

# A case control study of fasting insulin levels in normal pregnancy and pre eclampsia patients

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## Abstract

**Objective:** To study the levels of fasting plasma insulin levels in normotensive pregnant women and Pre eclamptic women. To co relate the elevation of fasting insulin levels in relation to the severity of pre-eclampsia. **Design:** Case control study, **Setting:** Father Muller Medical College Hospital. **Population:** 70 pre-eclamptic women as cases, 30 normotensive women as control **Methods:** A case control study was conducted between August 2010 – July 2012 who satisfied the inclusion criteria. Blood samples were collected and analysed by CLIA technique for fasting plasma insulin levels among both control and cases. **Results:** Pre-eclamptic women had significantly higher fasting plasma insulin levels (n=70, mean 17.893µunits/ml) than controls (n=30, mean 2.1713µunits/ml,  $p = <0.001$  vhs) and levels of fasting plasma insulin levels were directly proportional to the severity of the disease. (mean = 7.85 in mild PE, 21.23 in severe Preeclampsia and 29.48 in eclampsia,  $p < 0.001$  vhs). **Conclusion:** Fasting plasma insulin levels are increased during the normal pregnancy with levels being maximum in third trimester. In women with pregnancy complicated by pre-eclampsia an exaggeration of the insulin resistance is seen with the resultant hyperinsulinemia. The results of the study also showed that hyperinsulinemia was directly proportional with the severity of the disease.

**Key Words:** Hyperinsulinemia, pre-eclampsia, fasting plasma insulin levels, normotensives, pregnancy.

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## INTRODUCTION

Pre eclampsia is a pregnancy specific condition characterized by hypertension and proteinuria in women with no prior incidence of these sequences and that, which remits after delivery. A great deal of research into the course of pre eclampsia has been in progress all over the world but none of these have gained universal acceptance. Pre eclampsia is associated with deficient or abnormal placentation leading to increased vascular resistance and reduced placental perfusion and the changes that are seen are due to endothelial dysfunction.

However the factor that causes the disturbance has not been identified. Fasting plasma insulin levels are increased during the normal pregnancy and is maximum in third trimester probably due to increased amounts of several insulin antagonistic hormones<sup>1234</sup>. In women whose pregnancies are complicated by hypertension there appears to be an exaggeration of insulin resistance and the associated metabolic changes. From the area of cardiovascular research there is increased evidence that hyperinsulinemia can cause increased endothelial damage. This study was done with an aim to test the hypothesis that fasting plasma insulin levels are increased in women with pre eclampsia as compared to normotensive women.

## MATERIALS AND METHODS

Hundred pregnant women (70 tests and 30 controls) admitted to Father Muller Medical College Hospital during the study period (August 2010- July 2012) was enrolled for the studies, who satisfied the inclusion criteria. The study was approved by the Institutional Ethical Committee and a written and informed consent was sought from all the patients enrolled in the study.

**Method Of Collection Of Data:** A case control study was conducted on 100 pregnant women in their 3<sup>rd</sup> trimester who were enrolled in the study based upon the fasting insulin levels and their co-relation with pre eclampsia and severity of pre eclampsia. All the women in the study were subjected to detailed history, examination and all were surveyed for the use of iron, folic acid, vitamins and any other drugs. Besides routine antenatal investigations in all pregnant women and special investigations in pre eclamptic women, all of them were subjected to fasting plasma insulin levels. For the measurement of fasting plasma insulin levels, 3 ml of blood from the antecubital vein in the fasting state was taken after overnight fasting. All the specimens were transported to the laboratory within 2 hours of collection. There after the specimens were centrifuged 5 to 7 minutes at 2000 rpm. Clear serum obtained was transferred in a plastic vial and stored in a refrigerator until analysis. The samples were then subjected to Chemiluminescent Immunoassay (CLIA) technique using the FDA APPROVED REAGENTS AND KIT with BACKMAN COULTER equipment, USA.

#### Plan for data analysis

Statistic analysis of the collected data was done by 't' test, Fischer's test, chi-square test,  $p < 0.05$  was taken as statistically significant

#### Inclusion Criteria

After the written and informed consent women diagnosed to be pre eclamptic were taken as cases and the control group were the women with pregnancy uncomplicated by pre eclampsia or proteinuria or other risk factors. All antenatal pregnant women between 28-40 weeks. Normotensives (Control). Hypertensives (Cases)

#### Exclusion Criteria

- Diabetes Mellitus
- Renal disorders
- Chronic hypertension
- Liver disorders
- Coagulopathies
- Overt Diabetes Mellitus
- Collagen vascular disorders
- Abruptio placentae
- Neural tube defects

## RESULTS AND ANALYSIS

**Table 1: Number of women in the study**

Group	Number
Normotensive	30
Preclampsia	70
<b>Total</b>	<b>100</b>

The present study was conducted on 100 women out of which 30 control who were normotensive and 70 cases who were preeclamptic.

**Table 2: Severity of hypertension**

Group	No.	%
Mild	23	32.9%
Severe	38	54.3%
Eclampsia	9	12.9%
<b>Total</b>	<b>70</b>	<b>100%</b>

According to the NHBPEP 2000 classification the cases was further classified into mild pre-eclampsia, severe pre eclampsia and eclampsia. Among the cases in the study 32.9% (23) were in mild pre-eclampsia group, 54.3% (38) were in severe pre-eclampsia group and 12.9% (9) were in eclampsia group.

**Table 3: Gestational age at the time of sampling**

Group	28-32	33-37	>37
Control	0 (0%)	4 (13.34%)	26 (86.66%)
Mild	2 (2.85%)	13 (18.57%)	8 (11.42%)
Severe	5 (8.57%)	22 (31.42%)	10 (21.3%)
Eclampsia	1 (1.42%)	3 (4.9%)	5 (7.14%)

Fishers exact test  $p = 0.0001$ , HS

86.66% women in control, 32.84% with pre eclampsia were at term at the time of sampling. 13.34% of women in control and 54.27% of women with pre eclampsia were sampled at earlier gestational age.

**Table 4: Fasting Insulin levels**

	N	Mean	SD
Normotensive	30	2.1713	1.88039
Pre eclampsia	70	17.893	12.55491

$Z = 7.048$ ;  $p = < 0.001$  HS

In the present study, the mean fasting insulin levels in normotensive group was  $2.17 \mu\text{units/ml}$  and in pre eclamptic group was  $17.893 \mu\text{units/ml}$ . The results obtained shows that fasting insulin levels was more in pre eclamptic group in comparison to normotensive pregnant women and the results were statistically significant,  $p = < 0.001$  vhs

**Table 5: Fasting insulin levels**

	N	Mean	SD
Normotensive	30	2.17	1.88
Mild	23	7.85	2.09
Severe	38	21.23	10.93
Eclampsia	9	29.48	17.36

$F = 4.609$ ;  $p = < 0.001$  HS

The mean fasting insulin levels in mild pre eclampsia was  $7.85 \mu\text{ units/ml}$ , in severe eclampsia it was  $21.32 \mu\text{ units/ml}$  and in eclampsia it was  $29.48 \mu\text{ units/ml}$ . All 3 groups of cases had higher values of fasting insulin levels as compared to the normotensives ( $2.17 \mu\text{ units/ml}$ ), and difference among the group was statistically significant with  $p = < 0.001$  vhs. It was also noted that among the

study group, the fasting insulin levels was higher in severe pre-eclampsia and eclampsia group in comparison to mild pre-eclampsia.

## DISCUSSION

Preeclampsia is a leading cause of maternal mortality. Although the exact cause of pre eclampsia is still unknown, we have learnt that in pre eclampsia the basic pathology is endothelial dysfunction and intense vasospasm. Increased fasting insulin levels has been recognized as a risk factor for coronary heart disease and peripheral vascular disease for more than 25yrs. This risk is proposed to promote the modification of endothelial function as a result of insulin exposure. The exact mechanism by which insulin promotes endothelial dysfunction remains unclear, but it appears to involve both cytotoxic and oxidative stress mechanism similar to those postulated to promote endothelial dysfunction in pre-eclampsia. Furthermore, the patho-physiology of pre-eclampsia shares striking similarities to that of atherosclerosis. Therefore it was hypothesized that insulin concentration could be greater in patients with pre-eclampsia than in women with normotensive uncomplicated pregnancies.

Table 6:

	Normotensive μunits/ml	Pre-eclampsia μunits/ml	P value
Kaaja <i>et al</i> <sup>11</sup> (1994)	6.5 n=21	13.3 n=31	P <0.01
Hamaski T <i>et al</i> <sup>5</sup> (1996)	7.3 n=5.51	24.1 n=29	P < 0.05
Soloman <i>et al</i> <sup>6</sup> (1999)	7.9 n=31	13.3 n=31	P = 0.03
Chandana Tripathy <i>et al</i> <sup>7</sup> (1999)	6.33 ± 2.83 n=99	9 ± 5 n=104	P = 0.0004
Shobreh <i>et al</i> <sup>8</sup> (2002)	16.2 ± 1.3 n=16	25.3 ± 1.4 n=16	< 0.01
Moran <i>et al</i> <sup>9</sup> (2006)	10.83 n=43	14.8 n=43	P = 0.023
Lei Q <i>et al</i> <sup>10</sup> (2008)	8.92 ± 4.4 n = 200	11.44 ± 6.72 n = 33	0.005
Present study	2.17 n=30	17.893 n=70	P = <0.001 HS

In the present study we have compared fasting plasma insulin levels among the normotensive and pre-eclamptic women. The mean value of fasting plasma insulin levels in the present study among normotensive group was 2.17 μ units/ml and pre eclamptic group was 17.893 μ units / ml and the results were comparable with that of studies by lei Q *et al*<sup>10</sup>, Kaja *et al*<sup>11</sup>, Hamaski T *et al*<sup>5</sup>, Solomon *et al*<sup>6</sup>, Chandana Tripathy *et al*<sup>7</sup>, Sobreh *et al*<sup>8</sup>, Moran *et al*<sup>9</sup> as shown in the above table. According to Kaja *et al*<sup>11</sup> study, which was conducted among 21 normotensive and 31

preeclmaptic women, results showed increased fasting plasma insulin levels among women with pre eclampsia i.e. 13.3 μ units/ml v/s 6.5 μ units/ml in the normotensive women and the results obtained were statistically significant, p value < 0.01. Hamask T *et al*<sup>5</sup> performed study on 551 normotensives and 29 pre eclmaptic women with fasting plasma insulin values of 7.3 μ units/ml v/s 24.1 μunits/ml respectively which was comparable with the results of our study. Soloman *et al*<sup>6</sup> performed study on 31normentensive and 31 pre-eclamptic women with fasting insulin levels as follows. 7.9 μ units/ml- control group (n=31) 13.3 μ units/ml- study group (n=31), and found that P = 0.03, statistically significant. Another study conducted by Chandana tripathy *et al*<sup>7</sup> was done among 99 normotensive and 104 preeclmaptic women. The results were as follows. Control group 6.33 ± 2.83μunits/ml (n=99). Study group 9 ± 5μunits/ml (n= 104). P = 0.0004, statistically significant Shobreh *et al*<sup>8</sup> conducted the study wherein fasting plasma insulin levels were analyzed among 16 normotensive and 16 pre-eclamptic women. The result in the pre-eclampsia were higher 25.3±1.4μunits/ml as compared to normotensive pregnant women who had comparatively lower fasting plasma insulin levels of 16.2±13μunits/ml, p=<0.01. The results of the study was also comparable with our present study with statistically significant results. Moran *et al*<sup>9</sup> studied the relation of fasting plasma insulin levels among 43 pre eclmaptic and normotensive women with comparable results. Control group 10.83 μ units/ml (n=43). Study group 14.8 μ units/ml (n=43). P = 0. 023, which was statistically significant. According to the study done by Lie Q *et al*<sup>10</sup>, the mean fasting plasma insulin levels among the preeclmaptic women was 11.44 ± 6.72 μ units/ml which was higher than the control group i.e 8.92 ± 4.4μunits/ml, p = 0.005. The present study also showed that mean fasting plasma insulin levels for the control and the study group was statistically significant (p < 0.001). However, in a study done by Roberts *et al*<sup>12</sup> the results were not co relating to our hypothesis, where in the study emphasised that pre eclampsia was not associated with an increase in insulin resistance beyond that of a normal pregnancy. In conclusion, the fasting plasma insulin levels are increased in preeclampsia when compared to normotensive uncomplicated pregnancy, and this hypothesis was proved in the present study which had supportive results i.e. fasting plasma insulin levels were increased in pre eclampsia as compared to normontensive pregnancy. The levels of fasting plasma insulin levels in mild, severe, eclampsia and control were 7.85 μ units/ml, 21.23 μ units/ml, 29.48 μ units/ml and 2.17 μ units/ml and the results were statistically significant, p= <0.001 vhs Although no studies were found which compared the

severity of the disease with the values of fasting insulin levels, Significant positive co-relation was found among the various studies done showing a higher fasting plasma insulin levels among the pre eclamptic group when compared to normotensive group with the p values being statistically significant.

## SUMMARY

The study was a prospective comparable study conducted to determine fasting plasma insulin levels in normotensive and pre eclamptic women and their relationship with the severity of the disease. 100 pregnant women were included of which 30 were normotensives and 23 were mild pre eclamptic, 38 severe pre eclamptic and 9 had eclampsia. The mean age of the patient in the control group and study group was 25.73 and 26.89 respectively. The mean fasting plasma insulin level in all the 3 groups i.e., mild pre eclampsia was 7.85 $\mu$  units/ ml, severe pre eclampsia was 21.23 $\mu$  units/ ml and eclampsia was 29.48 $\mu$  units/ ml, which was significantly increased when compared to normotensive group 2.71  $\mu$  units/ml. The increase in the fasting plasma insulin levels was found to be directly proportional to the severity of the disease i.e.. the values in the severe pre eclampsia (21.23 $\mu$ units/ml) and eclampsia group(29.48 $\mu$ units/ml) was higher in comparison to mild pre-eclampsia (7.85  $\mu$ units/ml). Although no studies were found which compared the severity of the disease with the values of fasting insulin levels, Significant positive co-relation was found among the various studies done showing a higher fasting plasma insulin levels among the pre clamptic group when compared to normotensive group with the p values being statistically significant.

## CONCLUSION

Fasting plasma insulin levels are increased during the normal pregnancy and are maximum in third trimester probably due to increased amounts of several insulin antagonistic hormones such as human placental lactogen<sup>1,2</sup>, corticotrophin releasing hormones<sup>4</sup> and progesterone<sup>3</sup>. In women whose pregnancies are complicated by hypertension there appears to be an exaggeration of insulin resistance and the associated metabolic changes. Studies indicate that hypertensives tend to be hyperinsulinemic in comparison to normotensive individuals and that the relationship between insulin resistance and hypertension is independent of BMI, age or magnitude of glucose

tolerance. The present study not only signified that fasting plasma insulin levels was increased in women with pre eclampsia in comparison to normotensives, it also showed that the increase in the fasting insulin levels were directly proportional with the severity of the disease. Various studies done in the past on the levels of fasting plasma insulin levels in relation to hypertension also proved the similar hypothesis. Further studies are required to know the cause of hyperinsulinemia observed in pregnant women with preeclampsia which may help in pharmacological management of pregnant women at risk for pre eclampsia.

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