Original Research Article

Implication of Lipid and Fasting Blood Glucose in Hypertensive Pregnant Women in Nigeria

Comment [D1]: Type of study should be reflected in title

Comment [D2]: Many grammatical errors through the whole manuscript…..correct them

ABSTRACT

Background: Early pregnancy dyslipidemia is associated with an increased risk of Preeclampsia. Women with a history of preeclampsia have significant differences in lipid profile and an increased susceptibility to lipoprotein oxidation when compared with women who had normal pregnancy. Disorders of lipoprotein metabolism are reported to be a major cause of hypertension in preeclampsia.

Aim: This study was therefore aimed at evaluating the implication of lipid and glucose in hypertensive disorders of pregnancy (HDP) in Nigerian women**.**

Methodology: The study was a prospective cohort study. The participants were pregnant women attending the clinics for antenatal care in four different tertiary health facilities in Nigeria. A total of 521 participants were enrolled in the study out of which 34 developed different types of HDP. After an overnight fast, about 12 millilitres of venous blood sample was collected aseptically from the antecubital vein of each participant without HDP at baseline, second trimester, third trimester and those with HDP at point of development of hypertension respectively. Fasting blood glucose and lipid profile were assayed.

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Results: In the hypertensive women, the mean values of fasting plasma glucose, and lipid profile peaked at second and decline at third trimester respectively. Whereas in the normotensive women, there was a gradual increase in the mean values of triglyceride while fasting plasma glucose was gradually decreasing from first, second to third trimesters. The mean values of total cholesterol, HDL-C and LDL-C were gradually increasing from first trimester, peaked at second and decline at third trimester respectively.

Conclusion: The results of this present study showed that perturbations in lipid profile and fasting blood glucose were implicated in hypertensive disorders in pregnancy in Nigerian women. Early estimation of fasting plasma glucose and lipid profile in women with systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥ 80 mmHg at first antenatal booking seem to be useful in the prediction of subsequent development of hypertensive disorders during pregnancy.

Keywords: *Dyslipidemia; fasting blood glucose, hypertensive disorders in pregnancy; lipoprotein.*

1. INTRODUCTION

Normal pregnancy is associated with predicted changes in lipid metabolism and increases in lipid concentration as gestation progresses [1,2]. During the first trimester, there is marked deposition and hypertrophy of maternal adipocytes with increased expression of insulin receptors such that glucose is available to meet the metabolic demand of the growing fetus [3]. Increase in maternal insulin in addition to production of progesterone leads to lipogenesis with diminished lipolysis, and increased production of lipids, which then are transported across the placenta and metabolized; this signifies the essential role of lipids to normal fetal development [2].

One of the causal factors for perinatal morbidity and mortality could be the maternal atherogenic lipid profile early in pregnancy. During normal pregnancy, women show an increase in lipid levels, including levels of triglycerides (TG) and total cholesterol (TC) as gestational age progresses [4]. Both TG and TC are taken up by the placenta and metabolized and transported to the fetus in various forms; this shows that both lipids are essential for the development of the fetus [5]. However, high levels of maternal TC and/or TG are associated with preterm birth (PTB), pregnancy-induced hypertension (PIH), preeclampsia, and large for gestational age [6,7]. Conversely, decreased levels of TC during pregnancy are associated with PTB and an increased risk of the infant to be born small for gestational age [2,8].

Obesity and pre-pregnancy overweight are important risk factors for hypertensive disorders of pregnancy [9-11]. Maternal obesity is associated with a complex interplay of metabolic abnormalities including hypertension, insulin resistance, dyslipidaemia, hypercoagulability, impaired endothelial function, inflammatory up-regulation and altered adipokine profiles [7,12].

The ability to predict pregnancies at high risk of developing HDP is a major challenge [13]. Early biomarkers that reflect the underlying pathology of the disease are lacking and diagnosis is based solely on the clinical presentation [14]. Several factors have been implicated in the pathogenesis of HDP. These include: maternal age, parity, obesity, metabolic syndrome, previous history of HDP, family history of HDP, pre-existing diabetes, renal disease, antiphospholipid syndrome impaired glucose tolerance and dyslipidemia with African American race [15-18].

It has been shown that lipids accumulate in arterial intima cells causing endothelial dysfunction and an altered lipid profile leads to a decrease in the prostacyclin: thromboxane ratio which is an important pathway in the pathogenesis of pregnancy induced hypertension [19]. Increase in small dense LDL and triglycerides may also contribute to impaired endothelial function [20]. In pregnancy, perturbation in lipid profile is associated with poor perinatal outcomes and preterm birth [21].

Normal pregnancy is a carbohydrate-intolerant state characterised by a progressive increase by the dose response of insulin to glucose, suggesting that women who are pregnant become insulin resistant with the duration of gestation. Pre-existing hyperinsulinaemia and/or hyperglycaemia has been documented in early or mid-pregnancy, before the development of preeclampsia, gestational hypertension or both women with pregnancy induced hypertension during the third trimester of pregnancy displayed marked hyperinsulinism in response to an oral glucose tolerance test (OGTT) compared with normotensive controls [22].

Hyperinsulinemia and insulin resistance are hallmarks of normal pregnancy [17]. Insulin resistance increases during pregnancy, peaks in the third trimester and rapidly returns to pre-pregnancy levels after delivery. The basis of the insulin resistance seen in normal pregnancy is not well understood. Various hormonal changes of pregnancy have been implicated including human placental lactogen, cortisol, progesterone, and estrogen [23]. Insulin resistance is associated with hyperglycemia, hyperinsulinemia and dyslipidemia [24]. It has been recognized that the insulin resistance syndrome also may involve other metabolic abnormalities, including increased concentrations of plasminogen activator inhibitor (PAI)-1, leptin, and tumor necrosis factor-a (TNF-a) [24]. Although these markers are surrogate measures of insulin sensitivity, observed associations between many of these markers and pregnancy induced hypertension risk further suggest a role for insulin resistance in the development of pregnancy induced hypertension [25]. Negrato *et al.* [23] indicated a strong association between glucose intolerance, insulin resistance and subsequent development of hypertension in pregnancy, particularly the preeclampsia subtype.

Indices of metabolic syndrome (insulin resistance, impaired glucose tolerance and

dyslipidaemia) have been related to the development of cardiovascular disease in pregnant women with hypertensive diseases [26,27]. Insulin resistance is correlated positively with HDP [25]. In Nigeria, Isezuo and Ekele [28] demonstrated metabolic syndrome in a cohort of pregnant women with eclampsia. They suggested that markers of metabolic syndrome might be useful in screening for eclampsia among pre-eclamptic women. An increase in plasma antiphospholipids antibodies has been implicated in the pathogenesis and incidence of pre-eclampsia -eclampsia but poorly understood [29,30].

Furthermore, changes in lipid metabolism may contribute towards the endothelial lesions observed in preeclampsia. The severity of both hypertension and proteinuria seems to reflect the degree of endothelial damage [31]. The possible correlation between the altered lipid profile and the severity of renal lesions, as reflected by proteinuria, may contribute towards clarify the complex pathophysiology of preeclampsia [32].

Although it is still unclear whether hypertriglyceridemia becomes a risk factor for preeclampsia or whether there is any causal association between them, high triglyceride levels seem to increase the risk of placental vascular disorders, which trigger endothelial dysfunction, atherosclerosis and thrombosis [33]. The development of atherosclerosis in the placental spiral arteries of preeclamptic women indicates that elevated levels of triglycerides are involved in this disorder. The fact that the patients with preeclampsia presented dyslipidemia, characterized by high levels of triglycerides and VLDL, indicates that there are common interfaces between preeclampsia and the endothelial lesions that occur in atherosclerosis [32].

Early pregnancy dyslipidemia is associated with an increased risk of Preeclampsia [34]. Women with a history of preeclampsia have significant differences in lipid parameters and an increased susceptibility to lipoprotein oxidation when compared with women who had normal pregnancy [35]. Disorders of lipoprotein metabolism are reported to be a major cause of hypertension and proteinuria in preeclampsia [36]. This study was therefore aimed at evaluating the implication of lipid and glucose in hypertensive disorders in pregnant women from Ekiti and Oyo states, Nigeria

2.0 MATERIALS AND METHODS

2.1 Study Design

The study was a prospective cohort study. The participants were pregnant women attending the clinics for antenatal care in four different tertiary health facilities in Nigeria, namely: Ekiti State University Teaching Hospital, Ado-Ekiti, Federal Medical Centre, Ido-Ekiti, University College Hospital, Ibadan and Adeoyo Maternity Hospital, Ibadan. The hospitals are the major referral centres and therefore attract people from different part of the area. Participants were recruited from June 2011 to October 2012 and involved women at first visit (booking day) without hypertension in their first or second trimester of pregnancy and were followed up to delivery.

2.2 Inclusion Criteria

Inclusion criteria include women first seen at first or second trimester (< 20 weeks at booking) with systolic blood pressure below 140 mm/Hg and diastolic blood pressure below 90 mm/Hg and participants that gave consent.

Comment [D4]: Specify which type of consent?.....Verbal or written?

2.3 Exclusion criteria

Exclusion criteria include pregnant women first seen at ≥20 weeks of pregnancy, women who are already hypertensive at entry into the study or had proteinuria by the dipstick measurement greater than 300 mg/L (1+).

Comment [D5]: Any specific age limit is there?

2.4 Ethical Consideration

The ethical approval for the study was obtained from the University of Ibadan/University College Hospital (UI/UCH) Joint Ethics Committee Ibadan, Oyo State, Nigeria. (UI/UCH EC Registration Number: NHREC/05/01/2008a; UI/UCH Ethics Committee assigned number:

UI/EC/10/0195). A written informed consent was obtained from each participant before recruitment into the study.

2.5 Study population

A total of 521 participants were enrolled in the study out of which 34 developed different types of HDP. The remaining 487 which were referred to as censored (those who did not develop HDP till the end of the study period, those whose outcome of pregnancy were not known till the end of the study period, those who were lost for follow up and those who dropped out from the study for reasons unrelated to the study), 50 were lost for follow-up whose outcomes of pregnancy were not known. The remaining 437 were normotensive till the end of the study period. The various trimester of follow-up for both hypertensive and normotensive women are shown in table 1.

Socio-demographic characteristics of the study population- age, place of residence, marital status, educational background, occupation, ethnic group, diet history and social history, family history, past medical history/medication and gynaecological/obstetrical history were obtained from each participant through a semi pretest questionnaire.

Table 1: Summary of Participant's Recruitment

Event	Normotensive n=487	Hypertensive n=34	Total n=521
Yes	0	34 (100.0%)	34
No (Normotensive)	437 (89.7%)	0	437
Lost for follow-up	50 (10.3%)	0	50
Trimester			
1, 2 & 3	69 (14.2%)	9 (26.5%)	78
2 & 3	64 (13.1%)	8 (23.5%)	72
1 & 2	26 (5.3%)	3 (8.8%)	29
1 & 3	69 (14.2%)	4 (11.8%)	73
1	158 (32.4%)	0	158
2	101 (20.7%)	10 (29.4%)	111

Values are in number of participants with percentage in parenthesis, % = percent, n= number of participants, HDP = hypertensive disorders, 1= first trimester, 2= second trimester, 3= third trimester

2.6 Sample Collection

After an overnight fast (10-12 hrs), about 10 millilitres of venous blood sample was collected aseptically from the antecubital vein of each participant without HDP at baseline, second trimester, third trimester and those with HDP at point of development of hypertension respectively. Prior to their scheduled second and third trimester visits, reminder telephone calls were made to each participant. Blood samples collected were dispensed into fluoride oxalate bottles and EDTA-containing sample bottles to obtain plasma after centrifugation at 4000 rpm for 5 minutes. . Plasma obtained were stored in small aliquots at -20°C until analysed.

2.7 Determination of Fasting Plasma Glucose

Fasting plasma glucose was determined by glucose oxidase method, as described by Barham and Trinder [37] (Dialab, Austria)

2.8 Determination of Lipid profile

The plasma triglyceride concentration was determined using the enzymatic method as described by Owoade *et al*. [38] (Randox, United Kingdom). The plasma cholesterol concentration was determined using the enzymatic method as described by Trinder [39] (Randox, United Kingdom). The plasma high density lipoprotein cholesterol determination was carried out using the enzymatic method as described by Frieldwald *et al*. [40] (Randox, United Kingdom). Low density lipoprotein concentration was calculated using Friedewald's formula [40].

2.9 Statistical Analysis

Statistical Package of Social Sciences (SPSS) software version 22.0 (SPP, Inc, Richmond, CA) was employed for analysis of data from study population. Paired student's t-test was used to test the significance of difference between mean values. Analysis of variance (ANOVA) was used to test the significance of variations among group means. Post-Hoc was used for comparison of multiple variable. The relationship between all the variables was assessed by Pearson correlation coefficient. Chi square analysis was used for comparison of means for qualitative (non- quantitative) variables. Survival analysis (time to event analysis) was employed using Cox proportional hazard regression model analysis as the technique to measure the survival and hazard function. A two sided probability value $p<0.05$ was considered statistically significant. Values are reported as mean ± standard deviation or standard error of mean as appropriate.

3. RESULTS

Table 2 shows the lipid profile and fasting blood glucose of hypertensive women in the three trimesters. Significant differences were observed in all the parameters when compared using ANOVA. None of the parameters was statistically significant when comparing first and second trimesters. The mean values of fasting plasma glucose, and lipids (triglycerides, total cholesterol, HDL-C and LDL-C) peaked at second and decline at third trimester respectively. Table 3 shows the lipid profile and fasting blood glucose of normotensive women in the three trimesters. Significant differences were observed in all the parameters using ANOVA. There was a gradual increase in the mean values of triglyceride while fasting plasma glucose was gradually decreasing from first, second to third trimesters. The mean values of total cholesterol, HDL-C and LDL-C were gradually increasing from first trimester, peaked at second and decline at third trimester respectively.

Table 4 shows adjusted cox regression of the lipid profile and fasting blood glucose in women with HDP during first trimester. No significant difference was observed in the lipid profile and fasting blood glucose. Table 5 shows adjusted cox regression of the lipid profile and fasting blood glucose in the women with HDP during second trimester. An increase in LDL-C of 1.0 will be associated with a 1.3 fold increase in development of HDP in second trimester of pregnancy. For each additional unit of LDLC, development of HDP is 1.3 times higher (HR =1.284, B coefficient = 0.217). In lipids, development of HDP is reduced by 2.4% [100%- (100% X 0.976)] and 33.0% [100%- (100% X 0.770)] for each additional unit of triglycerides and total cholesterol respectively. (HR =0.976 and 0.770). The negative B coefficient means that higher values of triglycerides and total cholesterol in HDP women will be associated with lower risk of development of HDP in second trimester of pregnancy (B coefficient = -0.024 and -0.262).

In table 6, adjusted cox regression of the lipid profile and fasting blood glucose in women with HDP during second trimester is shown. After controlling or adjusting for all the biochemical parameters, fasting plasma glucose, was statistically significant (p= 0.043). An increase in fasting plasma glucose of 1.0 will be associated with a 1.1 fold increase in development of HDP in second trimester of pregnancy. That is for each additional unit of fasting plasma glucose, development of HDP is 1.053 times higher (HR =1.053, B coefficient = 0.639). Table 7 shows un-adjusted cox regression of the lipid profile and fasting blood glucose in women with HDP.

Table 2: Lipid Profile and Fasting Blood Glucose in Women with Hypertensive Disorders in Pregnancy

Index	1st trimester n=10	2nd trimester n=10	3rd trimester n=10	P1	P2	P3	P4

TG (mg/dL)	70.4±8.7	86.6±16.7	80.4±13.0	0.000*	0.425	0.774	0.629
TC (mg/dL)	155.8±10.4	191.2±17.0	174.4±12.0	0.000*	0.128	0.468	0.347
HDL (mg/dL)	52.2±5.6	65.0±6.2	59.2±10.3	0.000*	0.119	0.685	0.570
LDL (mg/dL)	89.5±10.6	108.9±11.8	99.3±13.6	0.000*	0.326	0.577	0.538
FPG (mg/dL)	65.8±5.5	76.1±4.1	74.5±6.7	0.000*	0.149	0.809	0.332

Values are reported as means ± standard error of mean, P1 =values obtained from ANOVA, P2=values compared between 1st and 2nd trimester, P3=values compared between 2nd and 3rd trimester, P4=values compared between 1st and 3rd trimester, TG = Triglyceride, TC = Total cholesterol, HDL = High density lipoprotein, LDL = Low density lipoprotein, FPG = Fasting plasma glucose, n = number of participants, * = significant at $p < 0.05$ (2-tailed), p = significant level.

Table 3: Lipid Profile and Fasting Blood Glucose in Normotensive Pregnant Women.

Index	N	1st trimester	2nd trimester	3rd trimester	P1	P2	P3	P4
TG (mg/dL)	58	73.6±4.3	79.8±6.5	100.6±6.5	0.000*	0.422	0.017*	0.001*
TC (mg/dL)	58	157.1±4.1	184.4±6.7	178.5±6.8	0.000*	0.000*	0.482	0.006*
HDL (mg/dL)	58	46.9±2.3	70.6±4.7	70.0±5.3	0.000*	0.000*	0.933	0.000*
LDL (mg/dL)	58	95.1±3.9	98.0±6.8	89.2±5.6	0.000*	0.694	0.311	0.360
FPG (mg/dL)	82	78.1±2.6	73.0±1.4	71.4±1.5	0.000*	0.081	0.472	0.016*

Values are reported as means ± standard error of mean, P1 =values obtained from ANOVA, P2=values compared between 1st and 2nd trimester, P3=values compared between 2nd and 3rd trimester, P4=values compared between 1st and 3rd trimester, TG = Triglyceride, TC = Total cholesterol, HDL = High density lipoprotein, LDL = Low density lipoprotein, FPG = Fasting plasma glucose, n=number of participants, * = significant at $p < 0.05$ (2-tailed), p = significant level.

Table 4: Adjusted Cox Regression of Lipid Profile and Fasting Blood Glucose in Women with Hypertensive Disorders in Pregnancy during 1st Trimester

Index	B coefficient	Hazard ratio	Confidence interval: Lower	Upper	p-value
Glucose (mg/dl)	-0.007	1.009	0.994	0.967	1.021
Triglyceride (mg/dl)	-0.031	0.840	0.969	0.612	1.534
Total cholesterol (mg/dl)	0.271	2.593	1.311	0.132	13.033
HDL (mg/dl)	-0.270	0.388	0.763	0.077	7.560

LDL (mg/dl)	-0.257	0.387	0.773	0.078	7.683

*= significant at p<0.05, p= significant level, HDL = High density lipoprotein, LDL = Low density lipoprotein

Table 5: Adjusted Cox Regression of Lipid Profile and Fasting Blood Glucose in Women with Hypertensive Disorders in Pregnancy during 2nd Trimester (Without HDL)

Index	B coefficient	Hazard ratio	Confidence interval: Lower	Upper	p-value
Glucose (mg/dl)	0.069	1.072	0.997	1.152	0.060
Triglyceride (mg/dl)	-0.024	0.976	0.955	0.998	0.031*
Total cholesterol (mg/dl)	-0.262	0.770	0.624	0.950	0.015*
LDL (mg/dl)	0.250	1.284	1.044	1.579	0.018*

*= significant at p<0.05, p= significant level, LDL = Low density lipoprotein

Table 6: Adjusted Cox Regression of Lipid Profile and Fasting Blood Glucose in Women with Hypertensive Disorders in Pregnancy during 2nd Trimester

Index	B coefficient	Hazard ratio	Confidence interval: Lower	Upper	p-value
Glucose (mg/dl)	0.052	1.053	1.002	1.108	0.043*
Triglyceride (mg/dl)	-0.008	0.992	0.830	1.186	0.933
Total cholesterol (mg/dl)	-0.002	0.998	0.409	2.436	0.997
HDL (mg/dl)	-0.019	0.981	0.404	2.380	0.966
LDL (mg/dl)	-0.005	0.995	0.406	2.436	0.991

*= significant at p<0.05, p= significant level, HDL = High density lipoprotein, LDL = Low density lipoprotein

Table 7: Un-adjusted Cox Regression of Lipid Profile and Fasting Blood Glucose in Women with HDP

Index	B coefficient	Hazard ratio	Confidence interval: Lower	Upper	p-value
Glucose 1	-0.010	0.990	0.971	1.009	0.305

Glucose 2	0.011	1.011	0.994	1.028	0.210
Triglyceride 1	0.005	1.005	0.993	1.016	0.417
Triglyceride 2	-0.002	0.998	0.989	1.008	0.730
Total cholesterol 1	-0.003	0.997	0.986	1.008	0.616
Total cholesterol 2	-0.003	0.997	0.988	1.006	0.545
High density lipoprotein1	0.009	1.009	0.987	1.031	0.434
High density lipoprotein 2	-0.001	0.999	0.986	1.012	0.904
Low density lipoprotein 1	-0.005	0.995	0.984	1.007	0.406
Low density lipoprotein 2	-0.003	0.997	0.988	1.005	0.452

*= significant at p<0.05, p= significant level, 1= first trimester, 2= second trimester, 3= third trimester

4. DISCUSSION

One of the causal factors of perinatal morbidity and mortality could be the maternal atherogenic lipid profile early in pregnancy [41]. During normal pregnancy, women show an increase in lipid levels, including levels of triglycerides (TG) and total cholesterol (TC) as gestational age progresses [2,41]. Both TG and TC are taken up by the placenta, metabolized and transported to the foetus in various forms. This shows that both lipids are essential for the development of the foetus [2,5]. However, high levels of maternal TC and/or TG are associated with HDP and preterm birth [2,36].

In this study, only triglycerides significantly increased at second and third trimester of pregnancy among the normotensive women. Total cholesterol, high density lipoprotein cholesterol (HDLC) and low density lipoprotein cholesterol (LDLC) significantly peaked at second trimester and declined at third trimester in both hypertensive and normotensive women. In normotensive women, significant increases in mean differences of total cholesterol and HDLC between first and second trimester, and of triglycerides when second and third trimesters were compared were observed. Similarly, the comparison of first and third trimester revealed significant increases in triglycerides, total cholesterol and HDLC among the normotensive women. No significant mean difference was observed in the lipids (triglycerides, total cholesterol, HDLC and LDLC) when first, second and third trimesters were compared among the hypertensive women.

In this study, triglycerides, total cholesterol and LDLC were observed as biomarkers and predictors of hypertensive disorders of pregnancy (HDP) in the second trimester of pregnancy. While LDLC is a risk factor, triglycerides and total cholesterol are positive factors of HDP development in the second trimester. Development of HDP was reduced by 2.4% and 33.0% for each additional unit of triglycerides and total cholesterol respectively. Higher values of triglycerides and total cholesterol in HDP women will be associated with lower risk of development of HDP in second trimester of pregnancy (B coefficient = -0.024 and -0.262). On the osssssther hand, for each additional unit of LDLC, development of HDP is 1.284 times higher in the second trimester of pregnancy (HR =1.284, B coefficient = 0.217). The highest mean values were significantly observed in the second trimester in all lipid fractions of hypertensive women (p<0.05).

The findings of this present study are similar to previous reports of positive association between maternal lipid profile and pregnancy outcome [42,43]. However, some previous studies reported negative association between maternal lipid profile and pregnancy outcome [2,19,36]. These conflicting results might (in part) be explained by differences in research design [e.g. case-control studies [42,43] versus cohort studies [7,44], small sample size [7,43], incomplete adjustment for confounders [43,44], or differences in study populations [42,43,45].

Insulin is an anabolic hormone that plays an important role in the regulation of glucose, lipid

homeostasis and energy storage through its metabolic effects on classic insulin-responsive tissues [46]. Specifically, insulin promotes the storage of glucose as glycogen in liver and skeletal muscles, and facilitates deposition of fatty acids in the form of triglycerides in adipose tissue [47]. During insulin resistance, insulin-mediated anabolic metabolic effects are inhibited in the classic insulin-responsive tissues. In physiological condition insulin stimulates endothelial nitric oxide production to exert a vasorelaxation and anti-inflammatory effect [24]. Whereas, in the state of insulin resistance, the insulin-stimulated nitric oxide pathway is selectively impaired and the compensatory hyperinsulinemia may activate Nitrogen-Activated Protein Kinase (MAPK) pathway, resulting in enhancement of vasoconstriction, pro-inflammation, increased sodium and water retention and the elevation of blood pressure [24].

5. CONCLUSION

The results of this present study showed that perturbations in lipid profile and fasting blood glucose were implicated in hypertensive disorders during pregnancy in Nigerian women. Early estimation of fasting plasma glucose and lipid profile in women with systolic blood pressure ≥130 mmHg and diastolic blood pressure ≥ 80 mmHg at first antenatal booking seem to be useful in the prediction of subsequent development of hypertensive disorders in pregnancy.

Comment [D6]: Provide the limitations of the present study ….also provide the further scope

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