

Insulin changes in preeclamptic women during pregnancy

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BACKGROUND: The etiology of preeclampsia remains obscure. To study the role of insulin resistance in preeclampsia, we compared fasting insulin and glucose changes during the second and third trimesters in preeclamptic women with a normal control group.

PATIENTS AND METHODS: In a nested case-control study, subjects were selected from a population-based cohort of 674 pregnant women from whom serum was collected for this study between the 20th and 24th week of gestation. For 16 women who developed preeclampsia (cases), 16 women who remained normotensive were selected as controls. Controls were matched with each case for pregestational body mass index, age, gestational age, and parity. Fasting glucose and insulin levels of the second trimester (20th to 24th weeks) of pregnancy were compared based on serological data. The comparisons were also carried out in the third trimester when preeclampsia occurred.

RESULTS: Fasting insulin levels increased from 15.3 ± 1.3 μ U/mL to 25.3 ± 1.4 μ U/mL between the second and third trimesters in the preeclamptic group ($P < 0.01$) and from 10.4 ± 0.9 μ U/mL to 16.2 ± 1.3 μ U/mL in the control group ($P < 0.01$). There was no significant change in glucose levels during pregnancy in either group.

CONCLUSION: Women who develop preeclampsia have higher insulin levels before clinical evidence of disease than women who remain normotensive during pregnancy. The increase in insulin levels in the third trimester was greater in preeclamptic than in non-preeclamptic women.

KEYWORDS: Preeclampsia, insulin, glucose, nested case-control study

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Preeclampsia complicates 6 to 8% of all pregnancies.¹ Its etiology remains obscure.² Although uteroplacental hypoperfusion caused by inadequate trophoblastic invasion of the spiral arteries is a feature of preeclampsia and may be pathogenic,² abnormal placentation is also a feature of intrauterine growth retardation when it occurs without preeclampsia.³ This has led to the suggestion that maternal factors must interact with reduced placental perfusion to result in preeclampsia in some cases.^{2,4} During the last decade many studies have found a significant positive association between pregnancy induced hypertension and insulin resistance,^{5,6} but not all investigators agree with this conclusion.⁷⁻⁹ Some of these studies were cross-sectional and others were flawed due to failure to use proper methods, as well as insufficient addressing of confounders, and insufficient sample size.¹⁰ In addition there are reports of a higher prevalence of insulin resistance in Asia.^{11,12} According to our review of the literature, no study has examined changes in the fasting insulin of preeclamptic women during pregnancy between the second and third trimesters in comparison with uncomplicated pregnancies. The objective of this study was to determine such changes.

Patients and Methods

Subjects in this nested case-control study, conducted from October 1999 to March 2002, were selected from a population-based cohort of 674 pregnant women attending 16 family health centers in Kermanshah, Iran. Women with a history of overt or gestational diabetes mellitus, chronic hypertension, renal failure, ischemic heart disease, and hyperlipidemia were excluded at the first visit as were those who had a fasting blood sugar ≥ 95 mg/dL, a pre-pregnancy body mass index ≥ 25 kg/m², and proteinuria or urinary tract infections during the earlier stages of the current pregnancy. Between 20 and 24 weeks of pregnancy, fasting blood samples were collected at 8 AM and after 10 hours of fasting. All women who enrolled in this study provided informed consent to obtain a blood sample. After centrifugation sera were stored at -30°C until further analysis. All women were followed to the end of pregnancy.

Preeclampsia was defined as new onset hypertension with blood pressure consistently $\geq 140/90$ mm Hg in previously normotensive women and new onset proteinuria (defined as ≥ 300 mg per 24 hours or $\geq 2+$ by dipstick) occurring after the 20th week of gestation and that was observed 6 hours apart on at least two occasions. During the follow

up, if blood pressure was raised and an obstetrician confirmed a diagnosis of preeclampsia, the woman was selected as a case. A second blood sample was taken and stored. Sixteen preeclamptic women were selected as the case group. Once a preeclamptic case was determined, a normotensive woman of the same age and pre-pregnancy body mass index was selected from the same cohort of the pregnant woman. The control and case were also matched with regard to gestational age at the time of the second serum sample (when clinical manifestation of preeclampsia occurred in each case). Then a blood sample was taken and stored in the same way as in the case group. Blood pressure was measured according to the guidelines of Canadian Hypertension Society.¹³ Glucose was measured using the glucose oxidase method and insulin was measured using radioimmunoassay (DRG Ins. GmbH, Germany).

In a two-way analysis of variance (group-time interaction) of glucose and insulin levels, the case and control groups were analyzed as the between-subjects factor (group) and the first and second blood sampling time during pregnancy in each group was the within-subjects factor (time). To compare the increase in these biochemical parameters at the third trimester (second blood sampling) with the levels in the second trimester (first blood sampling between the 20th and 24th week of pregnancy), a paired two-sided Student *t*-test was used.¹⁴ Statistical analyses were performed with the SPSS Win9 (SPSS Inc., Chicago, IL) package. Results are expressed as mean±SD and were considered significant with *P*<0.05.

Results

The cases and controls were similar with respect to matched demographic factors (Table 1). Serum concentrations of fasting glucose and insulin by gestational age are presented in Table 2. Fasting glucose levels were similar in cases and controls both in the second and the third trimesters. The glucose level showed no significant changes in either the preeclamptic women or the controls during pregnancy (*P*>0.5). The results of the two-way-ANOVA for insulin changes indicate there were significant within-group changes as well as between-group differences at the first and second blood sampling (Table 3 and 4). There were significant differences between the two groups in the first blood sampling (the 20th to 24th week of pregnancy) for fasting insulin levels (*t*=2.98, d.f.=30, *P*<0.01). The increase in insulin during pregnancy

Table 1. Demographic characteristics of subjects.

	Preeclamptic (n=16)	Controls (n=16)	<i>P</i> value
Age (years)	24.6 ± 0.8	24.2 ± 0.6	NS (t test)
Body mass index (kg/m ²)	24.2 ± 0.3	24.0 ± 0.2	NS
Gestational age (weeks)	33.2 ± 0.9*	33.5 ± 0.8	NS
Null parity (n, percent)	14 (87%)	13 (81%)	NS

Mean±SE; * Time of occurrence of preeclampsia in cases; time of selection in controls.

Table 2. Insulin and glucose levels in subjects.

	Preeclamptic (n=16)	Controls (n=16)	
Glucose (mg/dL)			
Weeks 20-24	83.7 ± 2.2	84.5 ± 1.9	.8 (t test)
Weeks 29-36	81.6 ± 1.5	80.1 ± 2.0	.5
Insulin (μIU/mL)			
Weeks 20-24	15.3 ± 1.3	10.4 ± 0.9	.011
Weeks 29-36	25.3 ± 1.4	16.2 ± 1.3	.001

Mean±SE

was significant in both groups (*P*<0.01). The increase in insulin levels between the second and third trimester in the preeclamptic group was more than that in the controls (10±1.5 μIU/mL vs. 5.8±1.4 μIU/mL, *P*<.03). In statistical terms, there was a group-time interaction (Table 3).

Discussion

We found no difference in serum glucose levels in the second trimester between women who later developed preeclampsia and those who remained normotensive. Other investigators have come up with the same results.¹⁵⁻¹⁸ There were no changes in glucose levels in preeclamptic or normotensive women during pregnancy. According to our knowledge no study has previously compared fasting glucose changes between preeclamptic and normotensive women during pregnancy. Our results suggest that the fasting glucose levels in preeclamptic women are similar to those in uncomplicated pregnancies.

Our finding indicates that women who developed preeclampsia had higher fasting insulin levels at the second trimester, before the appearance of clinical signs of preeclampsia. This finding is supported by previous studies,^{16,17} which were cross-sectional or did not determine changes in insulin levels before and after clinical manifestation of preeclampsia. In contrast to our results, Grobman et al found no relationship between insulin levels at the second trimester and the subsequent development of preeclampsia.⁸ What is the explanation for these differences? In Grobman's study the interval between the last meal of the subjects and blood sampling was about 3 hours. Also, subjects belonged to different races, including white, black, and Hispanic. These

Table 3. Within-subjects effects in analysis of variance test on serum insulin values.

Effect		Value	F	P value
Insulin*	Wilks lambda	0.28	76.3†	<0.01
Insulin group††	Wilks lamda	0.85	5.2	<0.03

*Within-subject factor

†Exact statistic

††Refers to cases and controls

Table 4. Between-subjects comparison in analysis of variance test on serum insulin values.

Source	df	Mean square	F	P value
Intercept	1	18070.1	475.2	<0.01
Group	1	781.2	20.5	<0.01
Error	30	38.02	-	-

factors can result in considerable but statistically insignificant variance in insulin values. Cioffi et al reported that the connection between insulin levels and preeclampsia was confounded by obesity.¹⁸ In our study, the two groups had a similar pre-gestational body mass index.

Although there are some studies of the relationship between preeclampsia and insulin levels or insulin secretion in the third trimester,^{6,9,19-21} no study has compared insulin changes between preeclamptic and uncomplicated pregnant women during pregnancy. In our study, fasting insulin levels increased in both groups from the second to the third trimester. Laakso reported that fasting insulin levels should be

used as a marker of insulin resistance.²² Insulin resistance may lead to hypertension by changes in the levels of intracellular cations, sympathetic nervous system overactivity and renal sodium retention.²³ In addition, some studies have indicated that preeclamptic women have insulin resistance for months after delivery,^{24,25} which suggest a persistent maternal factor. Significant increases in intracellular sodium have been observed in hypertensive pregnant women compared with normotensive women. This can reduce the sodium/calcium exchange and result in rising intracellular calcium, which could produce an elevation of vascular smooth muscle tone and hence blood pressure.²⁶ The marked reduction of Na-K ATPase activity in hypertensive pregnant women could explain the increase in intracellular sodium.²⁷ Insulin might induce activation of Na-K ATPase and cause vasorelaxation in normotensive pregnant women.^{28,29} We suggest that the resistance of Na-K ATPase activity to insulin effects leads to an increase in intracellular calcium and finally ends in hypertension. To the best of our knowledge there are no studies related to this hypothesis, so we have this called the ionic insulin resistance model. However, our study does not allow us to comment on the predictive value of insulin levels for the development of preeclampsia in the second trimester.

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