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Insulin Resistance to Estrogen Therapy

Minimizing Elective Induction of Labor Risks

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Individual Dose Response of Insulin Resistance to Estrogen Therapy

Kevin Jovanovic, M.D., and Hugh S. Taylor, M.D.

OBJECTIVE: To determined the dose response of insulin resistance (IR) to estrogen in individual patients.

STUDY DESIGN: Eighteen subjects meeting inclusion criteria were enrolled, and 9 completed the study. Each subject was treated for 3 months with 0.3, 0.625 and 1.25 mg of conjugated equine estrogens (CEE) in random order, for a total of 9 months of treatment. Fasting serum insulin and glucose levels were obtained.

RESULTS: The fasting glucose/insulin ratio and quantitative insulin-sensitivity check index (QUICKI) were calculated. No significant change was noted in either parameter with any dose of CEE in a single subject.

CONCLUSION: This was the first study to examine the dose response of IR to estrogen using paired measurements from individuals. IR does not vary in individuals when doses of estrogen are altered. (J Reprod Med 2007;52:667–669)

Keywords: estrogen, insulin resistance, menopause.

IR does not vary significantly within individual patients when doses of estrogen are considerably altered.

Insulin resistance (IR) and diabetes have become increasingly prevalent in Western societies and are well characterized contributors to cardiovascular disease. Disorders of carbohydrate metabolism affect 20–44% of women after the menopausal transition. This increased incidence may be related to aging as well as estrogen loss. As the incidence of obesity, insulin resistance and diabetes increases, it becomes increasingly important to consider the impact of estrogen on this process.

The effect of estrogen therapy (ET) on IR is controversial. Several large, prospective trials demonstrated that, on average, hormone therapy affects IR favorably. In the Women's Health Initiative (WHI), women receiving a conventional dose of conjugated equine estrogen/medroxyprogeserone acetate (CEE/MPA) had a lower incidence of diabetes as compared to the placebo group and a lower incidence of insulin resistance as compared to baseline.[1] The Women's Health, Osteoporosis, Progestin, Estrogen (HOPE) trial demonstrated dose-dependent effects.[2] While there were no changes noted in fasting insulin, estrogen therapy decreased the insulin area under the curve (AUC) in women receiving

From the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, New Haven, Connecticut.

Address correspondence to: Hugh S. Taylor, M.D., Department of Obstetrics, Gynecology and Reproductive Sciences, Yale University School of Medicine, 333 Cedar Street, P.O. Box 208063, New Haven, CT 06520-8063 (hugh.taylor@yale.edu).

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CEE, 0.45 mg, with MPA, 1.5 mg, as compared with baseline or placebo. However, several clinical parameters are known to influence insulin response to estrogen; examples include age, body mass index (BMI), fat distribution, hypertension, estrogen dose, use and type of progestin, transdermal or oral route of administration and preexisting insulin resistance, among other factors.[3-8] Patient selection and individual variation appear to have a large effect on insulin response to estrogen. Widely different and opposite effects on individuals with distinct baseline characteristics may, on average in large groups, result in absence of a net effect.

Considering these confounding variables, it is difficult to determine how to care for diverse types of patients. Large studies minimize the individual patient. Individuals may have either an increase or decrease in IR. Large trials make extrapolation to individual patient care decisions difficult by taking an average of a large population, thus negating the differences in diverse populations. No prior study has administered varying doses of estrogen to single patients and determined the effect on IR. We determined the dose response of IR to estrogen in individual subjects who had undergone surgical menopause.

Methods

We identified all patients from the gynecology clinic who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy at Yale–New Haven Hospital from January 1, 2000, to June 30, 2002. Chart review identified 1,468 women. Subjects were excluded if they were > 60 years old and had a gynecologic malignancy, diabetes, arterial thromboembolic disease (stroke, myocardial infarction), breast cancer, endometrial cancer, deep vein thrombosis/pulmonary embolism, hypersensitivity to conjugated estrogens, endometriosis, epilepsy or history of migraine headache. Upon entering the study, patients on ET discontinued use for 3 months to allow a washout period. The study was approved by the institutional review board of the Yale University School of Medicine.

Ninety patients met the inclusion criteria. Individuals were recruited by telephone. Eighteen patients agreed to enroll in the variable-dose trial, and 9 completed the study. Each subject was treated for 3 months with each of 3 regimens: 0.3, 0.625 and 1.25 mg of CEE. Each of the 3 estrogen dosing regimens was assigned in random order, for a total of 9 months of treatment. At the end of each dosing regimen, fasting serum insulin and glucose levels were obtained. In several studies the quantitative insulin-sensitivity check index (QUICKI) model was found to have the best correlation with the glucose clamp, the gold standard for IR.[9] The fasting glucose/insulin ratio has also been shown to be a reliable and economical predictor of IR.[10]

The variables over time were analyzed using ANOVA for repeated measures. The study was powered to detect clinically significant differences in the glucose/insulin ratio of 5 or QUICKI of 0.2 at an α of 0.05. We had 80% power to detect this magnitude of difference using a sample size of 9.

Results

The demographics of the subjects are demonstrated in Table I. The mean age was 49 years. The mean BMI was 27.5. The range of BMI varied greatly,

Table I *Demographics*

Patient no.	Age (yr)	BMI	Months from surgery	Race/ ethnicity
1	41	29.1	20	Hispanic
2	53	25.1	12	Black
3	57	24.8	3	White
4	43	28.4	8	White
5	51	35.8	5	White
6	49	24.5	6	Black
7	52	26.2	24	Black
8	46	22.9	12	White
9	48	31.2	16	White

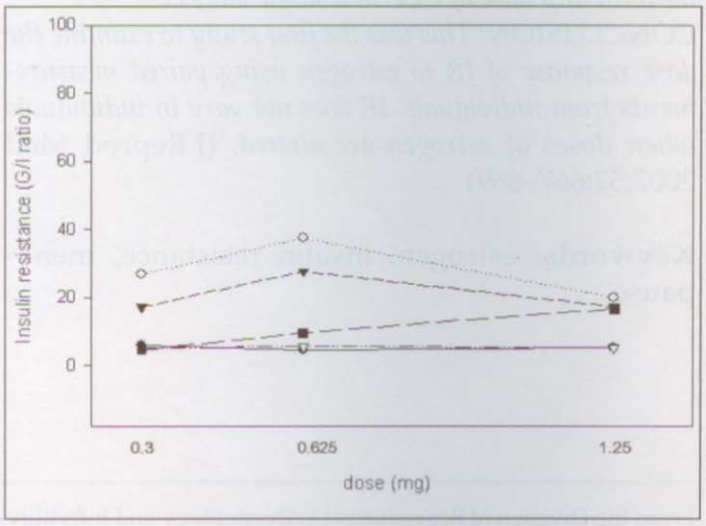

Figure 1 Individual glucose/insulin ratio dose response. Each line corresponds to an individual patient. Five representative patient results are shown. The glucose/insulin ratio was calculated after 3 months of CEE therapy at each dose.

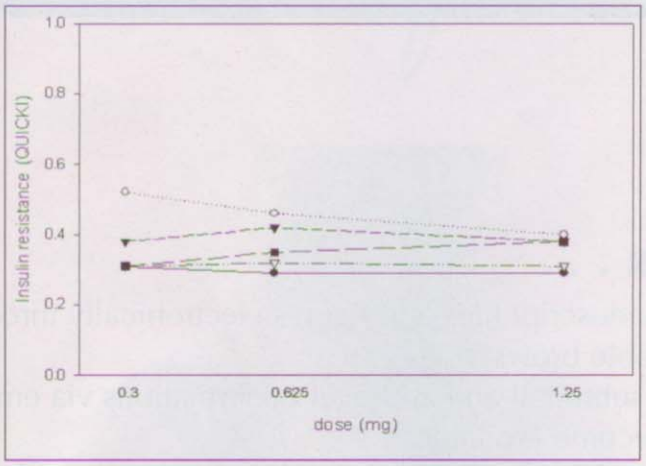

Figure 2 Individual QUICKI dose responses. Each line corresponds to an individual patient. Five representative patient results are shown. QUICKI was calculated after 3 months of CEE therapy at each dose.

from 22.9 to 35.8, allowing comparison of the effects of ET on IR in individuals with different BMIs. The ethnic and racial backgrounds were also diverse.

The fasting insulin and glucose results were analyzed using the fasting glucose/insulin ratio (Figure 1) and QUICKI (Figure 2) models for assessing IR. The average QUICKI result was 0.34. The average glucose/insulin ratio was 13.9. There was no significant change in either parameter with any dose of CEE ($p > 0.05$) using ANOVA for repeated measures. No clinically significant change was observed within individuals.

After adjusting for weight, none of the 3 doses altered IR when compared on a milligram per kilogram basis ($p > 0.05$). Comparing subjects with a BMI ≤ 30 to those with a BMI > 30, there was a lack of dose response ($p > 0.05$) in obese vs. nonobese patients.

Discussion

There was no effect on IR of different doses of ET within the same individual. This is clinically reassuring for patients who wish to use lower doses of therapy currently available without concern about alteration of metabolic parameters. There is very little agreement in the literature on the role of ET and metabolic parameters. Individuals respond differently to the same dose of ET. Distinct differences between response to different types of hormone replacement, route of delivery and populations may be why there is such great variation in the published data. These discrepancies make it difficult to counsel patients regarding treatment. However, in our study the same individual was not affected by different doses. This focus on the individual highlights the decisions that are made in clinical practice in an attempt to find the optimal dose of estrogen.

This was the first study to examine the dose response of IR to estrogen in individuals. Although the number of subjects was small, the objective was to identify significant changes in individual patients rather than small differences in large populations. These results show that IR does not vary significantly within individual patients when doses of estrogen are considerably altered.

References

1. Margolis KL, Bonds DE, Rodabough RJ, et al: Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: Results from the Women's Health Initiative Hormone Trial. Diabetologia 2004;47:1175–1187
2. Lobo RA, Bush T, Carr BR, et al: Effects of lower doses of conjugated equine estrogens and medroxyprogesterone acetate on plasma lipids and lipoproteins, coagulation factors, and carbohydrate metabolism. Fertil Steril 2001;76:13–24
3. Cucinelli F, Paparella P, Soranna L, et al: Differential effect of transdermal estrogen plus progestagen replacement therapy on insulin metabolism in postmenopausal women: Relation to their insulinemic secretion. Eur J Endocrinol 1999;140:215–223
4. Assali AR, Jabara Z, Shafer Z, et al: Insulin resistance is increased by transdermal estrogen therapy in postmenopausal women with cardiac syndrome X. Cardiology 2001;95:31–34
5. Borissova AM, Tankova T, Kamenova P, et al: Effect of hormone replacement therapy on insulin secretion and insulin sensitivity in postmenopausal diabetic women. Gynecol Endocrinol 2002;16:67–74
6. Sites CK, Brochu M, Tchernof A, et al: Relationship between hormone replacement therapy use with body fat distribution and insulin sensitivity in obese postmenopausal women. Metabolism 2001;50:835–840
7. Ryan AS, Nicklas BJ, Berman DM: Hormone replacement therapy, insulin sensitivity, and abdominal obesity in postmenopausal women. Diabetes Care 2002;25:127–133
8. Kawecka-Jaszcz K, Czarnecka D, Dembinska-Kiec A, et al: Insulin resistance and lipids in hypertensive women on hormone replacement therapy. Blood Press 2002;11:28–34
9. Katz A, Nambi SS, Mather K, et al: Quantitative insulin sensitivity check index: A simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402–2410
10. Legro RS, Finegood D, Dunaif A: A fasting glucose to insulin ratio is a useful measure of insulin sensitivity in women with polycystic ovary syndrome. J Clin Endocrinol Metab 1998;83:2694–2698