Original Article

Study the association of midtrimester insulin resistance with development of pre-eclampsia among primi gravidae

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Abstract

Objective: To determine the development of pre-eclampsia among primigravidae midtrimester pregnant women with insulin resistance. **Method:** 500 primigravidae normotensive women were included for the study on first come first basis and fasting insulin and fasting glucose was done on all of them. Insulin resistance was calculated by homeostasis model assessment of insulin resistance (HOMA-IR). Women having HOMA-IR ≥75 percentile were included in study group and women with HOMA-IR <75 percentile were included in control group. These women were followed up and again seen at time of delivery. **Results:** In our study we found that out of 376 control subjects (<75th percentile HOMA-IR), 351 (93.35%) were normotensive, 17 (4.52%) developed gestational hypertension and 8 (2.13%) subjects had preeclampsia at the time of delivery and in 124 cases (≥75th percentile HOMA-IR), 99 (79.84%) were normotensive, 11 (8.87%) developed gestational hypertension and in 14 (11.29%) cases we found to have preeclampsia at the time of delivery. **Conclusion:** Study results showed that raised mid trimester maternal insulin resistance is associated with a significant increase in risk of having preeclampsia later in pregnancy.
Keywords: HOMA-IR, IR.

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INTRODUCTION

Insulin is an essential peptide hormone whose metabolic actions maintain whole body glucose homeostasis and promote efficient glucose utilization.[1] The maximal effect of insulin defines "insulin responsiveness," whereas the insulin concentration required for a half-maximal response defines "insulin sensitivity".[2] Insulin resistance is typically defined as decreased sensitivity or responsiveness to metabolic actions of insulin, such as insulin-mediated glucose disposal and inhibition of hepatic glucose production (HGP). Insulin r Normal pregnancy can be considered as a state of insulin resistance, and fasting insulin concentrations double during the course of gestation. Insulin resistance peaks in the 3rd trimester and rapidly returns to pre-pregnancy levels after delivery.[3] The reasons for this insulin resistance in normal pregnancy been suggested that placental hormones, such as lactogen, cortisol, progesterone, and estrogen, and tumor necrosis factor α^3 may be responsible.[3] Normal pregnancy is characterized by lower fasting, higher postprandial glucose values, and hyperinsulinemia.10 The insulin resistance progress until the third trimester to facilitate the transfer of glucose to the fetus and insulin returns to a normal level after delivery.[4,5] Hypertensive disorders complicate 5-10% of all pregnancies and preeclampsia is identified in 3.9% of all pregnancies. 15 Several lines of evidence suggest that both preeclampsia and gestational hypertension may be associated with greater degrees of insulin resistance than

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characteristic of normal pregnancy. The usual onset of PIH in late pregnancy a time when the insulin resistance characteristic of pregnancy is maximal, supports a possible association. Postulated mechanism through which insulin resistance might increase blood pressure in pregnancy, as in essential hypertension include sympathetic nervous system activation renal sodium retention, increased cation transport and associated endothelial dysfunction.[3] Insulin sensitivity in vivo during pregnancy can be estimated using a variety of techniques. The gold standard, however, is the hyperinsulinemic euglycemic clamp techniques as described by DeFronzo *et al* (DeFronzo *et al*. 1985). More common clinical methods include HOMA-IR and QUICKI by using fasting plasma glucose and fasting insulin level.[6] Homeostasis model assessment (HOMA) was developed in 1985.[7] It is a model of interactions between glucose and insulin dynamics that is then used to predict fasting steady-state glucose and insulin concentrations for a wide range of possible combinations of insulin resistance and β-cell function.[7, 8, 9]

MATERIAL AND METHODS

A hospital based prospective observational study to determine the association of insulin resistance with development of preeclampsia among midtrimester primigravidae at the Department of Obstetrics and Gynaecology, Gangori Hospital, S.M.S Medical College, Jaipur. During one year of study period around 500 primigravidae normotensive women with singleton pregnancy at 22-26 weeks of gestation attending antenatal clinic were screened and enrolled for this study after applying inclusion and exclusion criteria with written consent. Known case of diabetes mellitus, chronic hypertension, multiple pregnancy, hypertensive disorder of pregnancy, nephropathy, UTI, obesity were excluded. All women enrolled in this study underwent thorough antenatal check-up including general physical examination and per abdominal examination. Height, weight and blood pressure was measured at mid trimester. Routine antenatal investigations were done. At the same time insulin resistance was calculated from fasting maternal plasma glucose and fasting insulin concentration by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). These women were followed up and again seen at time of delivery. The values of HOMA-IR were arranged in ascending order and the women with $<75^{th}$ percentile were taken as controls (376) and values $\geq 75^{th}$ percentile were taken as cases (124).

RESULTS

Mean fasting insulin of case group was 10.64 μIU/mL and mean fasting insulin of control group was 2.605 μIU/mL. On applying 't' test P-value came out to be <. 001 which showed that the difference was statistically significant (Table-1). Mean of fasting sugar of case group is 9.1950 mmol/L and control group is 8.873 mmol/L. We observed a significant difference between both groups as P-value was <. 05 (Table-2). Mean insulin resistance of case group is 4.169 and mean of control group was 1.045. P-value was <. 01 so there was statistically significant difference between case and control group (Table-3). Mean systolic blood pressure at time of delivery in case and control group were 121.6 and 116.2 mmHg respectively. On applying 't' test P-value was <. 05 so there was statistically significant difference between both groups. Mean diastolic blood pressure at time of delivery in case and control group were 82.9 and 80.8 mmHg respectively. We observed a statistically significant difference as P-value was <. 05 (Table-4). In our study we found that out of 376 control subjects, 351 were normotensive, 17 (4.52%) developed gestational hypertension and 8 (2.13%) subjects had preeclampsia at the time of delivery and in 124 cases, 99 (79.84%) were normotensive, 11 (8.87%) developed gestational hypertension and in 14 (11.29%) cases we found to have preeclampsia at the time of delivery (Table-5). We observed that 22 participants developed preeclampsia out of which 14 (63.64%) were cases and only 8 (36.36%) were controls. This difference was statistically significant. On statistical analysis P-value came out to be <. 05 so the difference was statistically significant (Table-6).

Table 1: Mean of the Fasting Insulin Level of Participants at Midtrimester

Group	N	Mean	Std. Deviation	Std. Error Mean
Control	376	2.6052	.97047	.05005
Case	124	10.6427	7.43310	.66751

t = 20.485, d.f. = 498, P <. 001 Sig

Table 2: Mean of the Fasting Sugar of Participants at Midtrimester

Group	N	Mean	Std. Deviation	Std. Error Mean
Control	376	8.8734	.79232	.04086
Case	124	9.1950	.77755	.06983

t = 3.937, d.f. = 498, P <. 05 Sig

Table 3: Mean of the Insulin Resistance of Participants at Midtrimester

Group	N	Mean	Std. Deviation	Std. Error Mean
Control	376	1.04538	.3452	.01780
Case	124	4.16954	2.6803	.2407

t = 22.095 d.f. = 498, P <. 01 Sig

Table 4: Mean Systolic and Diastolic BP at Delivery

	Group	N	Mean	SD	SEM	Value
Systolic Blood Pressure	Control	376	116.23	8.99427	.46384	t - 4.974, P <. 05
	Case	124	121.61	14.16437	1.27200	
Diastolic Blood Pressure	Control	376	80.8191	3.71939	.19181	t - 4.502, P <. 05
	Case	124	82.9032	6.22272	.55882	

Table 5: Distribution of Participants According to Blood Pressure

Blood Pressure	Group				Total	
	Control		Case			
	No.	%	No.	%	No.	%
Normotensive	351	93.35	99	79.84	450	90.00
Pre-eclampsia	8	2.13	14	11.29	22	4.40
Gestational Hypertension	17	4.52	11	8.87	28	5.60
Total	**376**	**100.00**	**124**	**100.00**	**500**	**100.00**

χ^2 = 22.83, d.f. = 2, P <. 05 Sig

Table 6: Distribution of Participants According to Development of Preeclampasia

	No. of Preeclampsia	% of Preeclampsia Women
Case Group (124)	14	63.64
Control Group (376)	8	36.36
Total	**22**	**100.00**

χ^2 = 18.62, d.f.= 1, P <. 01 Sig

DISCUSSION

Normal pregnancy can be considered as a state of insulin resistance, and fasting insulin concentrations double during the course of gestation. Insulin resistance peaks in the 3rd trimester and rapidly returns to pre-pregnancy levels after delivery.[3] Several lines of evidence suggest that both preeclampsia and gestational hypertension may be associated with greater degrees of insulin resistance than characteristic of normal pregnancy.[3] Hence we conducted a hospital based prospective observational study to determine the association of insulin resistance with development of preeclampsia among midtrimester primigravidae at the Department of Obstetrics and Gynaecology, Gangori Hospital, S.M.S Medical College, Jaipur. During one year of study period around 500 primigravidae normotensive women with singleton pregnancy at 22-26 weeks of gestation attending antenatal clinic were screened and enrolled for this study after applying inclusion and exclusion criteria with written consent. All women enrolled in this study underwent thorough antenatal check-up including general physical examination and per abdominal examination. Height, weight and blood pressure was measured at mid trimester. Routine antenatal investigations were done. At the same time insulin resistance was calculated from fasting maternal plasma glucose and fasting insulin concentration by Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). These women were followed up and again seen at time of delivery. HOMA-IR is a simple and accurate method to determine insulin resistance compared to other method. Wallace *et al* (2002)[10] and Borai A *et al* (2007)[11] also found similar finding that HOMA-IR is useful in large population studies where a relatively simple, inexpensive assessment is necessary. The values of HOMA-IR were arranged in ascending order and the women with <75th percentile were taken as controls (376) and values ≥75th percentile were taken as cases (124). At mid trimester mean fasting insulin level in the case group was 10.64 uIU/ml and 2.6 uIU/ml in the control. There was significant difference in mean fasting insulin levels on comparing both the groups (P-value <.001). Mean of the Fasting sugar level f cases and controls was 9.1950 mmol/l and 8.873 mmol/l respectively. The difference was statistically significant. This is explained by the fact that fasting insulin and fasting sugar levels rise in parallel to insulin resistance and similar findings were observed by Sokup A *et al* (2013)[12]. Mean of the Insulin resistance of case group was 4.169 and mean of control group was 1.045. P-value came out to be <.01 so there was statistically significant difference between case and control group. Again these women were seen at the time of delivery and compared on the basis of weight, BMI and blood pressure. There was no significant difference on the basis of weight and BMI. Mean systolic blood pressure at the time of delivery was 116.23 mmHg in control group and 121.61 mmHg in case group and mean diastolic blood pressure 82.90 mmHg and 80.81 mmHg in the case and control group respectively. On applying t-test the difference was statistically significant (P-value <.05). In our study we found that out of 376 control subjects, 351 (93.35%) were normotensive, 17 (4.52%) developed gestational hypertension and 8 (2.13%) subjects had preeclampsia at the time of delivery. And in 124 cases, 99 (79.84%) were normotensive, 11 (8.87%) developed gestational hypertension and in 14 (11.29%) cases developed preeclampsia. On statistical analysis P-value came to be <.05 so difference was statistically significant (Table-15). We found that out of the 22 participants who developed preeclampsia, 14 (63.64%) belonged to the case group and 8 (36.36%) were controls. This difference was statistically significant. Earlier study done by Elena Parretti *et al* (2006)[13] and John C Hauth *et al* (2011)[14] found that maternal mid trimester insulin has a role in development of preeclampsia, and our study results also showed that mid trimester maternal insulin resistance is associated with a significant increase in risk of having preeclampsia later in present pregnancy.

CONCLUSION

Our study results showed that raised mid trimester maternal insulin resistance is associated with a significant increase in risk of having preeclampsia later in pregnancy. While there are many predictors of preecampsia in use at present, insulin resistance can be measured by a simple and cost effective method such as HOMA-IR and is a good predictor of this condition. Therefore, we recommend measurement of insulin resistance in second trimester pregnant women. This would help to identify women with raised insulin resistance who are at high risk for developing preeclampsia. These women can then be monitored carefully as high risk cases thereby helping in early diagnosis and management of preeclampsia.

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