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Original Research Article

Hypertensive disorders of pregnancy: a manifestation of insulin resistance

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ABSTRACT

Background: Pregnancy is a unique physiological diabetogenic state characterised by increased insulin resistance that ensures adequate supply of nutrients to the developing fetus. The insulin sensitivity falls to upto 50 percent in the late pregnancy. Thus insulin resistance and the resultant hyperinsulinemia are the characteristics features that are evident in the normal pregnancy during third trimester. In Hypertensive disorders of pregnancy (HDP), there is exacerbation of the physiological insulin resistance that occurs in normal pregnancy resulting in increased fasting serum insulin level.
Methods: This is a case control study conducted on 90 antenatal women, during the study period of one and half years (from December 2020 to June 2022) in IMS and SUM Hospital, Bhubaneswar. With informed written consent and after fulfilling the criterias, 60 normotensive patients were chosen as controls and 30 pregnant patients with hypertensive disorders of pregnancy were chosen as cases. After 8 hours of overnight fasting, 2ml of blood is drawn and processed by CMIA technology to detect fasting serum insulin levels. The mean fasting serum insulin levels were compared between the cases and the controls.
Results: The mean fasting serum insulin level of controls was found to be 9.27 and the mean fasting serum insulin level of cases was found to be 15.01 which was higher than controls. This was found to be statistically significant with a P value of 0.000.
Conclusions: Increased fasting serum insulin level is observed in women with HDP than normotensive pregnant women.

Keywords: CMIA technology, Fasting serum insulin, Hypertensive disorders of pregnancy, Insulin resistance

INTRODUCTION

Hypertensive disorders of pregnancy (HDP) is a complication unique to human pregnancy affecting about 2-8% of pregnant women. It has significant maternal and neonatal mortality and morbidity.[1] WHO states, HDP remains a leading cause of direct maternal mortality. It is associated with abruptio placenta, cerebral haemorrhage, disseminated intravascular coagulation (DIC), hepatic failure and renal failure.

Hypertension and/or proteinuria is the leading risk factor in pregnancy associated with stillbirth. PIH is also associated with fetal growth restriction (FGR), low birth weight, respiratory distress syndrome (RDS), cerebral palsy (CP) and increased admissions to neonatal intensive care unit.

According to American College of Obstetrics and Gynecologist (ACOG) and National High Blood Pressure Education Programme Working Group (NHBPEP) the

threshold used for defining hypertension in pregnancy is 'systolic blood pressure of 140 mmHg or higher and diastolic blood pressure of 90 mmHg or higher. These measurements are to be confirmed on at least two occasions about 4-6hours apart but within a maximum of a week period. NHBPEP classifies Hypertensive disorders of pregnancy (HDP) into 4 categories as gestational hypertension, pre-eclampsia-eclampsia, chronic hypertension and chronic hypertension with superimposed preeclampsia. [2]

Normally a pregnancy is associated with various metabolic, biochemical, physiological and immunological changes that revert back after delivery. In the normal pregnant women, the physiological adaptation that ensures the adequate supply of nutrients to the growing fetus is the resistance to actions of insulin. Insulin resistance is decreased biological response to the given insulin dose in the target tissue. Due to insulin resistance, the insulin level increases that leads to increased protein synthesis and also provides a ready source of transfer of amino acids to fetus.

Insulin is an endocrine hormone secreted by the beta cells of pancreas. It is a polypeptide hormone and it is also known as " hormone of nutrient abundance". Insulin is an anabolic hormone that plays an important role in the regulation of blood glucose levels. The insulin exerts its physiological effects by binding to the insulin receptors that are present on the plasma membrane bound receptors of the target cells.[3]

As the pregnancy advances, there is increase in insulin insensitivity up to 50% thus leading to insulin resistance. This necessitates the beta cells of pancreas to increase the insulin secretion to compensate, resulting in increased fasting plasma insulin level.[4] These changes are attributed to the actions of various insulin antagonist hormones like Human Placental Lactogen (HPL), progesterone, cortisol, prolactin, human chorionic growth hormone (hCG) and Corticotrophin Releasing Hormone (CRH).[5]

In HDP, there is exacerbation of the physiological insulin resistance than that of the normal pregnancy thus leading to increased fasting plasma insulin level.[6] It is also associated with inflammatory pathway activation and altered immune responses.

Insulin resistance in normal pregnancy

Pregnancy is a unique physiological condition that is characterised by a diabetogenic state, due to the progressive increase in the insulin resistance throughout the pregnancy. These changes are attributed due to the actions of various hormones that are primarily secreted by the placenta like growth hormone (GH), corticotrophin releasing hormone (CRH), human placental lactogen (HPL), cortisol, prolactin, estradiol and progesterone. Also throughout the pregnancy, there occurs redistribution of the maternal adipose tissue. The adipose tissues are metabolically active and produce adipocytokines such as leptin and adiponectin that are involved in the process of insulin resistance.[7] In late pregnancy adiponectin is also secreted by the placenta. The inflammatory molecules such as interleukin -6 (IL-6) and C-reactive protein (CRP) are also involved in the development of insulin resistance in pregnancy.

Insulin resistance is decreased biological response to the given insulin dose in the target tissue .The insulin sensitivity decreases up to 50 percent as the pregnancy advances to third trimester. In a normal pregnancy, the changes in the insulin sensitivity is overcome by increased secretion of insulin by the pancreas.[8] These metabolic changes shunt the adequate supply of nutrients to the growing fetus. Thus insulin resistance and the resultant hyperinsulinemia are the characteristics features that are present in normal pregnancy that is especially maximally observed in the third trimester. The degree of maternal resistance directly correlates with the amount of glucose load transferred from mother to fetus.

Insulin resistance in hypertensive disorders of pregnancy

In women with hypertensive disorders of pregnancy (HDP), there occurs exaggeration of insulin resistance that than of normal pregnancy.[6] P-IPG (Phosphoglycan-P-type) molecule plays a vital role in insulin resistance and plays an inevitable role in the metabolic and growth promoting effects of insulin. In HDP, there occurs dysregulation of P-IPG molecule and in these women, increased amount of P-IPG molecule in amniotic fluid and cord blood is seen.[9] The role of insulin in the regulation of blood pressure remains unclear. However, various mechanisms have been proposed.

Endothelial dysfunction

Hyperinsulinemia causes endothelial damage that eventually leads to endothelial dysfunction. These endothelial changes increases the formation of endothelin, thromboxane and decreased formation of vasodilators such as prostacyclin and nitric oxide and also leads to increased vascular sensitivity to angiotensin II.

Retention of sodium

In normal pregnancy, there occurs a physiological phenomenon of sodium retention. This physiological adaption in exaggerated in HDP than in normal pregnancy. Therefore insulin has been considered as a regulator of hypertension.

Stimulation of sympathetic system

In pregnancy complicated by pre-eclampsia, there occurs exaggerated insulin resistance and resultant hyperinsulinemia. The hyperinsulinemia causes the stimulation of sympathetic nervous system and increase in catecholamine concentration leading to increase in peripheral vasoconstriction and elevated blood pressure.

Sensitivity to vasopressors

The defects of insulin action leads to increase in vascular tone and increased sensitivity to vasopressors leading to vasoconstriction of the peripheral vessels. These mechanisms have been postulated as the effects of insulin in women with development of hypertensive disorders of pregnancy.

METHODS

This was a case control-observational study conducted for one and half years from Dec 2020 to June 2022. Total 90 pregnant women (30-cases and 60-controls) who were admitted in the IMS and SUM Hospital, during the study period were enrolled for the study. After written and informed consent, singleton uncomplicated pregnancies between 28-40 weeks of gestation were included for the study after fulfilling the inclusion and the exclusion criteria.

Inclusion criteria

Inclusion criteria for controls were the normotensive women of 28-40 weeks of gestation and women of 28-40 weeks of gestation diagnosed with hypertensive disorders of pregnancy (HDP) for cases.

Exclusion criteria

Exclusion criteria were pre-pregnancy BMI >25, history of PCOS, any medical illness like chronic hypertension, diabetes mellitius, thyroid dysfuction, liver diseases, kidney disorders, heart diseases and anemia, under medications like progesterone, rifampicin, glucocorticoids, isoniazid and risperidone, beta blockers, diuretics etc.

Patients were subjected to thorough history taking, clinical examination and laboratory investigations such as blood grouping, complete blood count, fasting and 2 hour postprandial blood sugar levels, urine routine and microscopy, renal function test and liver function test, thyroid function test and USG obstetrics. For the measurement of fasting serum insulin level, 2ml of blood sample was collected after overnight fasting (>8 hours). The specimen was transported to the laboratory within two hours of sample collection.

The quantitative determination of the insulin level in the collected sample was estimated by CMIA (chemiluminescent microparticle immunoassay) technology in the biochemistry laboratory of IMS and SUM hospital.

Statistical analysis

All the collected data was entered into MS-excel sheet and after appropriate filtrations, the data was transferred and analysed using SPSS. 't' test, Fischer's test, Pearson chi-square test and One-way ANOVA test was used to analyze continuous data. Descriptive statistics were described in proportion and percentage. P<0.05 was taken as statistically significant.

RESULTS

The study is conducted among 90 pregnant women, of which 30 women who were diagnosed with hypertensive disorders of pregnancy were taken as cases and 60 normotensive women were taken as control showed in Table 1. Based on NHBPEP 2000 classification, the cases were further categorised into gestational hypertension, preeclampsia, severe preeclampsia and eclampsia. Among the cases in this study, 50% (n=15) were gestational hypertension, 20% (n=6) were pre-eclampsia, 23.3% (n=7) were severe pre-eclampsia and 6.6% (n=2) were eclampsia.

Table 1: Distribution of study population with the severity of hypertension.

Study population	Group	Number	Percentage (%)
Control	Normotensive	60	66.7
Cases	Gestational hypertension	15	16.7
	Pre-eclampsia	06	6.7
	Severe pre-eclampsia	07	7.8
	Eclampsia	02	2.2
Total		90	100.0

Table 2: Distribution of study population according to age, parity and BMI.

Study group	Mean age	Parity	Mean BMI
Control	26.57	Primi-35 (58.3%) Multi-25 (41.6%)	24.42
Cases	27.63	Primi-15 (50%) Multi -15 (50%)	25.46

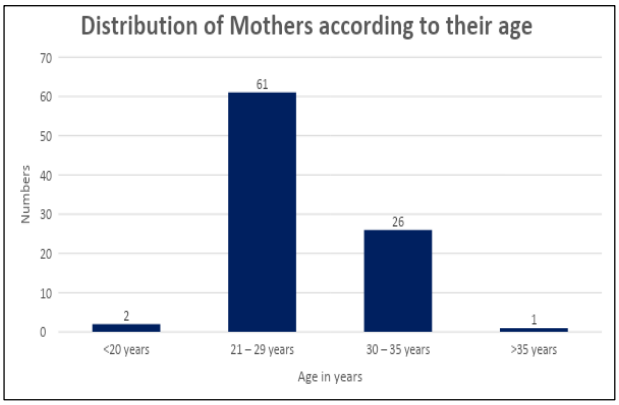

Figure 1: Distribution of women according to their age.

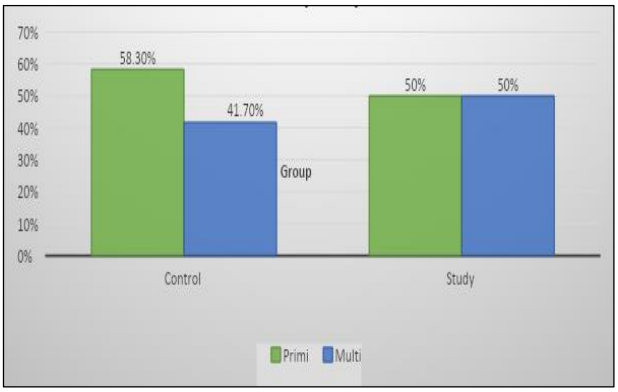

Figure 2: Distribution of study population according to parity

As shown in Figure 1, the mean age of the mothers in the control group is found to be 26.57 and that of cases is 27.63 which is comparable with both the groups. The maximum number of women were in the age group between 21-29 years 67.8% (n=61) in control and study groups. The results obtained were statistically not significant (X^2=5.729, p=0.929).

In the study population as shown in Figure 2, the primigravida in the control group is found to be 58.3% (n=35) and of the study group is 50% (n=15). The multigravida women in the control group constituted 41.7% (n=25) and in the study group it is 50% (n=15). The results obtained were statistically not significant (independent sample t test X^2=0.563, p=0.053). The present study consisted of 47.8% of women who were more than 37 weeks of gestation at the time of sampling and which is found to the highest. Among the cases, most women belonged to gestational hypertension with 10% of them being between 33 to 37 weeks constituting the highest among the cases.

The mean BMI in the control group was 24.42 and that of the study group was 25.4380. Slightly increased BMI is observed in women with hypertensive disorders of pregnancy when compared to normotensive women which is statistically not significant (independent sample t test F= 3.004, P =0.087).

In the current study, the mean fasting serum insulin level in the normotensive women is 9.2753 units/ml and in the women with hypertensive disorders of pregnancy is 15.0173 units/ml as shown in Figure 3. These results indicate increased fasting serum insulin level in women with hypertensive disorders of pregnancy when compared to the normotensive pregnant women and the results are statistically significant using independent sample t test, F=13.40 and p=0.000 very highly significant.

The mean fasting insulin level in gestational hypertension is found to be 16.64µunits/ml, in pre-eclampsia is 13.70 µunits/ml. Among severe pre-eclampsia cases is 14.72 µunits/ml whereas among eclampsia is found to be 7.78 µunits/ml as shown in Figure 4. Comparatively the cases have higher levels of fasting insulin compared to normotensives. The difference among the group was found to be statistically significant with p value <0.05 (One way ANOVA, F= 3.693, P =0.008 was significant).

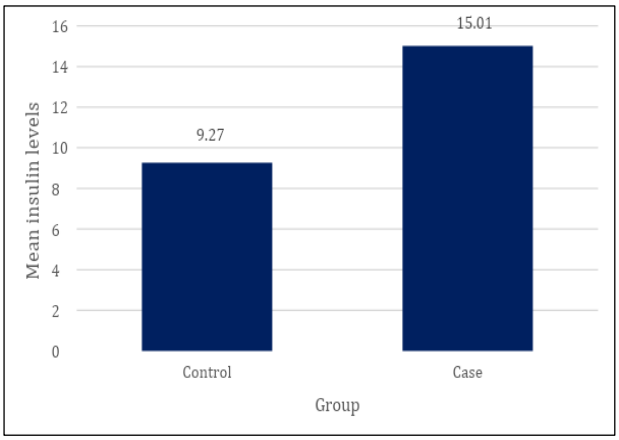

Figure 3: Mean fasting serum insulin level in controls and cases.

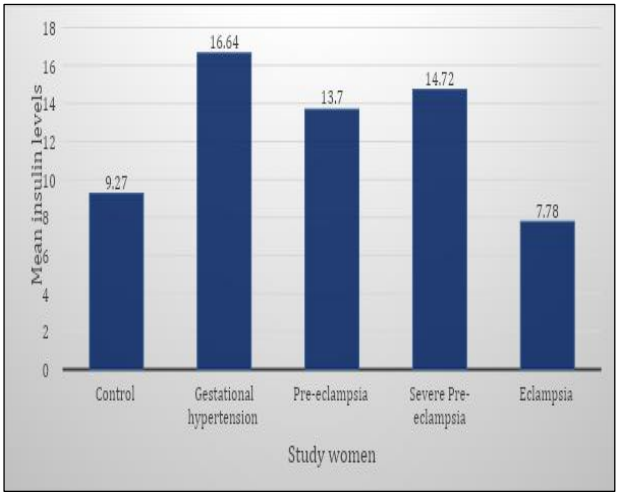

Figure 4: Fasting serum insulin level among various groups in the study.

DISCUSSION

Hypertensive disorders of pregnancy (HDP) is a pregnancy specific syndrome with significant maternal and fetal complications. A normal pregnancy is an immunocompromised diabetogenic state due to its various anatomical, physiological and biochemical changes required for the normal growth and development of the growing fetus. The changes in a normal pregnancy include development of insulin resistance, which increases as the pregnancy advances ensuring the adequate transfer of glucose, amino acids and fatty acids delivery to the fetus. Bauman et al first reported the association between the insulin levels and hypertension in pregnancy and documented that hypertensive patients were more hyperinsulinemic compared to normotensive patients.[10]

The insulin sensitivity decreases up to 50 percent as the pregnancy advances to third trimester. The Insulin resistance and the resultant hyperinsulinemia are the characteristics features that are evident in normal pregnancy that is especially maximally observed in the third trimester. These metabolic changes shunt the adequate nutrient supply to the developing fetus. As insulin resistance is highest in the pregnancy during the third trimester, pregnant women of 28-40 weeks of gestation were included in our study (controls=70, cases=30). Similarly, in a study by Fariedh et al, women of first trimester and third trimester were included for calculation of insulin resistance by HOMA-IR and the insulin resistance were calculated before and after the development of pre-eclampsia.[1] This study consisted of 47.8% of women who were more than 37 weeks of gestation at the time of sampling and is found to be the highest. Among the controls, 35.6 % of them being above 37 weeks period of gestation, constituting the highest among the controls and 26.7% of them being between 33-37 weeks period of gestation. Among the cases, most women belonged to gestational hypertension and with 10% of them being between 33 to 37 weeks constituting the highest among the cases. In a study by Hamaski et al, relationship between hyperinsulinemia and gestational hypertension was established.[11] Another study by Fuh et al, pre-eclamptic women were taken as cases and normotensive pregnant women as control.[12] Several other studies were done to know the relationship between preeclampsia and insulin resistance.[13,14,1] On the other hand, in this study we have women in different severities of hypertension. Among the cases of this study, 50% (n=15) were gestational hypertension, 20% (n=6) were pre-eclampsia, 23.3% (n=7) were severe pre-eclampsia and 6.6% (n=2) were eclampsia.

Age $\geq$35 years and <20 years are known risk factors for the development of HDP. Advanced maternal age is an independent risk factor for adverse outcomes in first-time mothers with preeclampsia.[15] The maximum number of women in our study were in the age group between 21-29 years 67.8% (n=61) in control and study groups. The mean age of the mother in the control group is found to be 26.57 and that of cases is 27.63 which is comparable with both the groups. The results obtained were statistically not significant.

Nulliparity is considered as a risk factor for development of hypertensive disorders of pregnancy. This is due to the fact that nulliparous pregnancies had higher circulating sFlt1 levels and sFlt1/PlGF ratios than multiparous pregnancies, suggesting an association with an angiogenic imbalance contributing to the development of HDP.[16] In the study population, the primigravida in the control group is found to be 58.3% (n=35) and of the study group is 50% (n=15). The multigravida women in the control group constituted 41.7% (n=25) and in the study group it is 50% (n=15). In this study, results obtained in regards with parity were statistically not significant.

Women with increased BMI are associated with the development of pre-eclampsia. Obesity increases the risk of preeclampsia about 3-fold and asymmetric dimethyl arginine (ADMA) is found to be an important endogenous inhibitor of nitric oxide synthase, which predisposes for the pathogenesis of pre-eclampsia.[17] Lucas et al stated that insulin may play a major role in the regulation of blood pressure in obesity.[18] A prospective study conducted by Thadani et al, involving >15 000 women, of whom 216 had gestational hypertension and 86 had preeclampsia.[19] When compared to lean women, the relative risk (age adjusted) was 1.9 for the development of preeclampsia and 2.2 for the gestational hypertension in the women with pre-pregnancy BMI $\geq$30 kg/m^2. In our study the mean BMI of the study group was 25.4380 that was slightly increased when compared to the control group with the mean BMI of 24.42. These results obtained were not statistically significant.

In HDP, there occurs dysregulation of P-IPG. This molecule is a second messenger of insulin playing an important role in the metabolic effects of insulin. Interestingly, in HDP women, an increased amount of P-IPG molecule is seen in amniotic fluid and cord blood. These molecular basis, has led to the hypothesis that increased insulin resistance is more common in women with hypertensive disorders of pregnancy (HDP) as compared to normotensive women. Lasko found fasting insulin level as a good marker of insulin resistance.[20]

In this study, the mean value of fasting serum insulin level was compared between the normotensive pregnant women and in women with hypertensive disorders of pregnancy. The mean fasting plasma insulin level among case was 15.0173 microU/mL that is found to be higher than that of the control group, with mean fasting serum insulin level of 9.2753 microU/mL and the results obtained were statistically significant with the p value of 0.000. This showed insulin resistance is more common in women with hypertensive disorders of pregnancy (HDP) as compared to normotensive women. These results are comparable with the nested case control study by Shoreh et al, with 16 pre-eclamptic women and 16 normotensive women comparing the fasting insulin levels in second and third trimester.[18] In pre-eclampsia women, the value 15.13±1.3 microU/mL obtained in the second trimester increased to 25.3±1.4 microU/mL in the third trimester, which was higher than the normotensive pregnant women with the value of 10.4±0.9 microU/mL and 16.2±13 microU/mL in the second and third trimester respectively. This study concluded that increase in insulin levels in the third trimester was greater in preeclamptic than in non-preeclamptic women and these results are very much similar to our study. Another study by Lei et al on 200 uncomplicated pregnant women and 33 pre-eclamptic women and the results showed fasting serum insulin value of 11.44±6.72 microU/mL in preeclampsia women and then 8.92±4.4 microU/mL in women with uncomplicated pregnancy.[21] These statistics are similar to our study findings. A case control study by Soloman et al, with 31

normotensive pregnant women and 31 pre eclamptic women, concluded higher fasting serum insulin level among the cases (13.3 microU/mL) than the controls (7.9 microU/mL) which was statistically significant.[19] These results were comparable with the results of our study. Similar to this study, Tripathy et al found elevated levels of fasting serum insulin level in pre-eclampsia women in comparison to normal pregnant women.[22] Another similar study by Fariedh et al, estimated the rate of insulin resistance using HOMA-IR and found significant difference in insulin resistance among the cases (HOME-IR =4.76) and the controls (HOME-IR 2.93) and the results were statistically significant.[1]

To conclude, insulin resistance is more common in hypertensive disorders of pregnancy as compared to normotensive women and this was emphasised in the present study with the supportive results.

CONCLUSION

The present study states that, women with hypertensive disorders of pregnancy tend to be more hyperinsulinemia than the normotensive pregnant women. It is also emphasised that the relationship between insulin resistance and hypertension is independent of age, BMI and parity. Thus the present study enlightens that the fasting serum insulin level was elevated in hypertensive disorders of pregnancy when compared to the normotensive pregnant women.

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