Jet-Injected Insulin Is Associated With Decreased Antibody Production and Postprandial Glucose Variability When Compared With Needle-Injected Insulin in Gestational Diabetic Women

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OBJECTIVE — To elucidate the glycemic response and antibody formation in gestational diabetic women treated with insulin injected by a needle or a jet. The American Diabetes Association's position statement on jet injectors raised the concern that "insulin could be denatured as a result of forceful injection through a tiny port, which could lead to an increase in antibody formation" (*Diabetes Care* 11:600, 1988). However, the pharmacokinetics of jet-injected insulin suggest that it might be useful in controlling postprandial glucose levels.

METHODS — We randomized 20 women with gestational diabetes mellitus (<34 wk gestation) who required insulin to receive either jet-injected or needle-injected human NPH and regular insulin. Variables of interest were evaluated at the start of therapy, weekly until delivery, and 6-wk postpartum that included: *1*) insulin antibodies in the mother and her infant, 2) HbA_{1c}, 3) insulin dose, 4) fasting and postprandial glucose levels, and 5) subject acceptance and preference.

RESULTS — Of the 10 women in the needle group, 6 developed significant insulin antibodies compared with 1 of 10 in the jet group ($P < 0.001$). HbA_{1c} and insulin doses were the same in both groups. During the test meal, glucose levels in the jet group were significantly lower ($P < 0.01$), yet none of the women in the jet group experienced blood glucose <70 mg/dl (3.89 mM) at 3–4 h after the meal, compared with 5 in the needle group ($P < 0.001$). Jet injection was associated with less variability ($P < 0.001$) in postprandial glucose values but slightly greater variability ($P < 0.05$) in fasting glucose. Jet-injected insulin was more readily accepted by subjects than needle injections.

CONCLUSIONS — Jet injection is associated with a diminished antibody response and postprandial variability compared with needle-injected insulin. Thus, this warrants consideration as a therapeutic option for women with gestational diabetes mellitus and may also be applicable to nonpregnant, insulin-requiring diabetic patients.

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GDM, gestational diabetes mellitus; type I diabetes, insulin-dependent diabetes mellitus; IgG, immunoglobulin G; ADA, American Diabetes Association; SMBG, self-monitoring of blood glucose; FBG, fasting blood glucose; RIA, radioimmunoassay; CV, coefficient of variation.

Maternal glucose freely crosses the placenta, but maternal insulin does not unless it is bound to maternal IgG antibodies (1). Such bound insulin may interfere with fetal insulin-glucose homeostasis (2). GDM provides an opportunity to study women without previous exposure to insulin. If insulin is necessary to treat the GDM woman during the index pregnancy, it may be necessary to reinstitute it with every subsequent pregnancy (3). Starting and stopping insulin may create high antibody titers (4). Even with human insulin, a significant insulin antibody response has been reported within weeks of starting therapy (5). Whether or not insulin antibodies, independent of glucose control, cause macrosomia is controversial (6–8). Until the definitive answer is available, it is prudent to use a method of injecting insulin that minimizes antibody production for GDM women.

It remains unclear whether the mode of administration of insulin modulates the antibody response. ADA's position statement on jet-injected insulin raised a concern that "insulin could be denatured as a result of forceful injection through a tiny port which could lead to an increase in antibody formation" (9).

Preliminary studies on the use of jet-injected insulin (in the treatment of nonpregnant, type I diabetic subjects) suggest that jet injection shortens the peak action of regular insulin, and therefore a lag time between injection and eating may not be necessary (10,11). In addition, the peak postprandial response is blunted in these studies (10). During pregnancy, blunting postprandial hyperglycemia is paramount to prevent subsequent macrosomia (12). Therefore, a technique of insulin administration that is acceptable, nonimmunogenic, and produces the best glycemic control would be preferable for GDM women. We therefore designed a randomized study of needle versus jet-injected human insulin in 20 GDM women to de-

Table 1—*Characteristics of GDM women*

	Insulin injection method	
	Needle	Jet
Naive to insulin therapy (*n*)	10	10
Age (yr)	27 ± 4	28 ± 5
Weight (kg)	83.6 ± 23	86.7 ± 19
Gestational wk	32 ± 2	31 ± 2
C-peptide (pM)	>3.0	>3.0

Data are means ± SD.

termine 1) insulin antibodies in the mother and her infant, 2) HbA_{1c}, 3) insulin dose, 4) fasting and postprandial glucose levels, and 5) subject acceptance and preference.

RESEARCH DESIGN AND METHODS— We studied 20 GDM women, diagnosed according to the Second International Gestational Diabetes Workshop/Conference (13). All studies were approved by the Institutional Review Board of the Santa Barbara Cottage Hospital, and each patient signed an informed, witnessed consent. After a trial of diet (14) if the results of their SMBG showed that their FBG levels were >90 mg/dl (5 mM) and/or their 1-h postprandial glucose levels were >140 mg/dl (7.77 mM) (12), subjects were offered participation in this study of insulin therapy by two different injection methods. After signing informed, witnessed consent, they were randomized (using a coded two-color card draw) between two groups: needle and jet injection. The needle group administered the insulin subcutaneously with conventional syringes (Micro-Fine IV 28 gauge, 12.7-mm needles with a 0.5-ml syringe, Beckton Dickinson, Franklin Lakes, NJ) 3 times/day. Insulin dosing consisted of a combination of human NPH and human regular insulin calculated to be 0.9 $U \cdot kg^{-1} \cdot day^{-1}$ (the morning injection consisted of NPH calculated to be 4/9 of the total dose of insulin and regular calculated to be 2/9 of the total dose; the second injection of the day was given before dinner calculated to be 1/6 of the total dose; and the third injection of the day was NPH given before bedtime calculated to be 1/6 of the total dose). The jet group administered the human NPH and human regular insulin with a jet-injection device (Tender Touch, Derata, Minneapolis, MN) also calculated to be 0.9 $U \cdot kg^{-1} \cdot day^{-1}$ given in the same distribution as the needle injection group. The protocols for insulin administration and adjustment have been reported in detail elsewhere (14).

Randomization divided the women into two comparable groups that were not significantly different from each other (Table 1). All women underwent the following laboratory determinations: HbA_{1c} by ion-exchange high-pressure liquid chromatography (normal value for this gestational week of 4.0 ± 0.5%), C-peptide (15), and insulin antibodies (16,17). Blood was drawn every 2 wk for HbA_{1c} and every week for antibodies. At delivery both maternal and cord antibodies were obtained. At 6 wk postpartum, the mother had a repeat HbA_{1c} and insulin antibody measurement.

Insulin antibodies were measured by a fluid-phase RIA using an acid charcoal methyl cellulose extraction step developed by Dixon (16) and modified by Sutton et al. (17), monoiodinated human insulin tracer, and displacement with an excess of unlabeled insulin for quantitation of specific binding. The results are expressed as the percentage of binding displaced by cold insulin with values >mean + 3 SD of normal control subjects (0.8%) being considered positive (18). The antibody levels are reported as a percentage of total counts in the tube. Because the assay depends on displacement, the 3 SDs cut point for positivity (0.08%) is the percentage of total counts bound in the absence of cold insulin minus the percentage of total counts bound in the presence of cold insulin, described in detail by Hegewald (18).

On the first day of insulin administration, an experiment was designed to observe if the customary lag time needed with needle-injected insulin could be eliminated with the jet injector. The prebreakfast injection of calculated regular insulin (2/9 of the total insulin requirement) was given either with a needle and a syringe or with a jet injector by the study nurse. A standard meal was then immediately eaten by the subject; the meal consisted of 40% carbohydrate, 40% fat, and 20% protein and composed of 10% of the total needs for the day (10% of 30 kcal/kg present pregnant weight) (19,20).

The nurse monitored blood glucose by glucose oxidase reagent strips and reflectance meter (One Touch, Life Scan, Milpitas, CA) referenced to a Yellow Spring International autoanalyzer (Yellow Springs, OH) by previously published methods (21). The blood glucose monitoring was conducted at fasting and every 15 min following the injection/ingestion of the standard meal for 1 h and then every 30 min for 3 h. The patients were then sent home to continue insulin therapy (calculated to be 0.9 $U \cdot kg^{-1} \cdot day^{-1}$ divided into the 3 injections as described) using the method of their assigned group (the jet or needles). In the case of needle-injected insulin, the patients were instructed to inject their prebreakfast and predinner regular insulins 45 min before the meal. Insulin adjustments were made weekly based on their 8 daily SMBG measurements (before and 1 h after each meal, before bedtime, and at 0300) and documented for an accurate comparison of the memory

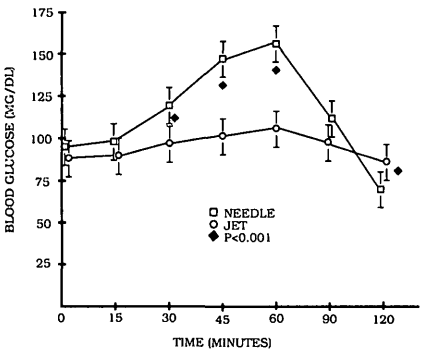

Figure 1—*Blood glucose response to the injection of regular insulin (2/9 of the total daily insulin requirement of 0.9 times the present pregnant weight in kg). Subjects immediately ate 10% of the total daily allowance of calories (10% of 30 kcal/kg present pregnant weight) composed of 40% carbohydrate, 40% fat, and 20% protein. The symbols represent the glucose response when insulin was administered with a syringe (n = 10) and when administered with a jet injector (n = 10). Error bars indicate SDs. The slope of the line drawn through the points on the graph at 60, 90, and 120 min is 4 times steeper for the needle injected insulin as compared with the jet-injected insulin: −1.42 vs. −0.33.*

data to the diary data. The nurse kept a record of the time required to teach each patient the injection technique. In addition, a questionnaire was given to the mothers at delivery to assess their opinion of the method used for administering insulin.

Statistical analysis

We used the Student's *t* test for unpaired samples (StatWorks for MacIntosh, Cupertino, CA) or statistical tables of frequency (22).

RESULTS— The blood glucose response when the insulin was injected immediately before the test meal is illustrated in Fig. 1. The needle injection technique was associated with a significant elevation of blood glucose compared with the jet group at the 30, 45, and 60 min time points (if the needle injected insulin had been given 45 min before the meal, the postprandial elevations of glucose would be blunted). In addition, the rate of the fall of blood glucose between 60 and 120 min was faster in the needle group. The slope of the line drawn through the points on the graph at 60, 90, and 120 min is 4 times steeper for the needle injected insulin compared with the jet-injected insulin: −1.42 vs. −0.33. In the needle group, 5 patients had blood glucose levels <70 mg/dl (3.89 mM) ($P < 0.01$) between 90 and 120 min compared with none in the jet group. On the other end of glycemic control, 7 in the needle group had a blood glucose >140 mg/dl (7.78 mM) compared with 0 in the jet group ($P < 0.001$).

Table 2 shows that prolonged good glucose control can be achieved with either the needle- or the jet-injected method of insulin administration, when patients are instructed to inject their needle-injected insulin 45 min before the meal. The jet-injected insulin group was able to eliminate the lag period between the injection and the meal ingestion. No significant difference was observed between the groups for HbA_{1c}, 24-h insulin requirement, or glycemic control as measured by mean fasting or 1-h postprandial glucose levels derived from the 6 wk of data on the SMBG diaries.

A significant difference was detected in glucose variability between groups. Glucose variability was defined as the CV and is expressed in Table 2 as the mean of each woman's SD of the mean fasting glucose divided by the mean glucose from 6 wk of daily glucose diary values times 100 (the 1-h postprandial glucose variability was calculated in the same fashion). The glucose variability was greater for the FBG in the jet group compared with the needle group (14 ± 4 vs. 8 ± 2%, $P = 0.05$). On the other hand, the glucose variability of the 1-h postprandial glucose levels was significantly less in the jet-injected insulin (CV 10 ± 4 vs. 21 ± 3%, $P < 0.001$).

The shortest amount of time needed to teach the needle technique was 30 min, whereas the jet technique could be taught in 10 min. The mean teaching time was 45 and 30 min in the needle and jet groups, respectively. One woman required >2 h to inject herself using a needle; whereas 40 min was the longest amount of time required to teach jet injection.

Jet-injected insulin appeared less immunogenic than needle-injected insulin (Table 3). Of the 10 women using a needle, 6 developed detectable insulin antibodies compared with 1 woman using the jet injector ($P < 0.001$). The time lag in days to peak antibody response was comparable: 56 ± 8 days for needle users versus 50 days for 1 women in the jet group. Those women who had positive serum antibody titers were the same

Table 2—*Outcome variables for the 6 wk of therapy*

	Insulin injection method		
	Needle	Jet	*P* value
HBA_{1C} (%)	4.3 ± 1.2	4.1 ± 1.4	NS
24-h insulin requirement ($U \cdot kg^{-1} \cdot day^{-1}$)	0.82 ± 0.1	0.84 ± 0.2	NS
Mean FBG (mg/dl)	84 ± 7	81 ± 9	NS
1-h postprandial (mg/dl)	112 ± 21	115 ± 12	NS
Individual glucose variability (CV)			
Fasting on SBGM (%)	8 ± 2	14 ± 4	<0.05
1-h postprandial on SBGM (%)	21 ± 3	10 ± 4	<0.001

Data are means ± SD.

Table 3—*Antibody results*

	Insulin injection method		
	Needle	Jet	*P* value
Antibody response >0.8 (*n*)	6	1	<0.001
Time to peak response (days)	56 ± 8	50	NS
Positive cord antibody response >0.8 (*n*)	6	1	<0.001
6-wk postpartum with positive antibody response >0.8 (*n*)	6	0	<0.001

Data are means ± SD.

women who had positive cord antibody titers. The positive antibody response in the needle group persisted at 6-wk postpartum and cessation of insulin. The 1 woman with positive antibodies in the jet group became negative by 6 wk. The mean peak antibody levels in those women using the needle was 4.6 ± 2.0%. The antibody level in the 1 woman in the jet group who had a positive antibody response was only 1.1%. No difference was found in neonatal birth weight or morbidity in the two groups.

CONCLUSIONS — Contrary to expectations, the insulin antibody response was less with jet-injected insulin compared with needle-injected insulin in GDM woman. Those women with a positive antibody response had infants born with a positive cord antibody level. The women using needles were documented to have the antibody response persist for 6 wk after the insulin was stopped at the time of delivery.

Our data confirms that jet-injected insulin allows for immediate premeal administration of insulin with less glycemic excursion than needle-injected insulin. Those women who used the jet-injection device also had less glucose variability in their postprandial glucose response. Their FBG level was more variable, perhaps attributable to more rapid absorption of bedtime NPH insulin when injected with a jet device.

We found jet-injected insulin more acceptable to GDM women naive to injections. At delivery, all 10 women in the jet group were happy that they randomized to the jet group, whereas all of the needle group reported that they were disappointed to be in the needle group. The quantity of time needed to teach the requisite skills was also significantly less with the jet injector compared with the needle-injected technique.

Jet-injection insulin was pioneered in the late 1940s by Hingson et al. (23). With jet injection, insulin is forced through a fine nozzle at high pressure. A microjet stream is produced that penetrates the skin and insulin is deposited subcutaneously in a dispersed fashion. In the years following 1947, these authors reported success with jet-injected insulin in the treatment of type I diabetes (24), but detailed studies evaluating the method were not performed until the early 1980s. Several authors have demonstrated a more rapid absorption of short-acting insulin after jet injection compared with conventional needle injection (25,26), consistent with our findings. The magnitude of peak plasma free insulin values was not significantly different comparing jet with conventional injection, but the peak insulin concentration was reached earlier in diabetic patients with less prolonged hyperinsulinemia (27). Thus, it is not surprizing that jet-injected insulin was more effective in blunting the postprandial peak glucose response and the subsequent rapidity of glucose fall than needle injected insulin in one study (28).

Human insulin is not completely free of an antibody response. Studies of nonpregnant, type I diabetic patients show that a significant antibody response develops within weeks of starting therapy in patients naive to insulin therapy (17). Although the exact mechanism whereby human insulin causes an antibody response in humans is not known, the answer probably is that the three-dimensional structure of conventional insulin is different from endogenous insulin, and hence it is immunogenic. Some concern (9) has arisen that the mode of injection of insulin may play a role in the degree of antigenicity of insulin via an adjuvant mechanism. Dahl-Jorgensen et al. (29) reported that when insulin was given as multiple daily injections or by an insulin infusion pump, the antibody production increased over that seen with conventional injection treatment. Antibody-bound insulin crosses the placenta (1) and may play a role in the development of neonatal macrosomia (6). However others have shown that stabilization of glucose levels prevents this macrosomia despite the antibody response (7,8). Although the ADA position statement (9) cautions concern that jet-injected insulin might be more immunogenic, the data reported here are the first to specifically address this issue and suggest that ADA's concern may be unwarranted. The sensitive and specific antiinsulin assay used in our study allowed us to clearly show that jet-injected insulin produces little to no antibody response in the short duration of insulin treatment needed in GDM, compared with needle therapy. Because maximum antibody response to injected insulin occurs after 4–6 mo of treatment (17), longer treatment of the two groups might show more of an antibody response, especially in the jet-injected patients.

In summary, jet-injected insulin is acceptable to GDM women and produces less hypo- and hyperglycemia after meals. In addition, less of an immune

response to insulin injected with a jet injector than with a syringe and needle has been observed. On the other hand, NPH insulin injected at 2300 by a jet injector produced increased variability in the FBG the morning following the injection when compared with NPH injected by needles. In view of studies showing that elevated postprandial glucose values are associated more with neonatal macrosomia than with fasting glucose values (12), clinicians may wish to offer jet-injected, premeal insulin as an option for GDM women. The findings of our study may have a broader application outside of GDM, particularly in patients using multidose intensive insulin regimens.

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References

1. Bauman WA, Yalow RS: Transplacental passage of insulin complexed to antibody. *Proc Natl Acad Sci USA* 78:4588–90, 1981
2. DiMario U, Falluca F, Gargiulo P, Tiberti C, Scardellato A, Arduini P: Insulin-anti-insulin complexes in diabetic women and their neonates. *Diabetologia* 27:83–86, 1984
3. Mylvaganam R, Stowers JM, Steel JM, Wallace J, MacHendry JC, Wright AD: Insulin immunogenicity in pregnancy: maternal and fetal studies. *Diabetologia* 24:19–25, 1983
4. Dixon K, Exon PD, Hughes HR: Insulin antibodies in aetiology of labile diabetes. *Lancet* 1:343–47, 1972
5. Leiper JM, Fineberg SE, Luman CB, MacCuish AC: Insulin antibodies in the maternal and foetal circulation of pregnant diabetic women treated with human insulin of recombinant DNA origin. *Diabetes Res Clin Pract* 1:75–81, 1984
6. Menon RK, Cohen RM, Sperling MA, Cutfield WS, Mimouni F, Khoury JC: Transplacental passage of insulin in pregnant women with insulin-dependent diabetes mellitus: its role in fetal macrosomia. *N Engl J Med* 323:309–15, 1990
7. Rosenn B, Miodovnik M, Combs CA, Williams T, Wittekind C, Siddiqi TA: Human versus animal insulin in the management of insulin-dependent diabetes: lack of effect on fetal growth. *Obstet Gynecol* 78:590–93, 1991
8. Jovanovic-Peterson L, Kitzmiller JL, Peterson CM: Lower birth weight and C-peptide response in infants of diabetic pregnant women receiving human versus animal source insulin. *Am J Obstet Gynecol* 167:1325–29, 1992
9. Golden MP, Haymond M, Hinnen DA, Kruger DF, Schumacher OP: Position statement on jet injectors. *Diabetes Care* 11:600–01, 1988
10. Worth R, Anderson J, Taylor R, Alberti KGMM: Jet injection of insulin: comparison with conventional injection by syringe and needle. *Br Med J* 281:713–14, 1980
11. Malone JI, Lowitt S, Grove NP, Shah SC: Comparison of insulin levels after injection by jet stream and disposable insulin syringe. *Diabetes Care* 9:637–40, 1986
12. Jovanovic-Peterson L, Peterson CM, Reed GF, Metzger BE, Mills JL, Knopp RH, Aarons JH, NICHD-DIEP: Maternal post prandial glucose levels and infant birth weight: the Diabetes in Early Pregnancy Study. *Am J Obstet Gynecol* 164: 103–11, 1991
13. Summary and Recommendations of the Second International Gestational Diabetes Workshop/Conference. *Diabetes* 34 (Suppl. 2):123–26, 1985
14. Jovanovic-Peterson L, Peterson CM: Dietary manipulation as a primary treatment strategy for pregnancies complicated by diabetes. *J Am Coll Nutr* 9:320–25, 1990
15. Heding EG, Persson B, Stangenberg M: B-cell function in newborn infants of diabetic mothers. *Diabetologia* 19:427–32, 1980
16. Dixon K: Measurement of antibodies to insulin in serum. *Clin Chem* 20:1275–81, 1974
17. Sutton M, Klaff LJ, Asplin CM, Clemons P, Tatpati O, Lyen K, Palmer JP: Insulin autoantibodies at diagnosis of insulin-dependent diabetes: effect on the antibody response to insulin treatment. *Metabolism* 37:1005–1007, 1988
18. Hegewald MJ, Schoenfeld SL, McCulloch DK, Greenbaum CJ, Klaff LJ, Palmer JP: Increased specificity and sensitivity of insulin antibody measurements in autoimmune thyroid disease and type I diabetes. *J Immunol Methods* 154:61–68, 1992
19. Jovanovic L, Peterson CM, Saxena BB, Dawood MY, Saudek CD: Feasibility of maintaining euglycemia in insulin-dependent diabetic women. *Am J Med* 68: 105–12, 1980
20. Jovanovic L, Druzin M, Peterson CM: Effect of euglycemia on the outcome of pregnancy in insulin-dependent diabetic women as compared with normal control subjects. *Am J Med* 71:921, 1981
21. Jovanovic-Peterson L, Peterson, CM, Dudley JD, Kilo C, Ellis B: Identifying sources of error in self monitoring of blood glucose. *Diabetes Care* 11:791–93, 1988
22. Linton M, Gallo PS Jr: *The Practical Statistician: Simplified Handbook of Statistics.* Monterey, CA, Brooks/Cole, 1975, p. 70–71
23. Hingson RA: Development of hypospray for parenteral therapy by jet injection. *Anesthesiology* 10:65–75, 1949
24. Cohn ML, Hingson RA, Narduzzi JV, Seddon JM: Clinical experience with jet insulin injection in diabetes mellitus therapy: a clue to the pathogenesis of lipodystrophy. *Ala J Med Sci* 11:265–72, 1974
25. Taylor R, Home PD, Alberti KGMM: Plasma free insulin profiles after administration of insulin by jet and conventional syringe injection. *Diabetes Care* 4:377–79, 1981
26. Pehling GB, Gerich JE: Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. *Mayo Clin Proc* 59:751–54, 1984
27. Houtzagers CMGJ, Berntzen PA, van der Stap H , Heine RJ, van der Veen EA: Absorption kinetics of short- and inter-

mediate-acting insulins after jet injection with Medi-Jector II. *Diabetes Care* 11: 739–42, 1988
28. Worth R, Anderson J, Taylor R, Alberti KGMM: Jet injection of insulin: comparison with conventional injection by syringe and needle. *Br Med J* 281:713–14, 1980
29. Dahl-Jorgensen KD, Torjesen P, Hanssen KF, Sandvik L, Aagenaes O: Increase in insulin antibodies during continuous subcutaneous insulin infusion and multiple-injection therapy in contrast to conventional treatment. *Diabetes* 36:1–5, 1987