Original Article

Effect of preeclampsia on insulin sensitivity

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Abstract

Objective: The objective of this study is to investigate whether preeclampsia is associated with exacerbation of insulin resistance. **Materials and Methods:** The study was conducted over a period of 7 months from November 2011 to May 2012, in a tertiary care hospital attached to a medical college. A total of 14 pregnant women in the third trimester with preeclampsia were recruited for this study and 14 well-matched normotensive women in the third trimester were taken as control. 15 g, 50% dextrose load was given intravenously and blood sampling was carried out for glucose and insulin levels up to 3 h afterward. Minimal model analysis of glucose and insulin levels was performed to arrive at results. **Results:** No significant changes in mean age, body mass index, gestation, serum lipid and progesterone, cortisol and androgen concentrations were recognized. No significant difference was found between the glucose decay curves and between the glucose clearance rate K, in the two groups (preeclamptic vs. normotensive: 2.1 ± 0.2 vs. 2.2 ± 0.3; $P = 0.48$). Therefore, there was a small but prolonged decrease in the insulin response of women with preeclampsia compared with women in the normotensive group. **Conclusion:** Preeclampsia *per se* is not a risk factor for development of insulin resistance.

Key words: Glucose tolerance, insulin sensitivity, preeclampsia

Introduction

Pregnancy induced hypertension (PIH) affects up to 8% of pregnant women with an important impact on morbidity and mortality in mothers and neonates.[1] The etiology of PIH is not completely known, but some factors as insulin resistance, malnutrition, subclinical infections, genetic and immunological factors have been involved in the risk of developing this disorder.[2] During normal pregnancy, some degree of insulin resistance is observed. The major degree of insulin resistance is achieved in the third trimester and returns to pre-pregnancy levels after delivery.[3] The usual onset of PIH in late pregnancy, at a time when the insulin resistance characteristic of pregnancy is maximal supports a possible association.[4] In addition, increased risks for preeclampsia have been reported with several conditions associated with insulin resistance. These include gestational diabetes, polycystic ovary syndrome, obesity and increased weight gain.[5]

Several cross-sectional third trimester studies linking insulin resistance to PIH exist. However, these studies either failed to describe proteinuria criteria[6,7] or were not adjusted for body mass index (BMI).[8,9] It is also known that insulin resistance in late pregnancy is independently influenced by Asian and South Asian ethnicity.[10] In this study, we aim to identify whether preeclampsia has the effect on insulin resistance in late pregnancy specifically in North Indian women.

Materials and Methods

Ethical clearance for the study was obtained from Institutional Ethical Committee. Participation in the test was voluntary and informed written consent was obtained from every participant. The study was conducted by joint collaboration of Department of Medicine, Department of Obstetrics and Gynaecology and Department of Biochemistry of a tertiary care hospital. It was done over a period of 7 months from November 2011 to May 2012. A total of 14 pregnant women in the third trimester with preeclampsia were recruited for

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this study and 14 well-matched normotensive women in the third trimester were taken as control.

At enrollment, none of the patients had multiple pregnancies, cardiovascular or renal disease. Preeclampsia was defined by blood pressure recording of at least 140/90 mmHg on two occasions 6 h apart and presence of proteinuria at least 0.3 g/dl. Mean arterial blood pressure (MABP) was calculated using the formula ([systolic BP + 2 × diastolic BP]/3).

For each participant an intravenous (IV) cannula was sited in each arm and fasting blood samples obtained. IV load of 15 g, 50% glucose was given in an arm and 4 ml blood samples for glucose and insulin were taken at −10, −1, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 20, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 160 and 180 min. Plasma glucose concentrations were determined using standard glucose oxidase method. Serum insulin concentrations were determined using chemiluminescent immunoassay kit.

We analyzed glucose and insulin concentration obtained by frequent blood sampling during the 3 h after an IV bolus of glucose. Kinetic simulation was performed using minimal model analysis using python simulator for cellular systems (PySCeS), python based open source systems simulator.[11] From modeling of the process following parameters were derived: Insulin sensitivity (S_I), glucose effectiveness (SG) and pancreatic beta cell responsiveness (first and second phase; Φ_1 and Φ_2). S_I is a measure of insulin-mediated glucose disposal and SG a measure of glucose-mediated glucose disposal. The glucose and insulin values were entered into minimal model using SciPy, scientific python module.[12] PySCeS was used to perform manual fitting of curves to the data by appropriate adjustment of the variable parameters. Subsequently, least sum of squares iterations performed to achieve the closest possible fits and determine final parameter values. Values for SI, SG, Φ_1 and Φ_2 were then derived from these parameters.

The IV glucose clearance rate (KG) was determined as the least square slope of the natural logarithm of glucose concentrations between 12 and 30 min after glucose bolus. Acute insulin response to IV glucose ($AIR_{glucose}$) was calculated as the mean of incremental plasma insulin concentrations from 0 to 10 min following IV glucose bolus.[13] Insulin-mediated, glucose-mediated and total glucose disposal during the glucose tolerance test were calculated.[14] Insulin-mediated glucose disposal was calculated as the product of the insulin sensitivity index SI and AIRglucose (S_I × AIRglucose); this calculation has the unit min −1 in common with glucose-mediated glucose disposal SG. Total glucose disposal during the tolerance test was calculated as the sum of insulin-mediated and glucose-mediated glucose disposal.

The data were obtained from the glucose tolerance tests were found to be normally distributed and were analyzed by parametric statistics. The derived measurements of glucose metabolism of the women in the matched study and control groups were compared using Student's *t*-test. Pearson's correlation analysis was used to examine the relation between MABP and both fasting insulin and insulin sensitivity.

Results

We compared retrospectively two study groups, group 1 (those with preeclampsia) and group 2 (control) (normotensive) of women for factors affecting insulin sensitivity. We compared following factors: Age, gestation and BMI and no significant changes were reported [Table 1]. Significant changes in mean lipid, progesterone, cortisol or androgen concentrations between the two groups were also absent [Table 1]. The study and control groups were thus matched for these parameters.

MABP (±standard deviation [SD]) at the time of the IV glucose tolerance test was 89 ± 7.5 mmHg in the control group and 122 ± 9.2 mmHg in the study group. Mean fasting insulin levels were found to be 15.2 ± 5.9 in normotensive control group and significantly lower 9.5 ± 4.1 ($P = 0.02$) in preeclamptic patients. Mean fasting glucose levels were not significantly different in control and study groups (3.8 ± 0.1 vs. 3.6 ± 0.2 mmol/L, $P = 0.32$).

Pearson correlation between total glucose disposal with the IV glucose clearance K, in the normotensive group of women was found to be significant ($r = 0.69$, $P = 0.001$). In the group with preeclampsia the relative contribution of glucose-mediated glucose disposal to total glucose disposal was significantly lower (25.8% ± 2.4 vs. 50.4% ± 5.0; $P = 0.003$) compared with the women in the control group. The MABP in the normotensive women significantly correlated with both fasting insulin ($r = 0.72$, $P = 0.02$) [Figure 1]. No such correlations were found with blood pressure in women with preeclampsia.

Table 1: Comparison of anthropometric data and biochemical factors which might influence insulin sensitivity between the study and control groups

Parameter	Group 1 (study group)	Group 2 (control group)
Age (years)	27.2±1.6	28.6±3.2
BMI (kg/m^2)	25.4±3.2	24.3±2.6
Gestational age (in weeks)	34.4±1.4	35.6±1.6
Cortisol (nmol/L)	640±49	760±58
Progesterone (nmol/L)	502±102	595±118
Testosterone (nmol/L)	4.2±0.3	3.7±0.3
Cholesterol (nmol/L)	5.7±0.5	4.2±0.4
Triglyceride (nmol/L)	4.0±0.3	3.3±0.2

BMI: Body mass index

Median plasma glucose and insulin levels during the course of the IV glucose tolerance test are shown in Figures 2 and 3. No significant difference between the glucose decay curves [Figure l], and between the glucose clearance rate K, in the two groups was found (preeclamptic vs. normotensive: 2.1 ± 0.2 vs. 2.2 ± 0.3; $P = 0.48$). Therefore, there was a small but prolonged decrease in the insulin response of women with preeclampsia compared with the women in the normotensive group [Figure 3].

Table 2 compares the derived parameters from minimal model analysis in the two groups of women. Mean ± SD insulin sensitivity was significantly higher in women with preeclampsia than in the controls ($P = 0.018$). This was accompanied by a significant decrease in mean glucose effectiveness in the preeclamptic group ($P < 0.001$). There was no significant difference in the first or second phase insulin response or in AIRglucose [Table 2].

Discussion

Several studies have investigated the role of insulin resistance in development of PIH. In this study, we investigated whether PIH can lead to increased insulin resistance.

The minimal model, developed by Bergman *et al.* in 1979 provides an indirect measurement of metabolic insulin sensitivity/resistance on the basis of glucose and insulin data obtained during a frequently sampled IV glucose tolerance test.[15] Minimal model based insulin sensitivity has greater heritability and determined more by genetic factors, rather than measures such as homeostatic model assessment, which reflect fasting insulin.[16] Full sample protocol was preferred as it detects small changes in Si in studies involving few subjects.[17] Although there are limitations with the minimal model and availability of simpler techniques like quantitative insulin sensitivity check index (QUICKI), it is known that QUICKI performs best in insulin-resistant subjects, whereas SI from the minimal model performs best in healthy, insulin-sensitive subjects.[15]

Table 2: Comparison of mean S_G, S_I, first and second phase insulin response (Φ_1 and Φ_2), and ($AIR_{glucose}$) between the control group and the group with (PE). Values are given as mean±standard deviation

	Normotensive (control group)	Preeclampsia (study group)	*P* value
SG (10^{-2}/min)	2.1±0.1	1.6±0.1	0.003
SI (10^{-4}/min/mU/L)	2.8±0.3	2.6±0.4	0.019
Φ_1 ,(mU/L/min/mg/dL)	13.6±2.2	12.6±2.3	0.70
Φ_2 , (mU/L/min^2/mg/dL)	68.8±10.8	64.2±19.2	0.84
$AIR_{glucose}$ (mU/L)	145.6±25.2	142.4±26.2	0.87

S_I: Insulin sensitivity; S_G: Glucose effectiveness; $AIR_{glucose}$: Acute insulin response and glucose; PE: Preeclampsia

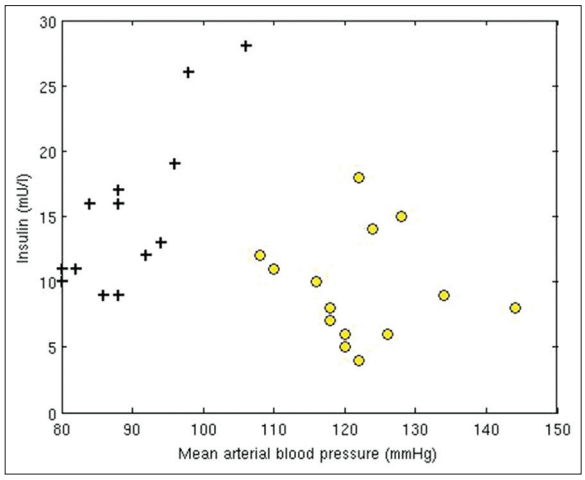

Figure 1: Correlation between mean arterial blood pressure and fasting insulin in normotensive (†) and preeclamptic (o) women. Normotensive: $r = 0.72$, $P = 0.018$; preeclamptic: $r = -0.32$, $P = 0.43$

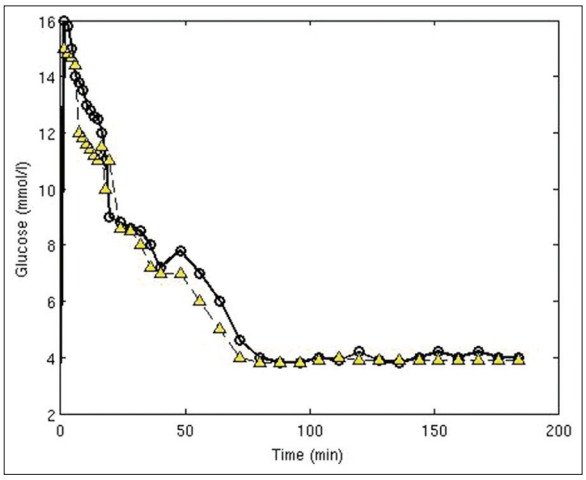

Figure 2: Profile of median glucose concentrations during the intravenous glucose tolerance tests in the preeclamptic (o) and normotensive (Δ) pregnant women

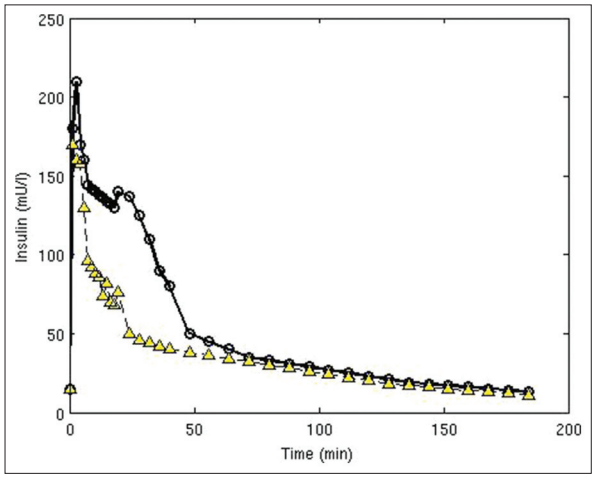

Figure 3: Profile of median insulin concentrations during the intravenous glucose tolerance tests in preeclamptic (o) and normotensive (Δ) pregnant women

The main result of this study is that women who developed preeclampsia did not have increased insulin resistance

compared with normotensive women in the third trimester of pregnancy. In fact the mean insulin sensitivity was found to be significantly higher in women with preeclampsia than in normotensive women. No significant difference in the glucose decay curves was found between the two groups. Both preeclamptic and normotensive women were able to clear glucose at similar rates ($P = 0.48$ for glucose clearance rate K)

We had been able to gather the pre-pregnancy BMI for each of the participants in this study. Higher pre-pregnancy BMI has been observed among women who develop PIH.[18] The cholesterol and triglyceride levels also matched well in the two groups.

Lorentz *et al*.[8] reported increased fasting insulin levels and after oral glucose tolerance testing in women with preeclampsia or gestational hypertension. However, a shortcoming in their study was that the sample population was not adjusted for BMI. Though the study of Martinez Abundis *et al*.[6] indicated similar fasting and post loading glucose levels in normotensive and preeclamptic women; they said there is increased insulin level in preeclampsia. An inherent problem with their selection was that proteinuria criteria had not been specified for all patients. It is possible that few women who were not falling into the category of preeclampsia had been thus labeled. It should be noted from studies of Madsen *et al*.[19] that the insulin resistance was present in preeclamptic women was based on the demonstration of relative hyperinsulinemia, not direct measurement of insulin mediated glucose disposal.

A shortcoming in our study was that we did not compare insulin sensitivity among pregnant versus non-pregnant women. Although there are studies supporting increased insulin resistance during pregnancy,[3] we might have benefitted from studying the same in this ethnic population.

Conclusion

Although it is widely accepted that insulin resistance is a causal factor in PIH, we found that the converse is not true. In this study group of North Indian pregnant women with preeclampsia in the third trimester no exaggerated insulin resistance was seen.

References

1. Walker JJ. Pre-eclampsia. Lancet 2000;356:1260-5.
2. López-Jaramillo P, García RG, López M. Preventing pregnancy-induced hypertension: Are there regional differences for this global problem? J Hypertens 2005;23:1121-9.
3. Catalano PM, Tyzbir ED, Roman NM, Amini SB, Sims EA. Longitudinal changes in insulin release and insulin resistance in nonobese pregnant women. Am J Obstet Gynecol 1991;165:1667-72.
4. Kühl C. Insulin secretion and insulin resistance in pregnancy and GDM. Implications for diagnosis and management. Diabetes 1991;40 Suppl 2:18-24.
5. Caren G, Solomon, Seely EW. Hypertension in pregnancy. A manifestation of insulin resistance syndrome? Hypertens 2011;37:232-9.
6. Martinez Abundis E, Gonzalez Ortiz M, Quiñones Galvan A, Ferrannini E. Hyperinsulinemia in glucose-tolerant women with preeclampsia. A controlled study. Am J Hypertens 1996;9:610-4.
7. Kaaja R, Tikkanen MJ, Viinikka L, Ylikorkala O. Serum lipoproteins, insulin, and urinary prostanoid metabolites in normal and hypertensive pregnant women. Obstet Gynecol 1995;85:353-6.
8. Lorentz B, Birkeland KI, Endersen MJ, Henriksen T. Glucose intolerance in women with preeclampsia. Acta Obstet Gynecol Scand 1998;77:22-7.
9. Caruso A, Ferrazzani S, De Carolis S, Lucchese A, Lanzone A, De Santis L, *et al*. Gestational hypertension but not pre-eclampsia is associated with insulin resistance syndrome characteristics. Hum Reprod 1999;14:219-23.
10. Retnakaran R, Hanley AJ, Connelly PW, Sermer M, Zinman B. Ethnicity modifies the effect of obesity on insulin resistance in pregnancy: A comparison of Asian, South Asian, and Caucasian women. J Clin Endocrinol Metab 2006;91:93-7.
11. Olivier BG, Rohwer JM, Hofmeyr JH. Modelling cellular systems with PySCeS. Bioinformatics 2005;21:560-1.
12. Jones E, Oliphant T, Peterson P. SciPy: Open Source Scientific Tools for Python, 2001. Available from: http://www.scipy.org.
13. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, *et al*. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes 1993;42:163-72.
14. Henriksen JE, Alford F, Handberg A, Vaag A, Ward GM, Kalfas A, *et al*. Increased glucose effectiveness in normoglycemic but insulin-resistant relatives of patients with non-insulin-dependent diabetes mellitus. A novel compensatory mechanism. J Clin Invest 1994;94:1196-204.
15. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance *in vivo*: Advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab 2008;294:E15-26.
16. Bergman RN, Zaccaro DJ, Watanabe RM, Haffner SM, Saad MF, Norris JM, *et al*. Minimal model-based insulin sensitivity has greater heritability and a different genetic basis than homeostasis model assessment or fasting insulin. Diabetes 2003;52:2168-74.
17. Steil GM, Murray J, Bergman RN, Buchanan TA. Repeatability of insulin sensitivity and glucose effectiveness from the minimal model. Implications for study design. Diabetes 1994;43:1365-71.
18. Solomon CG, Carroll JS, Okamura K, Graves SW, Seely EW. Higher cholesterol and insulin levels in pregnancy are associated with increased risk for pregnancy-induced hypertension. Am J Hypertens 1999;12:276-82.
19. Madsen SN, Hindberg I, Molsted-Pedersen L. Insulin response to oral glucose in patients with preeclampsia. Dan Med Bull 1973;20:13-5.

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