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Original Contribution

Prognosis of Pregnant Women with One Abnormal Value on 75g OGTT

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Summary: The aim of this study was to identify risk factors to allow us to detect patients at high risk of requiring insulin therapy, among Japanese pregnant women with one abnormal value (OAV) on a 75-g oral glucose tolerance test (75-g OGTT).

A total of 118 pregnant women with OAV on a previous 75-g OGTT between 1997 and 2010 were studied. We identified the factors which can predict patients at high risk of requiring insulin therapy among Japanese pregnant women with OAV, by comparing severe abnormal glucose tolerance (insulin treatment; n=17) with mild glucose tolerance patients (diet only; n=101). The following factors were examined; plasma level of glucose (PG) and immunoreactive insulin (IRI) at fasting, 0.5, 1 and 2 hours after loading glucose, insulinogenic index, homeostasis model assessment insulin resistance (HOMA-IR), insulin sensitivity index-composite (ISI composite), and HbA1c at the time of the 75-g OGTT.

Univariate analysis showed a positive correlation between insulin therapy and 2-h PG value, 0.5-h and 1-h IRI values, AUC-IRI and insulinogenic index ($p<0.05$). Multivariate analysis showed that the PG 2-h value and insulinogenic index were independent predictive factors of insulin therapy. A 2-h PG $\geq$153 mg/dl and an insulinogenic index of <0.42 had a sensitivity of 81.8%, a specificity of 83.8%, a positive predictive value of 60.0% and a negative predictive value of 93.9% for the prediction of patients who required insulin therapy among pregnant women with OAV.

These results suggest that a level of 2-h PG $\geq$153 mg/dl and an insulinogenic index of <0.42 on 75-g OGTT are predictive factors for insulin therapy in Japanese pregnant women with OAV.

Key words gestational diabetes mellitus, glucose tolerance test, plasma glucose, insulinogenic index, insulin therapy

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the common complications of pregnancy. It has been defined for many years as "any degree of glucose intolerance with its onset or first recognition during pregnancy" [1]. Although this definition facilitated a uniform strategy for detection and classification of GDM,

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Abbreviations: AUC, area under curve; BMI, body mass index; FDA, Food and Drug Administration; GA, glycated albumin; GCT, glucose challenge test; GDM, gestational diabetes mellitus; HAPO, Hyperglycemia and Adverse Pregnancy Outcome; IADPSG, International Association of Diabetes and Pregnancy Study Group; IRI, immunoreactive insulin; OAV, one abnormal value; OGTT, oral glucose tolerance test; PG plasma glucose; ROC, receiver operating characteristic SMBG, self-monitored blood glucose.

its limitations were recognized.

The incidence of GDM is growing around the world with the increasing prevalence of obesity and type-2 diabetes mellitus [2,3]. The severity of GDM is associated with maternal glucose levels that present a positive and direct correlation with the risk of fetal involvement [4-9]. In the case of pregnant women with GDM who do not achieve target glucose levels through diet, drug therapy should be initiated to reduce glucose levels, in order to maintain good fetal development and decrease neonatal complication [8,9]. The only drug approved by the Food and Drug Administration (FDA) so far for use in diabetic pregnant women is insulin [10,11]. On the other hand, insulin therapy for gestational diabetes mellitus is one of the risk factors for subsequent type Ⅱ diabetes mellitus [12].

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study [5], which is an international multicentric study, investigated associations between maternal blood glucose levels and adverse outcomes after excluding women with fasting plasma glucose (PG) ≥105 and/or 2-h PG ≥200 mg/dL. The study reported significant associations between an increase in glucose level and adverse events such as birth weight >90th percentile, preterm delivery, shoulder dystocia/birth injury, primary cesarean delivery, preeclampsia, and hyperbilirubinemia [5,13]. Based on these findings, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) recommended that GDM be identified by at least one abnormal PG value in a 75-g 2-h oral glucose tolerance test (OGTT): fasting PG ≥92 mg/dL (5.1 mmol/L), 1-h PG ≥180 mg/dL (10.0 mmol/L), or 2-h PG ≥153 mg/dL (8.5 mmol/L) [14].

Previous criteria in Japan for GDM were two or more abnormal PG values on a 75-g 2-h OGTT: fasting PG ≥100 mg/dL, 1-h PG ≥180 mg/dL, and 2-h PG ≥150 mg/dL [15]. However, we experienced some cases with only one abnormal value (OAV) on a 75-g OGTT who required insulin therapy for glycemic control. Thus since 1997 OAV women have been managed in practically the same way as GDM women at our institution. Recent modification of GDM criteria has caused an increase in the number of pregnant women diagnosed with GDM. In fact, Hiramatsu speculated that the probability of GDM would increase from 2.92% to 12.08% with this modification in Japan [16].

The aim of this study is to identify factors which can predict the need for insulin therapy in pregnant women with OAV.

MATERIALS AND METHODS

Patients

Study subjects were patients who were diagnosed with OAV between April 1997 and December 2010 at Kurume University Hospital. Screening for GDM was performed by occasional plasma glucose testing in the early weeks of pregnancy, and a 50-g glucose challenge test (GCT) between the 24th and 28th week of gestation. A 75-g OGTT was performed on women with an occasional plasma glucose level of more than 100 mg/dL in early pregnancy, or a glucose level of more than 140 mg/dL on 50-g GCT, between the 24th and 28th week of gestation. Pregnant women in the high-risk group, including cases of obesity (pre-pregnancy body mass index >25), prior history of GDM, delivery of large-for-gestational-age-infant, and family history of type 2 diabetes mellitus, were screened by a 75-g OGTT at their initial pregnancy visit. OAV was diagnosed with only one abnormal value on a 75-g OGTT (equal or exceeding fasting 100 mg/dL, 1-h 180 mg/dL, 2-h 150 mg/dL).

Treatment

Pregnant women with OAV were initially treated with diet. Nutritional guidance was individualized according to pre-pregnancy body mass index (BMI), weeks of gestational age, and presence or absence of obesity. Obesity was defined as a BMI equal to or greater than 25 kg/m^2. Regarding daily calorie intake, women with BMI less than 25 received 25-30 kcal/kg of actual body weight plus 150 kcal, those with a BMI equal to or greater than 25 received 25-30 kcal/kg of actual body weight, until the 28th gestational week. Women with a BMI less than 25 received 25-30 kcal/kg of actual body weight plus 250 kcal, and those with a BMI equal to or greater than 25 received 25-30 kcal/kg of actual body weight, after the 28th gestational week.

After initiation of diet, all OAV women had their plasma glucose level 2-h after meals and glycated albumin (GA) examined as outpatients every 2 weeks. Women who failed to achieve the plasma glucose level at 2-h after meal of <120 mg/dL or a GA concentration of <16% were hospitalized for glycemic control. During hospitalization, those patients self-monitored blood glucose (SMBG) at fasting and 2-h after meal. The glucose target levels were <100 mg/dL at fasting, and <120 mg/dL for 2-h after meal. Women who failed to achieve blood glucose target levels within one week were treated with insulin. None of the patients were treated with oral antihyperglycemic medicines.

Analysis

We used the patient's examination data, and analyzed retrospectively as follows: The total area under the PG curve (AUC-PG) and the immunoreactive insulin curve (AUC-IRI) during the 75-g OGTT was calculated using the trapezoidal rule. As a measure of early-phase insulin secretion, we used the insulinogenic index calculated as follows: (PG 0.5-h – fasting PG) / (IRI 0.5-h – fasting IRI). As a measure of insulin resistance, we used the homeostasis model assessment insulin resistance (HOMA-IR) calculated as follows: fasting IRI × fasting PG/405. Insulin sensitivity was estimated using the whole body insulin sensitivity index-composite (ISI-composite) derived from a 75-g OGTT as proposed by Matsuda and DeFronzo [17], calculated as follows: 10,000 / square root (fasting PG × fasting IRI × AUC-PG × AUC-IRI).

Univariate analysis using logistic regression was performed to compare PG values from 75g-OGTT, IRI values from 75g-OGTT, AUC-PG, AUC-IRI, HOMA-IR, insulinogenic index, ISI-composite, and HbA1c at 75g-OGTT between women maintaining glycemic control with diet only (n=101) and those requiring insulin treatment (n=17), adjusting for maternal age, nulliparity, delivery weeks and family history of diabetes. We conducted a multivariate logistic regression analysis using a stepwise selection method in which terms were retained if they reached the 0.2 level of significance. Receiver operating characteristic (ROC) curves were generated to determine predictability of cut-off value levels for insulin therapy. A level of significance of $p<0.05$ and a 95% confidence interval were adopted.

This study was approved by the Ethics Committee of Kurume University, and written informed consent was obtained from all patients.

RESULTS

A total of 118 women with OAV were analyzed. The patients were divided into 2 groups according to the presence or absence of insulin therapy for glycemic control: diet only (n=101) and insulin treatment (n=17). There was no significant difference between either group with respect to maternal age, maternal height, maternal pre-pregnancy body weight and BMI, family history for type-2 diabetes mellitus or neonatal birth weight (Table 1).

To predict the need for insulin therapy in OAV, univariate analysis of laboratory parameters was performed (Table 2). The insulin treatment group had significantly higher levels of 2-h PG on the 75-g OGTT, and lower levels of 0.5-h and 1-h IRI on the 75-g OGTT with a decreased AUC-IRI and insulinogenic index. There was no significant difference between groups in HOMA-IR or ISI-composite. Multivariate analysis showed that the 2-h PG value on the 75-g OGTT and insulinogenic index were independent predictive factors for insulin therapy (Table 3). To clarify the clinical utility of these parameters for the prediction of insulin therapy in OAV, the ROC curve revealed that cut-off levels of the 2-h PG value on the 75-g OGTT, and insulinogenic index, were ≥153 mg/dL, and <0.42, respectively (Figure 1). Additionally, a 2-h PG value on the 75-g OGTT ≥153 mg/dL, and an insulinogenic index of <0.42 could predict the need for insulin therapy (sensitivity 81.8%, specificity 83.8%, positive predictive value 60.0%, negative predictive value 93.9%).

TABLE 1.
Clinical characteristics of pregnant women with OAV treated with (insulin treatment) and without (diet only) insulin

	diet only n=101	insulin treatment n=17	p value
Maternal age (years)	33.6±4.9	32.9±4.0	0.525
Height (cm)	157.5±5.9	157.1±7.0	0.826
Pre-pregnancy weight (kg)	60.4±13.0	57.5±10.6	0.323
Pre-pregnancy BMI	24.3±5.1	23.4±4.2	0.437
Family history of diabetes (%)	30.7	52.9	0.073
Delivery weeks (weeks)	38.2±1.8	37.6±0.8	0.027
Birth weight (g)	2979.0±564.9	3001.2±454.1	0.859

OAV, one abnormal value on a 75-g oral glucose tolerance test; BMI, body mass index (weight [kg] ÷ height [m]^2).

TABLE 2.
Univariate logistic regression analysis of laboratory data for predicting the initiation of insulin treatment in pregnant women with OAV (adjusting for maternal age, nulliparity, delivery weeks, family history of diabetes)

	Odds ratio	95%CI	p value
Fasting PG	1.11	0.83-1.50	0.485
0.5-h PG	0.88	0.74-1.06	0.175
1-h PG	0.98	0.87-1.11	0.768
2-h PG	1.31	1.11-1.53	< 0.001
AUC-PG	1.01	0.88-1.16	0.846
Fasting IRI	0.67	0.31-1.45	0.307
0.5-h IRI	0.75	0.62-0.92	< 0.005
1-h IRI	0.83	0.73-0.95	< 0.007
2-h IRI	0.92	0.83-1.01	0.069
AUC-IRI	0.89	0.82-0.97	< 0.010
HOMA-IR	0.74	0.37-1.47	0.389
Insulinogenic index	0.81	0.70-0.95	0.010
ISI-composite	1.17	0.98-1.40	0.083
HbA1c at 75-g OGTT	1.12	0.97-1.28	0.115

OAV, one abnormal value on a 75-g oral glucose tolerance test; CI, confidence interval; PG, plasma glucose; AUC, area under curve; IRI, immunoreactive insulin; HOMA-IR, homeostasis model assessment for insulin resistance; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test. HbA1c was measured by JDS (Japan Diabetes Society) method.

TABLE 3.
Multivariate logistic regression analysis of laboratory data presenting statistical significance upon univariate analysis for predicting the initiation of insulin in pregnant women with OAV

	Odds ratio	95%CI	p value
2-h PG	1.06	1.02-1.10	< 0.01
insulinogenic index	0.03	0.00-0.50	< 0.05

OAV, one abnormal value on a 75-g oral glucose tolerance test; CI, confidence interval; PG, plasma glucose.

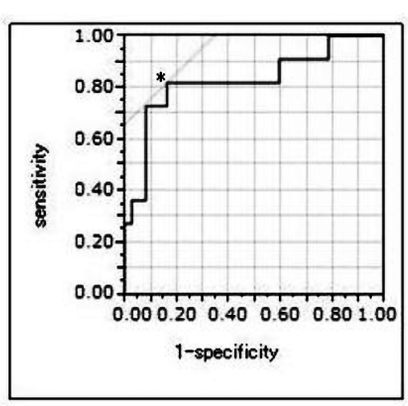

Fig. 1. Receiver Operating Characteristic (ROC) curve showing the diagnostic accuracy of the insulinogenic index and 2-h PG level on a 75-g OGTT for insulin requirement. Sensitivity 81.8%, specificity 83.8%, positive predictive value 60.0%, negative predictive value 93.9 %. (*indicated the point of insulinogenic index <0.42 and 2-h PG ≧153 mg/dL.)

DISCUSSION

The reason for insulin resistance in pregnancy is unknown [18]. Theoretically, it may be induced by either changes in insulin-receptor binding, post-receptor changes, or a combination of both [18]. Most pregnant women are able to counteract the insulin resistance by a compensatory increase in both basal and nutrient-stimulated insulin secretion [18]. However, 2-3% will have intolerance, because of their less than sufficient ability to secrete insulin [18].

The present study showed that a 2-h PG level and insulinogenic index value on a 75-g OGTT was predictive factor for insulin therapy in pregnant women with OAV. Therefore pregnant women with OAV who were treated with insulin supposedly secreted insufficient levels of insulin. Although there was a poor correlation between family history of type-2 diabetes mel-

litus and insulin therapy in pregnant women with OAV in the present study, a larger number of patients might reveal a significant relationship between family history of type-2 diabetes mellitus and OAV, because type-2 diabetes mellitus is one of the common important factors of GDM [19].

There have been several studies concerning the factors which predict abnormal glucose tolerance. Ergin et al. investigated insulin response in 100-g OGTT [20]. They showed that the insulinogenic index was significantly lower in the traditional GDM group (two or more abnormal values on OGTT) compared with the normal OGTT group [20]. Di Cianni et al. reported that pregnant women with OAV and the traditional GDM group were older and had higher BMIs than the group with normal glucose tolerance [21]. Therefore, pregnant women with normal glucose tolerance had the highest ISI-composite. Early-phase insulin secretion was found to be significantly reduced in pregnant women with OAV and the traditional GDM group, compared with pregnant women having normal glucose tolerance. They concluded that pregnant women with OAV and pregnant women with traditional GDM are clinically indistinguishable, and both groups are different from women with normal glucose tolerance [21].

Several studies reported a correlation between pregnant women with OAV and perinatal outcome. Pregnant women with OAV on a 100-g OGTT are connected to a higher frequency of adverse perinatal events when compared to a population with normal glucose tolerance [20,22]. The glycemic profile and characteristics of these pregnant women are similar to those of women with a diagnosis of traditional GDM. They suggested that pregnant women with OAV should be treated similarly to women with traditional GDM [5,13].

Although predictive factors for insulin therapy in pregnant women with OAV have not been reported, some articles describe the prediction of insulin therapy in pregnant women with traditional GDM [23-25]. Sapienza et al. reported that the probability of insulin therapy could be estimated in pregnant women with traditional GDM based on pre-pregnancy BMI, family history of diabetes, the number of abnormal points on a 100-g OGTT, and HbA1c concentration [23]. The probability of insulin requirement is directly linked to a higher sum of these quantified factors.

Akinci et al. indicated a statistically significant correlation between fasting PG levels and insulin therapy in traditional GDM. A cut-off value of 105 mg/dL had a fair specificity (91.89%) and positive predictive value (80.64%) for predicting women who would require insulin therapy [24]. Quintero et al. reported that gestational age at diagnosis, HbA1c concentration and fasting PG $>$95 mg/dL in the 100-g OGTT were independent predictors of insulin therapy [25]. These articles indicate that fasting PG levels and/or HbA1c are potent predictions of insulin therapy in women with traditional GDM. However, our present study showed no significant correlation between fasting PG levels and insulin therapy. Di Cianni et al. [21] showed that women with one abnormal glucose level at 1-h on 100-g 3hOGTT required more intensive treatment compared with the other OAV groups. Therefore fasting PG are characterized by an impairment in basal insulin secretion [21], and mild diabetes in pregnancy such as in women with OAV who might retain some basal insulin secretion ability. It might be one of the reasons that the fasting PG was not a significant factor in our present study.

Hospitalization is required for diabetic pregnant women for the initiation of insulin therapy. Therefore the latest revision of GDM criteria will increase the number of GDM patients who need to be hospitalized. The present study identified an insulinogenic index of $<$0.42 and a 2-h PG $>$153 mg/dL as indicators for those at high-risk of requiring insulin therapy among Japanese pregnant women with OAV. Thus, human and financial resources can be applied more appropriately to this high-risk group. The results of this study will facilitate the detection of high-risk pregnant women with OAV, and will permit more specific therapeutic management including hospitalization.

The present study used the previous Japanese criteria of GDM. We need to further study OAV using the new criteria for GDM.

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