Insulin resistance in oligomenorrheic infertile women with non-polycystic ovary syndrome

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Objective: To determine whether infertile oligomenorrheic women are insulin resistant, using an oral glucose tolerance test (OGTT).
Design: Retrospective study.
Setting: National Center for Child Health and Development.
Patient(s): One hundred twenty-seven infertile women with oligomenorrhea (oligomenorrheal group) and 177 infertile eumenorrheic women (normal menstrual group) were recruited.
Intervention(s): All women underwent an OGTT (75 g glucose).
Main Outcome Measure(s): A homeostasis model assessment of insulin resistance (HOMA-IR), area under the curve (AUC) of insulin after the glucose load, and plasma insulin level at 120 minutes after glucose loading (IRI 120) were used as an index of insulin resistance.
Result(s): The prevalence of insulin resistance (HOMA-IR ≥ 1.73) among oligomenorrheic women was 23.8%, which was significantly higher than that of eumenorrheic women, at 14.1%. The glucose AUCs (mean $\pm$ SE) in the oligomenorrheal group (13,609 $\pm$ 259 mg/min/dL) were similar to those for the normal menstrual groups (13,054 $\pm$ 196 mg/min/dL), but the insulin AUCs of the oligomenorrheal group (5333 $\pm$ 376 mU·min/L) were significantly higher than those of the normal menstrual groups (4517 $\pm$ 266 mU·min/L).
Conclusion(s): The prevalence of insulin resistance assessed using an OGTT was significantly higher among infertile oligomenorrheic women with non-polycystic ovary syndrome than it was among women with normal menstrual cycles. (Fertil Steril® 2008;90:373–7. ©2008 by American Society for Reproductive Medicine.)

Key Words: AUC insulin, HOMA-IR, insulin resistance, oligomenorrhea, oral glucose tolerance test

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age (1–3). Recently, peripheral insulin resistance and compensatory hyperinsulinemia have been observed in non-obese women with PCOS (3–5). Many studies have demonstrated that both lean and obese women with PCOS are insulin resistant (4, 5) and that this insulin resistance and its compensatory hyperinsulinemia play a key pathogenic role in the ovulatory dysfunction and infertility characteristic of PCOS. Moreover, insulin-sensitizing drugs effectively enhance spontaneous ovulation and induce ovulation in women with PCOS. Insulin-sensitizing drugs such as metformin are the first choice among PCOS patients with insulin resistance (6).

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The cause of PCOS is unknown (5). However, insulin resistance with compensatory hyperinsulinemia is a prominent feature of the syndrome and seems to have a pathophysiologic role in the hyperandrogenism of the disorder. The mechanism by which insulin resistance and the compensatory hyperinsulinemia impede ovulation also is yet to be determined. Hyperinsulinemia augments local ovarian production of androgens, leading to premature follicular atresia and ovulation (7). Hyperinsulinemia also may directly affect folliculogenesis and arrest growth of antral follicles after they have reached a diameter of 5–8 mm (8). Thus, the mechanism of ovulatory dysfunction in patients with PCOS could be explained by hyperinsulinemia.

If this hypothesis is correct, one would expect insulin resistance and compensatory hyperinsulinemia to be present in the oligomenorrheic women who do not have PCOS. However, the relationship between ovulatory dysfunction and insulin resistance in non-PCOS women has not yet been established. In this study, oligomenorrheic infertile non-PCOS women underwent a 75g oral glucose tolerance test (OGTT). Blood glucose and insulin concentrations were also measured at

each time point, and the insulin response to the glucose load in non-PCOS oligomenorrheic patients was evaluated to clarify the relationship between ovulatory dysfunction and insulin resistance.

MATERIALS AND METHODS

From October 2002 to January 2007, a total of 304 patients who underwent infertility treatment at the Division of Reproductive Medicine, Department of Perinatal Medicine and Maternal Care, National Center for Child Health and Development (Tokyo, Japan) were recruited for this study. Informed consent was obtained from all participating patients. One hundred twenty-seven patients were oligomenorrheic (oligomenorrheal group), and 177 patients were eumenorrheic (normal menstrual group). Oligomenorrhea was defined as menstrual cycles with intervals of 35–90 days (9). Patients with PCOS diagnosed by basal serum gonadotropin and T levels and by transvaginal ultrasound examination were excluded from this study (10). The patients who showed symptoms of diabetes mellitus in response to the 75g OGTT also were excluded from this study.

The 75g OGTT was performed on all patients from the third day to the ninth day of their menstrual cycle or the period when follicle diameters were $\leq$10 mm. They visited our hospital in the morning (08:30–09:00 AM) after an overnight fast of 8–12 hours. Serum glucose was measured in the fasting sample, and 30 minutes, 60 minutes, and 120 minutes after an oral glucose load of 75 g (Toleran G-75; Ajinomoto Pharma, Tokyo, Japan). Serum insulin was measured in samples collected at all four time points. Serum samples were not heparinized. Serum FSH, LH, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides also were measured in the fasting samples. Body height, body weight, abdominal circumference, and percentage body fat were measured for all patients. Body mass index was calculated as body weight (in kilograms)/height (in meters)^2.

Serum glucose was determined by the glucose oxidase method (Addams Glucose GS-1160; Arkray, Kyoto, Japan), and the intra-assay coefficient of variation of this method was <2.0%. Serum insulin was assayed by enzyme immunoassay (DPC IMMUNIZE Insulin II; Diagnostic Products Corp., Los Angeles, CA), and the intra-assay coefficient of variation of this method was <10%. Total cholesterol was measured by the UV-End Method with cholesterol dehydrogenase (T-CHO·KL; Sysmex Corp., Kobe, Japan). High-density lipoprotein cholesterol was measured directly (Cholestest N HDL; Daiichi Pure Chemicals Co. Ltd., Tokyo, Japan). The homogenous method based on an inactive detergent technology (Cholestest LDL; Daiichi Pure Chemicals Co. Ltd.) was used to calculate the amount of low-density lipoprotein cholesterol. Triglyceride was measured by the enzymatic method (Pureauto S TG-N; Daiichi Pure Chemicals Co. Ltd.). Follicle-stimulating hormone and LH were determined with commercially available ELISA kits (Immulize 2000; Diagnostic Products Corp.). Blood samples for FSH and LH measurements were obtained between the third and fifth days of a menstrual cycle.

Insulin sensitivity according to such criteria as the homeostasis model assessment of insulin resistance (HOMA-IR) and area under the curve (AUC) of insulin after the glucose load were determined by mathematical estimation. The AUC of insulin was calculated by the trapezoidal rule according to the formula of Tai (11). The AUC of glucose was also calculated by the same method. The AUC of insulin, HOMA-IR, and plasma insulin level at 120 minutes after glucose loading (IRI 120) were used as an index of insulin resistance for this study (12).

Values are expressed as the mean. The data were analyzed by the unpaired Student t-test and χ^2 test, and $P<.05$ was considered to be statistically significant.

RESULTS

The characteristics of the patients in the oligomenorrheal and normal menstrual groups are summarized in Table 1. The mean ($\pm$ SE) age of the oligomenorrheal group was 33.9 $\pm$ 0.4 years. This was significantly younger than that in the normal menstrual group (35.7 $\pm$ 0.3 years; $P<.05$). The body mass index and body fat percentage in both groups showed no significant difference. The basal LH and FSH levels were also similar in both groups. Concerning the lipid profile, plasma concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol did not show any significant variation between groups (Table 1).

The changes in serum glucose in response to the 75g OGTT are shown in Figure 1. The glucose concentration at each point in the oligomenorrheal group was similar to that in the control group, and no patient showed any diabetic patterns in either group. The insulin concentrations at each point in both groups are shown in Figure 2; there was no significant difference between groups at each point. The HOMA-IR in the oligomenorrheal group was 1.35 $\pm$ 0.09, and this value was comparable to that in the control group (1.19 $\pm$ 0.1; $P=.072$), but the mean value of IRI 120 in the oligomenorrheal group (49.9 $\pm$ 4.3) was significantly higher than that of the normal menstrual group (38.5 $\pm$ 2.3; $P=.013$) (Table 2). According to the previous report, the cutoff value for positive insulin resistance was set at $\geq$1.73 in HOMA-IR index (13). The incidence of patients showing insulin resistance in the oligomenorrheal group was 23.8%, which was significantly higher than that for the normal menstrual group (14.1%; $P<.05$). However, when the cutoff value for positive insulin resistance was set to $\geq$64 mIU/L in IRI 120 (13), the incidence in the oligomenorrheal group and the normal menstrual group was 16.5% and 9.6%, respectively. The trend for incidence of insulin resistance tended to be higher for the oligomenorrheal group than for the normal menstrual group ($P=.07$).