregnancy reduces many of these complications.

The poor fetal outcomes in preexisting diabetes are largely related to the degree of maternal glycemic control. This is very well documented for the risk of miscarriage, congenital malformations, and excessive fetal weight (3,6–8). Unfortunately, the currently available insulin preparations and the treatment paradigms used in an attempt to achieve normoglycemia are generally inadequate for the task. This is especially true for type 1 diabetes. Specifically, the current insulin therapies cannot mimic the complex physiology required to maintain normal blood glucose concentrations. In addition, exogenous insulin therapies are limited by the dangers of hypoglycemia. Many women with preexisting diabetes cannot achieve normoglycemia as estimated by the ability to achieve a normal HbA_{1c}. It is also worth reminding ourselves that insulin use alone is rarely sufficient to achieve optimal pregnancy outcomes. Insulin must be used skillfully as part of an overall management plan.

There is little evidence in the literature for the safety of the current insulin gold standards of human short-acting insulin preparations or protaphane, the long-acting/basal insulin. There is limited information on the short-acting analogs lispro and aspart. A systematic review and meta-analysis (9) of lispro versus regular insulin identified a higher rate of large-for-gestational-age infants (>90th percentile), despite similar HbA_{1c} levels in the lispro group (relative risk, 1.38 [95% CI 1.14–1.16]), but no differences in the rate of small-for-gestational-age infants. No advantage of lispro was demonstrated. Insulin aspart has been studied in a randomized control trial similar to the detemir study described in this issue of *Diabetes Care*. It demonstrated similar outcomes for aspart compared with regular human short-acting insulin (10). In both the lispro and aspart studies, there was a trend toward less hypoglycemia in the analog group, but the differences were not statistically significant. Despite the lack of safety information, short-acting insulin and protaphane are the default standard comparators because of the long experience with their use. Overall, the level 1 evidence base for insulin use in pregnancy is very small (9).

Given the deficiencies of our knowledge about insulin use in pregnancy, the article by Mathiesen et al. (10) is both timely and important. This multinational, open-label, randomized, parallel-group, prospective study compared detemir, a long-acting insulin analog, with protaphane in the treatment of women with preexisting diabetes who were pregnant or planning a pregnancy. The study was planned as a noninferiority study with the primary end point being the HbA_{1c} level at 36 weeks' gestation. There was no significant difference in the primary end point. From this outcome it was concluded that insulin detemir was not inferior to protaphane insulin. Why would a clinician responsible for the care of pregnant women with type 1 diabetes consider changing from protaphane to this newer, more expensive insulin with less established safety data? This study provides several tantalizing suggestions of benefit.

The study demonstrated that women receiving insulin detemir prior to conception were able to achieve lower fasting glucose levels and a lower HbA_{1c}. More women in the insulin detemir group were able to achieve the target of a normal HbA_{1c}. This point is very important in achieving the goal of reducing fetal congenital abnormalities in women with diabetes. Congenital abnormalities are a significant contributor to the increased perinatal mortality seen with preexisting diabetes and contribute to increased morbidity. The final difference in HbA_{1c} of 0.3% in favor of detemir was not large, although it could be clinically significant if real. The fasting plasma glucose was lower in the detemir-treated group without any increase in nocturnal hypoglycemia.

Two hypotheses are suggested. Insulin detemir as compared with protaphane insulin results in less nocturnal hypoglycemia and achieves better glycemic control, particularly in the very important preconception period. To establish or refute these hypotheses would require large randomized controlled trials.

The study does demonstrate that large, multicenter studies with hard end points are possible in preexisting diabetes, as has been recently demonstrated for gestational diabetes mellitus. Such studies are not easy but are necessary to move closer to achieving the goal of normalizing the outcome of pregnancies complicated by diabetes. Importantly, it demonstrates what can be achieved with experienced practitioners in a motivated patient population. Furthermore, a convenient treatment algorithm is provided, which may be useful to less experienced practitioners or those not achieving similar results.

The study does not "prove" the safety of insulin detemir. The essential perinatal outcomes will be published separately. They have been presented in abstract form (11). The study does provide reassurance for its use when the standard long-acting insulin preparations are not achieving appropriate glycemic control, safely. Because the study suggested that insulin detemir was able to achieve lower fasting plasma glucose concentrations without increasing the risk of the feared nocturnal hypoglycemia, it will influence the choice of long-acting insulin in women who have difficulty in safely achieving fasting glucose targets.

In an ideal world, this last point would be confirmed in another independent study. In the meantime, clinicians caring for women prior to conception and during pregnancy have the option to consider an alternative long-acting insulin that has been validated in an appropriate clinical trial.

AIDAN MCELDUFF, MB, BS, FRACP

From the Discipline of Medicine, Sydney University, Sydney, New South Wales, Australia, and the Northern Sydney Endocrine Centre, St Leonards, New South Wales, Australia.

Corresponding author: Aidan McElduff, aidan.mcelduff@sydney.edu.au.

DOI: 10.2337/dc12-0971

Acknowledgments—A.M. has acted as a speaker and consultant for Novo Nordisk and Eli Lilly, Australia. He has received travel support from both companies. He was an investigator for Novo Nordisk's inhaled insulin program. No other potential conflicts of interest relevant to this article were reported.

References

1. Confidential Enquiry into Maternal and Child Health. *Pregnancy in Women with Type 1 and Type 2 Diabetes in 2002–2003: England, Wales and Northern Ireland*. London, CEMACH, 2005, p. 134
2. Shand AW, Bell JC, McElduff A, Morris J, Roberts CL. Outcomes of pregnancies in women with pre-gestational diabetes mellitus and gestational diabetes mellitus; a population-based study in New South Wales, Australia, 1998-2002. Diabet Med 2008;25:708–715
3. Metzger BE, Lowe LP, Dyer AR, et al.; HAPO Study Cooperative Research Group. Hyperglycemia and adverse pregnancy outcomes. N Engl J Med 2008;358:1991–2002
4. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med 2005;352:2477–2486
5. Landon MB, Spong CY, Thom E, et al.; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med 2009;361:1339–1348
6. Mills JL, Simpson JL, Driscoll SG, et al. Incidence of spontaneous abortion among normal women and insulin-dependent diabetic women whose pregnancies were identified within 21 days of conception. N Engl J Med 1988;319:1617–1623
7. Nielsen GL, Møller M, Sørensen HT. HbA1c in early diabetic pregnancy and pregnancy outcomes: a Danish population-based cohort study of 573 pregnancies in women with type 1 diabetes. Diabetes Care 2006;29:2612–2616
8. Pregnancy in women with type 1 and type 2 diabetes 2002–2003: England, Wales and Northern Ireland: executive summary [PDF online], 2005. London, CEMACH. Available from http://www.bathdiabetes.org/resources/254.pdf. Accessed 18 May 2012
9. McElduff A, Moses RG. Insulin therapy in pregnancy. Endocrinol Metab Clin North Am 2012;41:161–173
10. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. Diabetes Care 2012;35:2012–2017
11. Hod M, McCance DR, Ivanisevic M, et al. Perinatal outcomes in a randomized trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes [abstract online], 2011. Available from http://professional.diabetes.org/Abstracts_Display.aspx?TYP=1&CID=88745. Accessed 18 May 2012