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Markers of insulin resistance as predictors of hypertension in pregnancy

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Abstract
Introduction: Insulin resistance, which has been linked to essential hypertension, may play a role in hypertension during pregnancy. We aimed to study the serum markers of insulin resistance in the first 20 weeks of gestation and see their correlation with onset of hypertension in pregnancy.
Methodology: We designed a cross-sectional study of pregnant females who presented to the Obstetric clinic of Department of Obstetrics and Gynaecology, Topiwala National Medical College and BYL Nair Hospital, Mumbai from June 2011 till May 2014. All consecutive pregnant females who were in the first 20 weeks of gestation were included in the study. All subjects were investigated for serum markers of insulin resistance. These variables were compared among normotensive and hypertensive subjects and logistic regression analysis was done to identify predictors of hypertension in pregnancy.
Results: We included 300 patients in our study, of which we identified 24 patients with hypertension. Fasting insulin, Hemostatic Model Assessment for insulin resistance (HOMA-IR), high sensitivity C reactive protein (hs-CRP), serum cholesterol and tumour necrosis factor (TNF) alpha were significantly different between hypertensive and normotensive study subjects. Additionally, we found fasting inulin (OR = 3.91, p = 0.02), HOMA-IR (OR = 2.57, p = 0.04) and CRP levels (OR = 1.12, p<0.01) to be good predictors of developing hypertension in pregnancy.
Conclusions: Our study found that fasting insulin, HOMA-IR and hs-CRP were the significant predictors of hypertension in pregnancy. A multi-centric study with large sample size is needed to support our findings.
***Keywords*:** hypertension, preeclampsia, insulin resistance, outcomes

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I. Introduction

Hypertension is a common and morbid complication of pregnancy for which the pathogenesis remains unclear. Insulin resistance, which has been linked to essential hypertension, may play a role in hypertension during pregnancy.[1] Insulin resistance is a pathological situation characterized by lack of physiological response of peripheral tissue to insulin action resulting in metabolic and hemodynamic changes.[2] The usual onset of preeclampia and gestational hypertension in late pregnancy, a time when the insulin resistance is a physiological characteristic of pregnancy, is maximal and this supports a possible association. Postulated mechanisms through which insulin resistance might increase blood pressure in pregnancy, include sympathetic nervous system activation, renal sodium retention, increased cation transport, and associated endothelial dysfunction.[1]

Additionally, the metabolic abnormalities linked to the insulin resistance syndrome are observed in women with hypertension in pregnancy to a greater degree than in normotensive pregnant women. These include glucose intolerance, hyperinsulinemia, hyperlipidemia, tumor necrosis factor- alfa, fasting insulin, and sex hormone binding globulin.[2] These observations suggest the possibility that insulin resistance may be involved in the pathogenesis of hypertension in pregnancy and that approaches that improve insulin sensitivity might have benefit in the prevention or treatment of this syndrome, although this requires further study.In light of this, we aimed to study the serum markers of insulin resistance in the first 20 weeks of gestation and see their correlation with onset of hypertension in pregnancy.

II. Methodology

Study Design and Sample population

We designed a cross-sectional study of pregnant females who presented to the Obstetric clinic of Department of Obstetrics and Gynaecology, Topiwala National Medical College and BYL Nair Hospital, Mumbai from June 2011 till May 2014. All consecutive pregnant females who were in the first 20 weeks of gestation were included in the study. We excluded any known case of type 1 or type 2 diabetes mellitus, essential or pre-gestational hypertension, chronic renal failure, chronic liver failure, known malignancy or those

patients who were on corticosteroids. For the diagnosis of hypertension in pregnancy we used the American College Of Obstetrics and Gynecology criteria[3]: new onset of hypertension (blood pressure is >140mmHg systolic and/or >90mm Hg diastolic) occurring in pregnant woman after 20 weeks of gestation who is previously normotensive or proteinuria defined as urinary excretion of more than 0.3gms protein in 24 hours.

Biochemical testing

All subjects were investigated for fasting glucose level, fasting insulin, Homeostatic model assessment for insulin resistance (HOMA-IR), high sensitivity C reactive protein (hs-CRP), sex hormone binding globulin (SHBG), tumour necrosis factor-alpha (TNF-α) and serum cholesterol. Ten millilitres of blood was collected only once for these tests in fasting status. Fasting insulin was tested using chemiluminescence, hs-CRP, SHBG, TNF-α were tested by enzyme immunoassay and serum cholesterol by cholesterol oxidase peroxidase. HOMA-IR was calculated using standard formula.

Data Collection and Data Analysis

After obtaining approval of the institutional ethics committee, we collected information about socio-demographic profile like age, race, family medical history, personal history regarding menstrual cycle, smoking, sedentary life style, food habits and exercise. History of any other associated medical conditions like hypertension, chronic liver or renal failure, malignancy, steroid treatment was inquired as well. This was followed by general and physical examination. Gestational age was also noted for all study subjects. Patients underwent routine follow up as indicated in the antenatal period and were regularly followed up after 20 weeks of gestation for blood pressure measurement and urine albumin by dipstick method to screen onset of hypertension in pregnancy along with the other routine components of antenatal check up. Variables like fasting insulin, HOMA-IR, SHBG, hs-CRP, TNF-α, serum cholesterol were compared among normotensive and hypertensive subjects by unpaired T- test (Mann-Whitney test in those variables, who failed the test of normality. Logistic regression analysis was done to identify predictors of hypertension in pregnancy, p value less than 0.05 was taken as statistically significant.

III. Results

We included 300 patients in our study. The mean age in present study was 24.61 ± 4.02 (range 18 to 39) years. Most of the females (48.3%) were in age group of 21-25 years. Around 70% of the females belonged to Hindu community while rest were Muslims, 96.3% had regular menses, 41% subjects were primigravida. We identified 24 (8%) patients who developed hypertension during pregnancy, 75% of which were diagnosed before 32 weeks of gestation. Patients in both hypertensive and normotensive group had fasting insulin levels below 22μU/mL (Table 1). Majority of the patients had fasting blood sugar between 76 and 100 mg% and HOMA-IR levels below 6.5. CRP levels greater than 15mg/L were found in 11 hypertensive patients while most of the normotensive patients (95.3%) had CRP levels below 15 mg/L. As for SHBG, levels less than 200 mmol/L were found in 25% hypertensives as compared to 10% normotensives. Serum cholesterol levels greater than 250mg% were found in 2 of the 24 hypertensive patients, which is statistically not significant while all normotensive patients had serum cholesterol levels below 250 mg%. When we compared the means of different biochemical variables between the two groupswe found a significant difference across both groups in all variables except SHBG (Table 2). In our study population, we found fasting inulin (OR = 3.91, p value = 0.02), HOMA-IR (OR = 2.57, p value = 0.04) and CRP levels (OR = 1.12, p value <0.01) to be good predictors of developing hypertension in pregnancy (Table 3).

IV. Discussion

The mean fasting insulin levels in hypertensive and normotensive subjects in the present study were 17.3 μU/mL and 11.9 μU/mL respectively (OR = 3.9, $p < 0.05$). Peters et al reported that fasting insulin concentrations were higher in hypertensive group ($p<0.002$) and concluded that women who develop hypertension during pregnancy may be metabolically challenged at early stages of pregnancy with hyperinsulinism.[4] Sowers et al in a longitudinal study also concluded that hyperinsulinemia may be related to the development of preeclampsia.[5] The finding that elevated second-trimester insulin levels is associated with the development of preeclampsia supported the hypothesis that hyperinsulinemia and associated insulin resistance might contribute to the pathogenesis of preeclampsia. Our study also found higher HOMA -IR index to be associated with the development of hypertension in pregnancy . Romero-Gutiérrez G et al supported the use of the HOMA-IR as an alternative index for the assessment of the risk for hypertension during pregnancy.[6] In 2006, Parretti et al evaluated the role of HOMA-IR index in predicting the risk of subsequent preeclampsia.[7] In their study, preeclampsia developed in 6.4% of the pregnant women and correlated positively with the 75th centile of HOMA-IR (P=0.001), with a sensitivity of 79% and a specificity of 97% . Given their high sensitivity and specificity, this index could be useful in predicting the development of preeclampsia in early pregnancy, before the disease become clinically evident.

Our study did not find an association between SHBG levels and development of hypertension in pregnancy. Kevin Spencer et al in a study to investigate the role of first trimester maternal serum SHBG concentrations found that the levels between those with normal outcome and those who developed subsequent preeclampsia were not significantly different (p>0.05, OR-0.95).[8] However, Wolf M et al demonstrated, that compared with controls, women who developed preeclampsia had significantly reduced first trimester SHBG levels (302 ± 130 vs. 396 ± 186 mmol/L; p value < 0.01).[9] After adjusting for covariates in a multiple logistic regression model, the association remained significant (OR = 0.65). They concluded that first trimester SHBG levels may be a useful biomarker for preeclampsia. In addition, we found the mean CRP levels in hypertensive and normotensive subjects to be significantly different (OR-1.12, p<0.05).Similar to our findings, Tjoa et al also reported that the mean CRP levels were significantly elevated (p=0.031) in women who later developed preeclampsia (mean = 15.8 mg/L) when compared with normotensive women (mean = 7.2 mg/L).[10]

Although our study could not demonstrate a significant association between serum cholesterol and development of hypertension, previous literature has suggested that high cholesterol can predict development of preeclampsia. A univariate analysis done by Dey et al revealed that there was statistically significant difference between the serum levels of cholesterol between normal and pre-eclampsia cases at 18-20 week (197.7 mg% vs 229.6 mg%), even after adjusting for covariates in a multiple logistic regression model.[11]Furthermore, Enquobahrie et al reported higher concentrations of LDL cholesterol, triglycerides, and LDL/HDL ratios in patients who developed hypertension during pregnancy.[12] Additionally, we found a non-significant association TNF- α levels and development of hypertension in pregnancy. Similar observations were made by Serinet al in their prospective study.[13]

V. Conclusion

Hypertension is a common and morbid pregnancy complication for which the pathogenesis remains unclear. Insulin resistance, which has been linked to essential hypertension, may play a role in hypertension in pregnancy. Our study found that fasting Insulin, HOMA-IR and hs-CRP were the significant predictors of hypertension in pregnancy. A multi-centric study with large sample size is needed to support our findings.

Table 1. Comparison of biochemical variables in hypertensive and normotensive patients

Variables	**Hypertensive (n=24)**	**Normotensive (n=276)**
Fasting Insulin level (μU/mL)		
2-12	7	187
13-22	10	71
23-32	7	10
33-42	0	7
43-52	0	1
Fasting blood sugar (mg%)		
50-75	3	107
76-100	17	166
101-125	4	3
Hemostatic Model Assessment for insulin resistance		
0-2.5	8	199
2.6-5	8	60
5.1-7.5	7	11
7.6-10	1	5
10.1-12.5	0	1
C-reactive protein (mg/L)		
0-15	14	263
16-30	3	9
31-45	4	2
46-60	3	2
Sex Hormone Binding Globulin (mmol/L)		
0-200	6	28
201-400	8	114
401-600	10	118
601-800	0	14
801-1000	0	2
Serum cholesterol level (mg%)		
50-150	5	108
151-250	17	168
251-300	2	0

Tumor Necrosis Factor-alpha (pg/dL)		
1-20	21	268
21-40	2	7
41-60	0	0
61-80	1	0
81-100	0	1

Table 2. Comparison of mean values of various biochemical markers in the patients

Variable	**Hypertensive**		**Normotensive**		**p value**
	Mean	SD	Mean	SD	
Fasting Insulin level (μU/mL)	17.32	7.73	11.90	6.44	<0.01
HOMA-IR	3.87	1.96	2.36	1.46	<0.01
SHBG (mmol/L)	330.78	120.50	383.07	134.59	0.06
CRP (mg/L)	21.09	16.43	7.14	6.44	<0.01
Serum cholesterol (mg%)	186.13	47.24	157.19	24.54	<0.01
TNF-α (pg/mL)	13.30	11.20	9.46	5.92	<0.01

SD: Standard Deviation; HOMA-IR: Hemostatic Model Assessment for insulin resistance; SHBG: Sex hormone binding globulin; CRP: C reactive protein; TNF-α: Tumor necrosis factor-alpha

Table 3. Predictors of hypertension in pregnancy in our study population

Variable	**Odds Ratio**	**p value**
Fasting Insulin level	3.91	0.02
Hemostatic Model Assessment for insulin resistance	2.57	0.04
Sex hormone binding globulin	1.00	0.63
C reactive protein	1.12	<0.01
Serum cholesterol	1.04	0.21
Tumor necrosis factor-alpha	1.02	0.61

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Dr.Roza Bardeskar Markers of insulin resistance as predictors of hypertension in pregnancy." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.11 (2017): 27-30.