Incidence and Significance of Islet Cell Antibodies in Women With Previous Gestational Diabetes

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Islet cell antibodies (ICAs) are markers for patients at risk for insulin-dependent diabetes and are associated with progressive β-cell destruction. This prospective study was performed to estimate the incidence of these antibodies in 187 women with previous gestational diabetes. With a specific protein A monoclonal antibody (MoAb) assay, the incidence of ICAs was only 1.6% (3 of 187). Oral and intravenous glucose tolerance tests were performed in these 3 women and compared with 6 women with previous gestational diabetes without ICAs and 5 control women. Glucose tolerance was impaired only in the 3 women with ICAs, who also had an increase ($P < 0.03$) in fasting plasma glucose and a decrease ($P < 0.03$) in early first-phase insulin response. We conclude that the more specific MoAb method indicates a lower incidence of ICA in women with a history of gestational diabetes than previously reported and that a decreased first-phase insulin response is associated with the presence of ICAs, suggesting progressive islet cell damage. *Diabetes Care* 13:478–82, 1990

Women with a history of gestational diabetes are at a greater risk for developing diabetes later in life than those with normal glucose tolerance during pregnancy (1). The proportion of women developing type I (insulin-dependent) or type II (non-insulin-dependent) diabetes is not well established. We previously reported that one of the underlying metabolic abnormalities in women with previous gestational diabetes is increased insulin resistance (2), and such women may be at increased risk for type II diabetes.

Islet cell antibodies (ICAs) directed against the β-cell of the pancreas, however, are a predictive marker only for those individuals at risk for type I diabetes (3). They are autoantibodies that are found in genetically susceptible individuals, i.e., those of HLA types DR3 and DR4. ICAs are present in most patients with recently diagnosed type I diabetes and result in progressive pancreatic β-cell destruction (4). The incidence of ICA in women with gestational diabetes found with an indirect immunofluorescence method is between 10 and 38% (5,6).

The purpose of this study was to determine the incidence of ICA with a specific monoclonal antibody (MoAb) technique in women after a pregnancy complicated by gestational diabetes (7) and to compare the functional status of the few women with positive tests to women with previous gestational diabetes but no demonstrable antibodies and to women without a history of gestational diabetes.

RESEARCH DESIGN AND METHODS

Subjects. The study was approved by the Institutional Review Board at the University of Vermont, and informed consent was obtained from each participant. One hundred eighty-seven women with gestational diabetes diagnosed according to the criteria of Carpenter and Coustan (8) and treated at the diabetic pregnancy clinic at the Medical Center Hospital of Vermont were

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tested for ICA. These women were tested within 1 wk of delivery in the pregnancy complicated by gestational diabetes to determine the incidence of ICA in women with a history of gestational diabetes.

Two prospectively evaluated control groups and ICA^+ subjects comprised our study population to assess functional status. One group consisted of six ICA^- women with gestational diabetes. The second group of five women had neither a history of gestational diabetes during a previous pregnancy nor the presence of ICAs. Oral (OGTT) and intravenous (IVGTT) glucose tolerance tests were used to assess β-cell function. Morphometric data, family history, and results of OGTT from the index pregnancy were also obtained from subjects in the study population.

Experimental protocol. ICA assays were made of serums from all subjects. The samples were spun, and the serums were frozen at −20°C for no longer than 60 days before shipment. The frozen serum was then sent to the Joslin Diabetes Center for protein A MoAb method to detect antibodies (7).

Three ICA^+ subjects and subjects in the two control groups completed the following tests. Each was given a 75-g OGTT as defined by the National Diabetes Data Group (9). The next day, an IVGTT was performed by administering 0.5 g glucose/kg body wt over 3 min. Samples for glucose and insulin were obtained at 0, 1, 3, 4, 5, 10, 15, 25, 30, 45, and 60 min after the start of the glucose infusion. The *K* value was estimated by the method of O'Sullivan et al. (10). First-phase insulin response was estimated by the sum of 1- and 3-min plasma insulin values. Total insulin response was taken as the area under the insulin curve from 0 to 60 min. Plasma insulin concentrations were measured by the radioimmunoassay method of Starr and Rubenstein (11). Plasma glucose was determined by the glucose oxidase method with a glucose analyzer (YSI, Yellow Springs, OH). In ICA^+ women who were HLA types DR3 and DR4, typing was performed by the method of Van Rood et al. (12).

The Kruskal-Wallis test was used to assess differences in morphometric measurements, OGTTs, *K* value, and first-phase and total insulin response in the three groups. Multiple comparisons (based on Kruskal-Wallis test ranks) were used to determine which group was significantly different from the others. The Wilcoxon two-sample test was used to detect differences in plasma glucose response to OGTTs during pregnancy in the two groups of women with gestational diabetes. Probability levels of <0.05 were considered significant. Statistical tests were performed on the Clinfo statistical system in the Clinical Research Center (Bolt, Deranek, Newman Software, Cambridge, MA).

RESULTS

Only 3 of 187 women (1.6%) with gestational diabetes had weakly positive tests (+1/+4) for ICAs. Two of the 3 ICA^+ women were HLA types DR3 and/or DR4.

The pregravid morphological characteristics of the three study groups are given in Table 1. There were no significant morphological differences among the three groups.

The three ICA^+ women were evaluated a mean of 7 mo postpartum (range 3–10 mo). All had impaired oral glucose tolerance by the National Diabetes Data Group criteria (9). In contrast, the women in the other two groups all had normal oral glucose tolerance. When we compared the results of the plasma glucose response in the nongravid OGTT in the three groups, the ICA^+ women had a significantly greater fasting (FPG) ($P < 0.03$) and 1-h ($P < 0.05$) plasma glucose than the other two groups (Table 2). When we reviewed the results of OGTTs during gestation in the two groups of women with gestational diabetes, only the FPG was significantly elevated ($P < 0.03$) in the ICA^+ group (Table 3).

Results of IVGTTs are shown in Figs. 1–3. The *K* values are depicted in Fig. 1 (normal *K* value is >1.2). All ICA^+ women had *K* values <1.2 (1.07, 1.12, 0.78), although there was one abnormal *K* value in each of the other two groups (1.10, 1.00). There was no significant difference in the *K* values among the three groups ($P = 0.06$); however, this borderline result may be because of the relatively small sample size.

There was a significant decrease ($P < 0.03$) in first-phase insulin response in ICA^+ women compared with the other two groups (Fig. 2). There was no difference ($P = 0.20$) in total insulin response among the three groups (Fig. 3).

None of the women without ICAs or gestational diabetes had a positive family history of diabetes mellitus.

TABLE 1
Pregravid morphological characteristics of three study groups

Group	Age (yr)	Height (cm)	Weight (kg)	Body mass index (kg/m²)	Parity
Gestational diabetes					
ICA^+ ($n = 3$)	29.3 ± 6.7	162.0 ± 5.2	64.3 ± 18.1	24.6 ± 7.5	2.0 ± 0.0
ICA^- ($n = 6$)	32.0 ± 4.2	168.0 ± 10.3	60.8 ± 6.6	21.4 ± 1.8	1.3 ± 0.8
Normal oral glucose tolerance					
ICA^- ($n = 5$)	29.2 ± 4.2	166.6 ± 8.2	57.4 ± 8.9	20.93 ± 2.7	1.6 ± 0.9

Values are means ± SD. Comparisons were not significant. ICA, islet cell antibody.

TABLE 2
Plasma glucose (mM) response to nongravid 75-g oral glucose tolerance test (OGTT)

Group	Fasting*	1 h†	2 h
Gestational diabetes			
ICA$^+$ (n = 3)	5.94 ± 0.4	9.86 ± 1.8	7.84 ± 0.9
ICA$^-$ (n = 6)	5.15 ± 0.3	8.40 ± 1.9	6.38 ± 1.2
Normal OGTT,			
ICA$^-$ (n = 5)	4.65 ± 0.5	5.82 ± 1.6	5.71 ± 1.0

Values are means ± SD. ICA, islet cell antibody.
*P < 0.03.
†P < 0.05.

In contrast, all of the women with gestational diabetes and who were ICA$^-$ had a positive family history of diabetes mellitus, with age at onset >25 yr. Interestingly, two of the three ICA$^+$ women with gestational diabetes had a negative family history for diabetes mellitus.

We have obtained clinical follow-up of the three ICA$^+$ women. All these women were instructed in a diet high in complex carbohydrates and fiber but low in fat by our clinic nutritionist at the time of discharge from the hospital. They were also encouraged to try to achieve ideal body weight and at least a moderate level of physical activity.

K.H. was 18 mo postpartum. Her HLA type was neither DR3 nor DR4, and she had no clinical signs or symptoms of diabetes. P.H. was HLA type DR3$^+$ and DR4$^+$. Ten months after delivery, she complained of weight loss, polydipsia, and polyuria. FPG at that time was 7.84 mM, and her postprandial glucose concentrations were in the 11.2–16.8 mM range. She has required 40–50 U Humulin insulin/day for control of hyperglycemia. She had the greatest body mass index of any of our study subjects and no family history of diabetes.

M.W. was diagnosed with gestational diabetes in 1983 and 1985. Her HLA type was DR3$^+$. The initial studies of carbohydrate metabolism were performed in 1984 and repeat studies in 1987. OGTT remains impaired and her K value was 0.92 (previously 1.07). Interestingly, first-phase insulin response increased from 330 to 761 pM, and total insulin response increased from 5608 to 35,950 pM. Her repeat ICA titer in 1987 was negative. She remains physically active, continues with her diet, maintains a normal weight, and is clinically without symptoms of diabetes. M.W. was the only ICA$^+$ subject who had a positive family history of diabetes mellitus. Her mother and maternal grandfather developed diabetes after the age of 25 yr. Her mother is treated with diet alone, whereas her grandfather requires diet and insulin therapy.

DISCUSSION

The incidence of ICA in our population (1.6%) was much less than previously reported. In 1980, Steel et al. (5) reported a 10% (5 of 50) incidence in women with impaired glucose tolerance during pregnancy. In 1980, Ginsberg-Fellner et al. (13) reported a 35% (28 of 80) incidence in women with gestational diabetes in late pregnancy. In 1981, Rubenstein (6) detected ICAs in 38% (20 of 52) of pregnant women with gestational diabetes. In the last two studies, ICAs were estimated by an indirect immunofluorescence method. However, the indirect immunofluorescence assay was later reported by the original authors of the methodology as having an unacceptably high false-positive rate compared with other methodologies (14).

One possible explanation for the lower incidence of ICA in our study is the use of the more specific protein A MoAb method used at the Joslin clinic (7). The protein A ICA assay is similar in sensitivity to the complement fixation ICA assay (15). Life-table analysis of the number of diabetes-free years after detection of ICAs was similar for both protein A MoAb and the complement fixation ICA methods (16). The incidence of ICA in a control population indicated by the protein A MoAb method is only 0.45% (3).

Another possible reason for the lower incidence of ICA in our study population is that our subjects were tested soon after delivery. The effect of the changes in immune response and hormonal milieu on the sensitivity and specificity of the ICA assay is unknown. In future studies of women with previous gestational diabetes, it would be worthwhile to determine whether the prevalence of ICA increases over time. O'Sullivan (1) reported an increase in the prevalence of abnormal glucose tolerance in women with a history of gestational diabetes compared with women with normal glucose tolerance during gestation. Prospective longitudinal evaluation of insulin response, insulin resistance, and type of obesity (central vs. peripheral), in addition to screening for ICA, would be of value in elucidating the pathogenesis of diabetes in this high-risk group.

TABLE 3
Plasma glucose (mM) response to 100-g oral glucose tolerance test in gestationally diabetic women

Group	Fasting	1 h	2 h	3 h
ICA$^+$ (n = 3)	6.05 ± 0.9 (5.46–6.64)	11.7 ± 2.4 (10.14–13.26)	11.03 ± 2.6 (9.34–12.72)	8.18 ± 0.6 (7.79–8.57)
ICA$^-$ (n = 6)	4.59 ± 0.3 (4.31–4.87)	10.5 ± 2.0 (8.6–12.4)	10.19 ± 0.81 (9.12–10.96)	8.18 ± 1.4 (6.85–9.51)

Values are means ± SD, with 95% confidence intervals in parentheses. ICA, islet cell antibody.

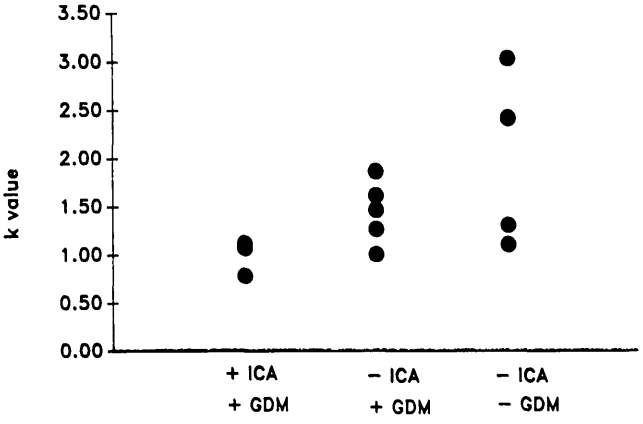

FIG. 1. Rate of glucose disappearance (*K* value) during intravenous glucose tolerance test. ICA, islet cell antibody; GDM, gestational diabetes mellitus.

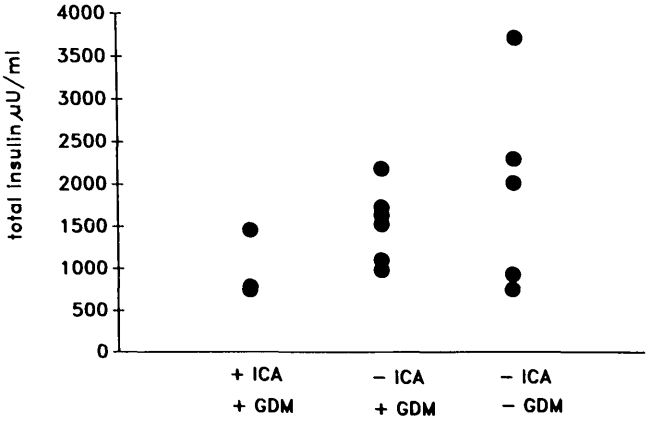

FIG. 3. Total insulin response (area under curve from 0 to 60 min) during intravenous glucose tolerance test. ICA, islet cell antibody; GDM, gestational diabetes mellitus.

ICAs are not normally distributed in the population because there is a genetic predisposition to type I diabetes. The incidence of HLA type DR3 or DR4 in the White population is ~40% (4). There is an 80% incidence of HLA type DR3 or DR4 in patients with type I diabetes (17); HLA type DR3 or DR4 was found in 77% of Ginsberg-Fellner et al.'s (13) and in 90% of Rubenstein et al.'s (6) ICA$^+$ subjects. Two of three subjects with ICAs in our study were HLA types DR3$^+$ and/or DR4$^+$.

In a previous study, Freinkel et al. (18) noted that there was an increased frequency of ICA in women with gestational diabetes. Furthermore, they found that the incidence of ICA significantly increased with increasing FPG; 1.3% in class A1 (FPG <5.88 mM), 8.7% in class A2 (FPG 5.88–7.28 mM), and 18.4% in class B1 (FPG >7.28 mM). These findings were confirmed in our study. Though there were no morphological differences in our three study groups, we also found FPG to be elevated in ICA$^+$ women compared with the other groups, both during pregnancy and the nongravid condition. Moreover, although an FPG >5.88 mM was found in 25% of our gestational diabetic subjects during pregnancy, two of three ICA$^+$ subjects had an FPG >5.88 mM.

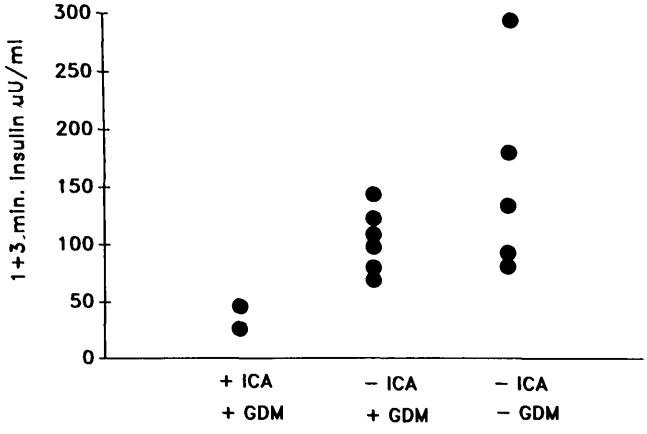

FIG. 2. First-phase insulin response (1- and 3-min insulin values) during intravenous glucose tolerance test. ICA, islet cell antibody; GDM, gestational diabetes mellitus.

The three ICA$^+$ women all had impaired oral glucose tolerance postpartum, which usually indicates an increased risk of type II diabetes (19). A decrease in first-phase insulin by itself is not specific for type I diabetes and occurs frequently in all types of women with gestational diabetes (20). However, the presence of ICA and an increase in first-phase insulin response increases the risk of the development of type I diabetes in these women. Srikanta et al. (3) have shown that a progressive decrease in first-phase insulin response during IVGTT antedates overt type I diabetes in patients with ICAs. Interestingly, the woman with the lowest first-phase insulin response (P.H.) developed clinical type I diabetes within a year of her participation in this study.

In addition to maternal morbidity, ICAs may potentially affect the developing fetus. ICAs are IgG and can cross the placenta. Tingle et al. (21) observed the transplacental passage of ICAs in 28% (10 of 36) of infants of diabetic women. They found no correlation between ICAs with fetal growth, congenital anomalies, or adverse neonatal outcome. Tingle et al. speculate, however, that these antibodies may play a role in the peri-insular inflammatory cell infiltrates and islet cell fibrosis in the pancreatic islets of some infants of diabetic mothers as described by Wellman and Volk (22).

In summary, the incidence of ICA in women with previous gestational diabetes with a MoAb method was 1.6%, much lower than previously reported with the indirect immunofluorescence method. In women with ICAs, however, we were able to note a significant increase in FPG and demonstrate a significant decrease in first-phase insulin response. The importance of ICAs in the long-term pathogenesis of diabetes in women with previous gestational diabetes and the possible effect of ICAs on fetal islet cells have yet to be examined.

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