

Point: Oral Hypoglycemic Agents Should Not Be Used to Treat Diabetic Pregnant Women

Studies in pregnancy indicate that the most important glucose concentration throughout the day is the peak postprandial glucose response; i.e., it is the highest blood glucose of the day, not the average, that predicts risk of untoward effects. The Diabetes in Early Pregnancy (DIEP) Study was a multicenter, case-controlled trial of type 1 diabetic women compared with healthy control women throughout pregnancy. Along with the primary objective of relating maternal glucose to risk of spontaneous abortions and malformations, they also studied the relationship between maternal postprandial glucose concentrations and risk of neonatal macrosomia (1). The DIEP Study identified 28.5% of infants from diabetic mothers who were above the 90th percentile of infant birth weight. Birth weight correlated positively with first-trimester maternal fasting blood glucose and A1C. When adjusted for fasting blood glucose and A1C, the 1-h postprandial maternal blood glucose concentration in the third trimester was an even stronger predictor of infant birth weight and fetal macrosomia. In addition, they reported that the risk of macrosomia is a continuum. They showed that any postprandial glucose peak was associated with an increased risk of macrosomia above the 10% risk seen in the general population.

Combs et al. (2) confirmed the findings of the DIEP Study and added the observation that elevated postprandial glucose was associated with an increased rate of macrosomia when higher maternal postprandial glucose concentrations were observed between weeks 29 and 32 of gestation. In a study of gestational diabetic women who failed a trial of diet and thus required insulin therapy, De Veciana et al. (3) described improved fetal outcome with less risk of neonatal hypoglycemia, macrosomia, and Cesarean delivery in women with gestational diabetes mellitus (GDM) when the women were managed by controlling 1-h postprandial glucose concentrations as opposed to action only based on preprandial glucose concentrations.

Hypothesized mechanism for glucose-mediated macrosomia

The peak postprandial plasma glucose response in healthy pregnant women is at the 1-h postprandial time point, and the highest blood glucose levels are <105 mg/dl, as reported by Parretti et al. (4). In addition, Frazier (5) reported that the peak glucose concentration is 1 h after eating (e.g., lunch at 12:00 P.M. and peak response at 1:00 P.M.). Recently, Yogev et al. (6) evaluated the ambulatory daily glycemic profile in the second half of pregnancy in normal healthy women for 72 consecutive hours per patient with continuous glucose monitoring by measurement of interstitial glucose levels in subcutaneous tissue every 5 min. They reported that the mean \pm SD fasting blood glucose level was 75 ± 12 mg/dl, the blood glucose level 83.7 ± 18 mg/dl, and the postprandial peak glucose value level 110 ± 16 mg/dl; the time interval needed to reach peak postprandial glucose level was 70 ± 13 min. A similar postprandial glycemic profile was obtained for breakfast, lunch, and dinner.

Postprandial glucose may play the most important role in causing overgrowth of the fetus by the following theory, which would explain the significance of a transient postprandial elevation of maternal glucose. The renal threshold for glucose in the fetus is probably <110 mg/dl. We know this fact from studies (7) of the renal threshold for glucose in premature neonates (<30 weeks of gestation). When the maternal glucose level is >110 mg/dl, the intravenous glucose load for the fetus causes fetal glycosuria. Therefore, uncontrolled maternal diabetes is associated with polyhydramnios from fetal polyuria. After 20 weeks of gestation, the fetus begins to swallow the amniotic fluid. Minor, transient elevations of blood glucose on the maternal side not only result in elevations of blood glucose on the fetal side but also result in glucose-enriched amniotic fluid ingested by the fetus for hours. The gut stimulus for insulin production in the fetus may be more potent than the transient intravenous hyperglycemia. Thus, hyperglycemia for <1 h once a day in the mother may produce a

fetal insulin stimulus, through the oral route, for hours. Elevations of maternal glucose levels more frequently (after every meal, for example) may produce a more prolonged oral glucose load for the fetus. The overnutrition of extra glucose provided to the fetus by both the intravenous route and the oral route produces an overfed, fat fetus.

All agree that the treatment for pregnancies complicated by diabetes is clearly intended to achieve and maintain normal glycemia. The means to achieve these goals remain controversial (8).

Dietary strategies to prevent neonatal macrosomia

The American Diabetes Association has not made specific dietary guidelines for gestational diabetic women. For obese women with GDM, there is even less of a consensus. In the American Diabetes Association *Clinical Practice Recommendations 2004* (8), there is no specific advice and nutritional recommendations for women with preexisting and GDM should be based on a nutrition assessment. Monitoring blood glucose levels, urine ketones, appetite, and weight gain can be a guide to developing an evaluation and appropriate individualized nutritional prescription and meal plan and to making adjustments to the meal plan throughout pregnancy to ensure desired outcomes. Obviously, this statement does not provide advice on the optimal diet for women with GDM.

Hypocaloric diets have been advocated for use in pregnancy since the 19th century for prevention of eclampsia and preeclampsia in diabetic patients (9–12). The recommendations for caloric needs during pregnancy have changed dramatically over the years until the recent recommendation of the National Academy of Science (13). Although there are no specific guidelines in the National Academy of Science report for obese women with GDM, there is reference to the caloric needs of obese, healthy women. In their summary and recommendations, it is suggested that no more than 15 lb need to be gained if a woman is >150% her ideal weight. However, a closer look at the out-

come of pregnancies in morbidly obese women revealed that the subsequent infant birth weight was optimal if the maternal weight gain was minimized to <3 kg or if no weight was gained.

The role of ketones in pregnancies complicated by diabetes has remained controversial (14). The initial evaluation of the offspring of mothers with ketonuria suggested that these children might have lower IQ scores than expected (15); however, this study has been questioned due to the methodology used and the concern that chorioamnionitis might have caused the intellectual impairment. Rizzo et al. (16) studied 223 pregnant women and their offspring: 89 women with type 1 diabetes, 99 with GDM, and 35 with normal glucose tolerance. No relation was found between maternal hypoglycemia and intellectual function of the offspring. However, scores on the Stanford-Binet tests inversely correlated with third-trimester β -hydroxybutyrate and free fatty acid plasma concentrations. The level of acetonuria did not correlate with test scores. Thus, there may be a difference between starvation ketosis and the ketosis that develops with poorly controlled diabetes (14). Ketonuria develops in 10–20% of normal pregnancies after an overnight fast and may in fact protect the fetus from starvation in the nondiabetic mother.

The Diabetes in Early Pregnancy Study also studied the β -hydroxybutyrate levels in the first trimester and showed that ketones are an independent predictor of macrosomia (17). They showed that for each of the weeks that β -hydroxybutyrate levels were measured, those of the diabetic group were significantly higher than those in the control group. Despite this ketone elevation, as the first trimester progressed, there was a consistent fall in β -hydroxybutyrate levels in the diabetic group. However, those in the diabetic group remained significantly higher than those in the control group. This study also showed that ketone levels were strongly correlated with glucose control in the diabetic group. Most likely, ketones reflect glucose control in diabetic patients and are not secondary to starvation. In the control group, β -hydroxybutyrate levels are negatively correlated with fasting glucose and thus probably reflect ketones of starvation. In addition, this study showed that the β -hydroxybutyrate levels are not elevated in women who delivered a malformed infant or had a spontaneous abortion. On the contrary, there seemed to be evidence that the mean β -hydroxybu-

tyrate levels were lower in diabetic and control subjects who had malformed infants or a spontaneous abortion. There was also evidence that the β -hydroxybutyrate level in the first trimester may be a prognostic indicator of subsequent macrosomia of the newborn. When birth weight is carefully controlled for sex and gestational week, the relationship between lower ketones and risk of macrosomia become highly significant. Further studies of β -hydroxybutyrate levels throughout pregnancy and in women with GDM are warranted to definitively show a relationship between β -hydroxybutyrate levels and birth weight (17).

Oral agents

Use of oral agents would be ideal for pregnancy since they are convenient, do not require intensive educational instruction at the time of initiation of therapy, and may increase adherence to treatment regimens. In 1988, I invited Dr. Edward Coetzee to write a chapter (18) in a book I edited. He outlined his clinical experience using oral agents in the treatment of pregnancy. His macrosomia rate was twice that seen in a general population—though one-half that seen in untreated diabetic women (20% in the treated diabetic group, 10% in the normal group, and 40% in untreated diabetic group). He and Prof. W.P.U. Jackson were using sulfonylureas and/or metformin. Although it may be proven that in the treatment of infertility in women with polycystic ovary syndrome, metformin decreases the spontaneous abortion rate from 30% when these women stop metformin at the time of diagnosis of pregnancy to 16% when they continue the drug through the first trimester (19), metformin clearly has been shown to cross the placenta. Also, metformin is not potent enough to treat postprandial hyperglycemia of the severity seen in pregnant type 2 diabetic women.

Regarding sulfonylureas, it is controversial whether they cross the placenta (20). Langer et al. (21) claim that the second-generation sulfonylureas do not cross the placenta. However, regardless of whether these agents cross, they too do not successfully blunt the peak postprandial glucose excursion. Glyburide has an onset of 2–3 h and peaks at 6–8 h. Glipizide is faster acting but still has an onset of 1 h and peaks 2 h after ingestion. Therefore, the main argument for using insulin when dietary strategies are not successful is to maintain postprandial glucose in the

normal range. Oral agents fail in this important mainstay of therapy.

Insulin analogs

In contrast, the rapid-acting insulin analogs, insulin lispro and insulin aspart, have been reported to be safe and to significantly improve postprandial glycemia excursions compared with human regular insulin in pregnancies complicated by diabetes (22). The first randomized study that evaluated the effect of insulin lispro treatment in pregnancy was that of Jovanovic et al. (23), in which 19 GDM patients on lispro and 23 on regular insulin were studied. In patients on insulin lispro, the number of maternal hypoglycemic episodes (plasma glucose <55 mg/dl) was 24% lower than that of patients on regular insulin. The number of episodes of postprandial hyperglycemia (1-h plasma glucose >120 mg/dl) was also significantly lower in patients on insulin lispro than in patients on human regular insulin. Moreover, treatment with insulin lispro caused a significantly greater reduction in A1C levels in the third trimester than human regular insulin. Others (24–26) have confirmed this initial finding.

The study reported by Wyatt et al. (27) was designed to determine the rate of congenital anomalies in offspring of type 1 diabetic women treated by insulin lispro before and during at least the first 12 weeks of gestation. This multinational, multicenter, retrospective study included mothers with diabetes (diagnosed before conception) who were treated with insulin lispro for at least 1 month before conception and during at least the first trimester of pregnancy. Anomalies were assessed by two independent dysmorphologists. The charts of 496 women were reviewed for 533 pregnancies, resulting in 542 offspring (500 live births, 31 spontaneous and 7 elective abortions, and 4 stillbirths). The dysmorphologists determined that 27 (5.4%) offspring had major congenital anomalies and that 2 (0.4%) had minor congenital anomalies. The rate of major congenital anomalies was 5.4% (95% CI 3.45–7.4) for offspring of mothers with diabetes treated with insulin lispro before and during pregnancy. The current published rates of major anomalies in infants born to diabetic mothers treated with insulin are between 2.1 and 10.9%, suggesting that the anomaly rate with insulin lispro treatment does not differ from the published major congenital anomaly rates for other insulin treatments.

Currently, there are very limited results regarding use of insulin aspart during pregnancy. Pettitt et al. (25,28,29) conducted the first clinical study to compare the short-term efficacy of insulin aspart, regular insulin, or no insulin in patients with GDM. Fifteen women with GDM received a standard meal test after administration of regular insulin or insulin aspart on 3 consecutive days (1 day was untreated baseline). Insulin aspart was administered 5 min before the meal, whereas regular insulin was administered 30 min before the meal. Postprandial glycemic control (as measured by glucose area under the curve above baseline) was significantly improved by insulin aspart compared with that when no exogenous insulin administered, whereas regular insulin did not show a significant difference compared with when no exogenous insulin was administered. These same investigators then observed a sample size of 27 women randomized to receive either insulin aspart or regular insulin for prandial treatment of carbohydrate intolerance. Both treatment groups maintained good overall glycemic control during the study. Insulin aspart was effective in reducing postprandial glucose concentration from baseline. The contribution of endogenous insulin to the overall insulin profile was ascertained by measurement of C-peptide values. C-peptide values for both insulin aspart and regular insulin treatments were slightly lower at week 6 than at week 0. However, insulin aspart treatment showed significantly lower C-peptide values at both week 0 and week 6 than regular insulin, as demonstrated by the significantly greater reduction in the change-from-baseline C-peptide values. No major hypoglycemic events were reported in this study. Antibody binding specific to insulin aspart and regular insulin remained relatively low (<1.5% binding of the specific antibodies) for both treatment groups throughout the study. Cord blood serum samples, collected immediately after delivery, only detected raised levels of insulin (either aspart or human regular insulin) if relatively high infusion rates of insulin and glucose were administered during labor and delivery (29). Neonatal birth weights were similar in both groups, and no cases of macrosomia were reported. These studies demonstrate that the overall safety and effectiveness of insulin aspart was comparable to that of regular human insulin in pregnant women with GDM. Insulin aspart was more effective than regular hu-

man insulin in providing postprandial glycemic control in women with GDM.

In a recent article, type 1 diabetic women ($n = 322$) who were pregnant or planning pregnancy were randomized to insulin aspart or to human regular insulin as mealtime insulin in an open-label, parallel-group, multicenter study (30). Major hypoglycemia occurred at a rate of 1.4 vs. 2.1 episodes/year exposure with insulin aspart and human regular insulin, respectively (relative risk [RR] 0.720 [95% CI 0.36–1.46]). Risk of major nocturnal hypoglycemia was 52% (0.48 [0.20–1.143]; $P =$ not significant) lower with insulin aspart than with human regular insulin. At the end of the first and third trimesters, average postprandial plasma glucose increments were significantly lower with insulin aspart than with human regular insulin ($P = 0.003$ and $P = 0.044$, respectively), as were mean plasma glucose levels 90 min after breakfast ($P = 0.044$ and $P = 0.001$, respectively). Maternal safety profiles and pregnancy outcomes were similar between treatments.

There are no randomized controlled clinical trials using insulin glulisine, insulin glargine, and insulin detemir, and thus no clinical recommendations can be made (30). However, based on the data for insulin lispro and insulin aspart, these two rapid-acting insulin analogs are both safe and efficacious premeal insulin for use by pregnant diabetic women requiring mealtime insulin. The rapid-acting analogs' favorable pharmacokinetics and postprandial blood glucose concentrations are improved compared with those of human regular insulin; thus, rapid-acting analogs may be considered a treatment choice for pregnant diabetic women.

Conclusions

Diabetic fetopathy resulting from maternal postprandial hyperglycemia can be minimized when the peak postprandial response is blunted. When medical nutritional therapy is not adequate to maintain normoglycemia, both fasting and in the postprandial state, insulin therapy must be initiated. Oral hypoglycemic agents may have enough data to prove that they do not harm the fetus; however, they clearly do not achieve the postprandial glucose response needed to normalize birth weight. The American Diabetes Association's treatment guidelines for pregnant diabetic women (8), which suggest that glucose levels can be as high as 140 mg/dl at the 1-h and 120 mg/dl at the 2-h

postprandial time points, are clearly recommending action only when glucose is in hyperglycemic ranges—despite the available literature. Perhaps maintaining such high thresholds for action in the treatment of diabetic pregnant women may have contributed to our sustained increased prevalence of macrosomia in infants of diabetic mothers despite “good glucose control.” It is time to reconsider our guidelines.

Dr. Coetzee concluded his chapter in my book (18) with the following observation: “The secret of successful perinatal outcomes in all pregnant diabetic patients lies more in the achievement of excellent blood glucose levels than in the means of achieving it.” On the same page, I added the following editorial comment: “Although the editor fully supports Dr. Coetzee's discussion, it must be noted that in the U.S. oral hypoglycemic agents are not approved for the use during pregnancy.” Of course, both parts of this comment are still true!

LOIS JOVANOVIC, MD

From the Sansum Diabetes Research Institute, Santa Barbara, California. E-mail: ljovanovic@sansum.org.

Address correspondence and reprint requests to Dr. L. Jovanovic, Sansum Diabetes Research Institute, 2219 Bath St., Santa Barbara, CA 93105.

Received for publication 5 July 2007 and accepted 6 July 2007.

DOI: 10.2337/dc07-1282

© 2007 by the American Diabetes Association.

References

1. Jovanovic L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH, the National Institute of Child Health and Human Development: Maternal postprandial glucose levels and infant birth weight: the Diabetes In Early Pregnancy Study. *Am J Obstet Gynecol* 164: 103–111, 1991
2. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK: Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care* 15:1251–1257, 1992
3. DeVeciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT: Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *N Engl J Med* 333:1237–1241, 1995
4. Parretti E, Mecacci F, Papini M, Cioni R, Carignani L, Mignosa M, La Torre P, Mello G: Third-trimester maternal glucose levels from diurnal profiles in non-diabetic pregnancies: correlation with

- sonographic parameters of fetal growth. *Diabetes Care* 24:1319–1323, 2001
5. Fraser R: Third trimester maternal glucose levels from diurnal profiles in non-diabetic pregnancies: correlation with sonographic parameters of fetal growth (Letter). *Diabetes Care* 25:1104, 2002
 6. Yogev Y, Ben-Haroush A, Chen R, Rosenn B, Hod M, Langer O: Diurnal glycemic profile in obese and normal weight nondiabetic pregnant women. *Am J Obstet Gynecol* 191:949–953, 2004
 7. Ostertag S, Jovanovic L, Lewis B, Auld P: Insulin infusion therapy for low birth weight infants. *Pediatrics* 78:625–630, 1986
 8. American Diabetes Association: Gestational diabetes mellitus (Position Statement). *Diabetes Care* 27 (Suppl. 1):S88–S90, 2004
 9. Jovanovic L, Pettitt DJ, Contempo Updates: Linking evidence and experience: gestational diabetes mellitus. *JAMA* 286: 2516–2518, 2001
 10. Jovanovic L, Peterson CM: Rationale for prevention and treatment of glucose-mediated macrosomia: a protocol for gestational diabetes. *Endocrine Pract* 2:118–129, 1996
 11. Jovanovic L, Bevier W, Peterson CM: The Santa Barbara County Health Care Services Program: birth weight change concomitant with screening for and treatment of glucose-intolerance of pregnancy: a potential cost-effective intervention. *Am J Perinatol* 14:221–228, 1997
 12. Coetzee EJ, Jackson WPU: Nutritional management of pregnant diabetic women. In *Contemporary Issues in Clinical Nutrition 8: Nutrition and Diabetes*. Jovanovic L, Peterson CM, Eds. New York, Alan Liss, 1985, p. 121–132
 13. Allen L, King J: *Nutrition During Pregnancy*. Washington, DC, National Academy Press, 1990
 14. Jovanovic L, Peterson CM: Sweet success, but an acid after taste? *N Engl J Med* 325:959–960, 1991
 15. Churchill JA, Berendes HW, Nemore J: Neuropsychological deficits in children of diabetic mothers: a report from the Collaborative Study of Cerebral Palsy. *Am J Obstet Gynecol* 105:257–268, 1969
 16. Rizzo T, Metzger BE, Burns WJ, Burns K: Correlations between antepartum maternal metabolism and intelligence of offspring. *N Engl J Med* 325:911–916, 1991
 17. Jovanovic L, Metzger BE, Knopp RH, Conley MR, Park E, Lee YJ, Simpson JL, Holmes L, Aarons JH, Mills JL, the NICHD-Diabetes in Early Pregnancy Study Group (DIEP): The Diabetes in Early Pregnancy Study: β -Hydroxybutyrate levels in type 1 diabetic pregnancy compared with normal pregnancy. *Diabetes Care* 21:1–5, 1998
 18. Coetzee EJ, Jackson WPU: Oral hypoglycemic agents in the treatment of gestational diabetes. In *Controversies in Diabetes and Pregnancy, Endocrinology and Metabolism*. Jovanovic L, Ed. New York, Springer-Verlag, 1988, p. 57–76
 19. Khattab S, Mohsen IA, Foutouh IA, Ramadan A, Moaz M, Al-Inany H: Metformin reduces abortion in pregnant women with polycystic ovary syndrome. *Gynecol Endocrinol* 22:680–684, 2006
 20. Jovanovic L: The use of oral agents during pregnancy to treat gestational diabetes. *Curr Diab Rep* 1:69–70, 2001
 21. Langer O, Yogev Y, Xenakis EM, Rosenn B: Insulin and glyburide therapy: dosage, severity level of gestational diabetes, and pregnancy outcome. *Am J Obstet Gynecol* 192:134–139, 2005
 22. Singh C, Jovanovic L: Insulin analogues in the treatment of diabetes in pregnancy. *Obstet Gynecol Clin North Am* 34: 275–291, 2007
 23. Jovanovic L, Pettitt DJ: Treatment with insulin and its analogs in pregnancies complicated by diabetes. *Diabetes Care* 30 (Suppl. 2):S220–S224, 2007
 24. Bhattacharya A, Brown S, Huges S, Vice PA: Insulin lispro and regular insulin in pregnancy. *QJ Med* 94:255–260, 2001
 25. Mecacci F, Carignani L, Cioni R, Bartoli E, Parretti E, La Torre P, Scarselli G, Mello G: Maternal metabolic control and perinatal outcome in women with gestational diabetes treated with regular or lispro insulin: comparison with non-diabetic pregnant women. *Eur J Obstet Gynecol Reprod Biol* 11:19–24, 2003
 26. Garg SK, Frias JP, Anil S, Gottlieb PA, Mackenzie T, Jackson WE: Insulin lispro therapy in pregnancies complicated by diabetes type 1: glycemic control and maternal and fetal outcomes. *Endocr Pract* 9:187–193, 2003
 27. Wyatt JW, Frias JL, Hoyme HE, Jovanovic L, Kaaja R, Brown F, Garg S, Lee-Parritz A, Seely EW, Kerr L, Mattoo V, Tan M; IONS study group: Congenital anomaly rate in offspring of pre-gestational diabetic women treated with insulin lispro during pregnancy. *Diabet Med* 21:2001–2007, 2004
 28. Pettitt DJ, Ospina P, Howard C, Zisser H, Jovanovic L: Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabet Med* 24:1129–1135, 2007
 29. Pettitt DJ, Ospina P, Kolaczynski J, Jovanovic L: Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care* 26:183–186, 2003
 30. Mathiesen ER, Kinsley B, Amiel SA, Heller S, McCance D, Duran S, Bellaire S, Raben A, the Insulin Aspart Pregnancy Study Group: Maternal glycemic control and hypoglycemia in type 1 diabetic pregnancy: a randomized trial of insulin aspart versus human insulin in 322 pregnant women. *Diabetes Care* 30:771–776, 2007