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Original Article

Obstetrics and Gynaecology Section

Comparison of Fasting Insulin Levels and Insulin Resistance Indices in Preeclamptic and Normotensive Pregnant Women: A Cross-sectional Study

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ABSTRACT

Introduction: Preeclampsia (PE), a pregnancy-specific disorder, is a leading cause of maternal and perinatal mortality. Women with PE exhibit significant hyperinsulinemia compared to normotensive women.

Aim: To determine the levels of Fasting plasma Insulin (FI) and Insulin Resistance (IR) in women with PE and normotensive women.

Materials and Methods: A cross-sectional study was conducted at Hindu Rao Hospital and North DMC Medical College, New Delhi, India from November 2020 to September 2021. Total 100 pregnant women (50 normotensive controls and 50 PE cases) were recruited. An oral glucose tolerance test with 75 grams of glucose was administered. Fasting plasma glucose (FPG), FI, and IR indices were calculated. Continuous variables of the case and control groups were compared using the t-test, and categorical variables were compared using the Chi-square test. A p-value of <0.05 was considered statistically significant.

Results: The mean Fasting Plasma Glucose (FPG) level in the normotensive group was 81.52±2.95 mg/dL, while it was 83.4±3.77 mg/dL in the PE group (p-value 0.007). The mean FI level in the normotensive group was 5.06±2.14 µunits/mL, compared to 27.41±3.09 µunits/mL in the PE group (p-value 0.001). The increase in mean FI level was statistically significant when Blood Pressure (BP) was ≥160/110 mmHg, with liver enzymes ≥80 IU/L, or with a platelet count ≤100,000/mL. The Quantitative Insulin Sensitivity Check Index (QUICKI) and Fast Glucose-to-Insulin Ratio (FGIR) were lower in the case group (p-value <0.001). Log FI was significantly higher in cases (p-value <0.001).

Conclusion: The FI levels were significantly increased in PE. FI and IR indices may serve as biomarkers of PE.

Keywords: Fasting glucose insulin ratio, Fasting plasma glucose, Hyperinsulinemia, Hypertensive disorders of pregnancy, Pregnancy

INTRODUCTION

The PE is a syndrome unique to pregnancy. Typically, the presentation includes hypertension in pregnancy, accompanied by significant proteinuria or end-organ damage. The global incidence of PE ranges from 1% to 9% [1-3]. It is one of the leading causes of maternal mortality and morbidity [4,5], accounting for 14% of maternal deaths [6]. The disease commonly presents in the third trimester, with characteristic post-delivery resolution. It is a multisystem disorder, affecting almost every organ system in the body. PE is characterised by vasospasm, endothelial dysfunction, and activation of the haemostatic system [7].

Despite various hypotheses over the decades, the exact aetiology of this disease remains an enigma! The pathogenesis is still unclear [5,8-10]. However, a common finding in the pathogenesis of all aspects of the multisystem damage exhibited in PE is endothelial cell injury and altered endothelial cell function [7].

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It is well-known that FI levels increase during pregnancy. These levels peak in the third trimester, likely due to elevated levels of several insulin-antagonistic hormones, such as human placental lactogen, progesterone, and corticotrophin-releasing hormones [10-13]. This associated hyperinsulinemia is exaggerated in pregnant women with PE, as evidenced by higher FI levels compared to normotensive pregnancy. The mechanism by which insulin regulates BP remains unclear. One possible mechanism is that insulin modulates intracellular cation pumps, increasing vascular tone and consequently, BP. Insulin also promotes renal tubular reabsorption of sodium; this resultant sodium and volume overload may contribute to hypertension [10]. Another hypothesis suggests that insulin may elevate BP by stimulating the sympathetic nervous system or inducing hypertrophy of vascular smooth muscle [10].

These findings indicate that IR and the resultant hyperinsulinemia are significant contributors to the development of hypertension in pregnancy [10-13]. This increased IR can be measured through simple tests, such as FI, the Quantitative Insulin Sensitivity Check Index (QUICKI), Log FI, and the fasting glucose-insulin ratio [14].

The association between IR and hypertension was first reported in 1966 [15], and numerous clinical and epidemiological studies have since confirmed this relationship [16-18]. According to these studies, hypertensive individuals tend to be more hyperinsulinemic compared to normotensive individuals. Furthermore, the relationship between IR and hypertension is independent of Body Mass Index (BMI), age, or the magnitude of glucose tolerance. There is a pressing need for a simple test that can serve as a biomarker to predict the severity of the disease. Such a test would facilitate increased surveillance, early transfer to a high-risk foetal-maternal unit, and timely delivery planning when necessary, ultimately reducing maternal morbidity and mortality [19]. FI and IR indices may serve as the needed biomarkers.

The present study was planned to test the hypothesis that FI levels are elevated in women with PE compared to normotensive women and to explore its association with the severity of PE.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Hindu Rao Hospital and North DMC Medical College in New Delhi, India, from November 2020 to September 2021. Prior to initiating the study, ethical clearance was obtained from the Institutional Ethical Committee (F.No: IEC/NDMC/2020/35). Informed consent was obtained from all study participants. Total 100 pregnant women with a gestational period of 28 weeks or more, meeting the inclusion criteria, were recruited for the study. The study was conducted during the Coronavirus Virus-2019 (COVID-19) pandemic.

Sample size: A convenient sample of 100 participants was taken.

Inclusion and Exclusion criteria: Pregnant women with a gestational period of 28 weeks or more who provided consent to participate. Women with PE were classified as cases, while women with normal BP were categorised as controls (systolic BP <140 mmHg and diastolic BP <90 mmHg). PE was defined according to the American College of Obstetricians and Gynecologists (ACOG) 2020 criteria [Table/Fig-1] [20]. Exclusion criteria included the presence of gestational or overt diabetes mellitus, chronic hypertension, liver or renal disorders, coagulopathies, collagen vascular disorders, abruptio placentae, and thrombocytopenia in normotensive women and women with abnormal OGTT results were excluded from the study.

Diagnostic criteria
Blood Pressure (BP) - Systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal BP - Systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 110 mmHg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy) And **Proteinuria** - 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection) or - Protein/creatinine ratio of 0.3 mg/dL or more or - Dipstick reading of 2+ (used only if other quantitative methods not available) **Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:** - Thrombocytopenia: Platelet count less than 100,000×10^9/L - Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease - Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration - Pulmonary oedema - New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

[Table/Fig-1]: Diagnostic criteria for preeclampsia [21].

Study Procedure

Cases were further divided into severe and non severe categories. Severe PE was defined according to the ACOG 2020 criteria [Table/Fig-2] [20]. A detailed history was taken from all participants, followed by a thorough examination. Blood Pressure (BP) was measured using a digital sphygmomanometer on the non dominant upper arm while the patient was sitting, after five minutes of rest.

Upon recruitment, a blood sample (after fasting for at-least six hours) was collected from the antecubital vein to test levels of FPG and FI. Following this, 75 grams of glucose was administered to all patients, consumed over 10 minutes. Plasma glucose levels were measured at one hour and two hours post-ingestion. The normal values for the Oral Glucose Tolerance Test (OGTT) in pregnancy, as per the International Association of Diabetes and Pregnancy Study Group (2010), were defined as fasting <92 mg/dL; at one hour <180 mg/dL; and at two hours <153 mg/dL [21]. The normal level of FI was set at <25 µIU/L [22]. FPG and FI were used to calculate indices for IR such as FGIR, QUICKI, and Log FI using the following formulas:

$$QUICKI = 1/(\log FPG \text{ in mg/dL} + \log FI \text{ in µIU/mL})$$

$$FGIR = FPG/FI.$$

Features
• Systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mmHg or more on two occasions at least four hours apart (unless antihypertensive therapy is initiated before this time) • Thrombocytopenia (platelet count less than 100,000×10^9/L • Impaired liver function that is not accounted for by alternative diagnoses and as indicated by abnormally elevated blood concentrations of liver enzymes (to more than twice the upper limit normal concentrations), or by severe persistent right upper quadrant or epigastric pain unresponsive to medications • Renal insufficiency (serum creatinine concentration more than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease) • Pulmonary oedema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses • Visual disturbances

[Table/Fig-2]: Preeclampsia with severe features [21].

STATISTICAL ANALYSIS

Statistical analysis of the collected data was performed using Statistical Packages of Social Sciences (SPSS) software version 20.0. Continuous variables of the case and control groups were compared using the t-test, while categorical variables were compared using the Chi-square test. A p-value <0.05 was considered statistically significant.

RESULTS

Among the cases, 26 (52%) were in the non severe group, and 24 (48%) were in the severe PE group. The mean age of women in the case group was 24.26±3.19 years, while in the control group, it was 24.38±4.02 years. In the non severe PE group, the mean age was 24.23±3.29 years, and in the severe PE group, it was 24.29±3.10 years [Table/Fig-3].

Parameters	Control group (n%)	Case non severe group (n%)	Case severe group (n%)	p-value
N (%)	50 (100%)	26 (52%)	24 (48%)	0.79#
Age (years) (mean±SD)	24.38±4.02	24.23±3.29	24.29±3.10	
Parity				
Primigravida	33 (66%)	17 (65.4%)	15 (62.5%)	0.51*
Gravida 2	14 (28%)	7 (26.9%)	7 (29.2%)	
Gravida 3	3 (6%)	2 (7.7%)	2 (8.3%)	
POG				
28-34 weeks	7 (14%)	8 (30.8%)	7 (29.2%)	
34-37 weeks	20 (40%)	7 (26.9%)	11 (45.8%)	
37 weeks	23 (46%)	11 (42.3%)	6 (25%)	
BMI (kg/m²) (mean±SD)	24.53±1.20	24.79±1.60	24.27±1.20	0.30#
Fasting Insulin (FI) (mean±SD) (µ/mL)	5.06±2.14	25.33±1.86	29.50±2.67	0.001#

[Table/Fig-3]: Demographic and baseline details of study subjects.
*Chi-square test, #t-test was used

The mean FI was elevated in the case group with severe features [Table/Fig-4]. As indicated in [Table/Fig-5], the values of QUICKI and FGIR were statistically lower in the case group (p-value <0.001). Log FI was higher in the case population, which is statistically significant (p-value <0.001). Log FI was also significantly higher in the severe PE group compared to the non severe PE group (p-value <0.001) [Table/Fig-6].

Parameters	n (%)	FI (mean±SD)	p-value*
Systolic blood pressure*			
140-159 mmHg	42 (84%)	26.53±2.55	<0.005
≥160 mmHg	8 (16%)	31.55±2.14	
Diastolic blood pressure			
90-109 mmHg	45 (90%)	26.92±2.91	<0.005
≥110 mmHg	5 (10%)	31.09±2.01	

Platelet levels			
<100000/mL	14 (28%)	30.07±3.04	0.0001
≥100000/mL	36 (72%)	26.27±2.41	
SGOT			
≥80 IU/L	20 (40%)	30.12±2.47	0.004
<80 IU/L	30 (60%)	25.48 ±1.80	
SGPT			
≥80 IU/L	19 (38%)	30.29±2.41	0.004
<80 IU/L	31 (62%)	25.52±1.02	
Creatinine			
≥1.1 mg/dL	9 (18%)	29.86±3.08	0.12
<1.1 mg/dL	41 (82%)	26.78±2.84	

[Table/Fig-4]: Comparison of mean insulin levels at different biomarkers of severe PE in case group.
*Chi-square test; SGOT: Serum glutamic-oxaloacetic transaminase; SGPT: Serum glutamic pyruvic transaminase

Insulin Resistance (IR) Indices	Cases (n=50)	Control (n=50)	p-value*
Fasting Plasma Glucose (FPG) (mean±SD) (mg/dL)	83.4±3.77	81.52±2.95	0.007
Fasting insulin (mean±SD) (μ/mL)	26.91±4.63	4.96±2.05	<0.001
QUICKI	0.3±0.02	0.39±0.03	<0.001
FGIR	3.61±3.72	19.59±8.57	<0.001
Log FI	1.42±0.15	0.66±0.18	<0.001

[Table/Fig-5]: Comparison of Insulin Resistance (IR) parameters in case and control.
*t-test. Values presented as mean±SD

Mean	Non severe PE	Severe PE	p-value*
QUICKI	0.3012	0.2947	0.007
FGIR	3.2945	2.8668	0.428
Log FI	1.4042	1.4688	<0.001

[Table/Fig-6]: Comparison of Insulin Resistance (IR) parameters in non severe and severe PE.
QUICKI=1/(log FPG in mg/dL+log FI in μIU/mL), FGIR=FPG/FI; *t-test

DISCUSSION

The PE is a complex condition encountered daily in antenatal clinics and labour rooms, making it one of the most intriguing problems in obstetrics. IR can be measured using QUICKI, FGIR, and Log FI. These indices can be calculated using simple tests like FPG and FI levels. Utilising two parameters (insulin and glucose) for calculating IR, as indicated in these formulas, is preferred due to their higher validity, as they represent the exchangeable kinetics between both parameters [23].

The mean age and BMI of the study population in the present study were similar to those in the study conducted by Sivalingam LP et al., where the mean age for cases and controls was 25.23±3.58 and 25.17±3.16 years, respectively [24]. The mean BMI was 28.25±2.68 kg/m^2 in the case group and 25.85±2.76 kg/m^2 in the control group [24].

The mean Period of Gestation (POG) was 35.3 weeks in the case group in the present study, similar to the studies conducted by Sonagra AD et al., [25] and Abhari FR et al., [14], who reported it as 34.03±3.46 weeks and 34.24 weeks, respectively. Laguado JS et al., reported the mean POG to be 22.6±5.5 weeks in women with hyperinsulinemia [26]. Most women in the present study were primigravida, similar to the findings of Hauth JC et al., [18]. However, in the study conducted by Abhari FR et al., the mean parity was reported as two [14].

The mean FI was 5.06±2.14 μU/L in the control group and 27.41±3.09 μU/L in the PE group, which was statistically significant (p-value <0.001). Sivalingam LP et al., Sonagra AD et al., and Laguado JS et al., also reported similar results, indicating statistically significant differences in the mean FI between the case and control groups [24-26].

The mean FPG in the control group was 81.52±2.95 mg/dL and 83.4±3.77 mg/dL in the PE group (statistically significant). This finding aligns with that reported by Sonagra AD et al., in their study [25]. Similarly, significant differences were reported by Ghosh A et al., and Stefanovic´ M et al., [27,28]. The elevation of FPG may be attributed to IR that is not compensated by hyperinsulinemia. These metabolic changes occur normally to meet the metabolic demands of the growing pregnancy. Even in normal pregnancy, mild IR is present in the form of higher plasma glucose and increased insulin secretion.

Ghosh A et al., reported that a decrease in microvascular blood flow was associated with elevations in anti-angiogenic mediators, which are linked to increased IR in women with PE. Hyperinsulinemia may directly predispose individuals to hypertension by increasing renal sodium reabsorption and stimulating the sympathetic nervous system. Elevated IR increases sympathetic tone, which may result in higher BP. It has been observed that drugs that reduce IR, such as thiazolidinediones, also lower BP. This suggests an association between IR and BP [27].

In the present study, IR was measured by QUICKI, FGIR, and Log FI in both the case and control groups. Both QUICKI and FGIR were significantly lower in the case group, indicating IR (statistically significant, p-value <0.001). Log FI was higher in the case group, which was also statistically significant (p-value <0.001). When compared between the non severe and severe PE groups, only Log FI was significantly elevated with the severity of the disease. The findings of the studies by Sonagra AD et al., and Parretti E et al., support the results of the present study [25,29].

Mean FI also increased with the severity of PE. Similar findings were reported by Sivalingam LP et al., and Sonagra AD et al., in their respective studies [24,25].

Elevated IR is associated with numerous maternal and foetal complications. IR also increases the risk of developing life-threatening medical disorders such as diabetes mellitus, hypertension, hyperlipideamia, and cardiovascular disorders later in life [16]. Sensitisation of these women at risk can lead to long-term measures for the prevention and early management of these diseases.

The strength of present study is that it was conducted in a tertiary care hospital serving all sectors of society, including both booked and unbooked women.

Limitation(s)

One limitation is the small sample size due to the COVID-19 pandemic. Future studies with larger sample sizes may be needed to confirm these findings and advocate the use of FI and IR indices as markers for the prediction of PE. Additionally, studies comparing FI and IR indices with other predictive factors may be undertaken.

CONCLUSION(S)

The IR and the resultant hyperinsulinemia are important factors in the development of hypertension in pregnancy. Determining IR and identifying susceptible women may allow for timely lifestyle and dietary modifications, thereby reducing the occurrence of serious complications.

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