Original Research Article

First trimester serum vitamin D, hs-CRP and second trimester uterine artery diastolic notching in predicting gestational hypertension and preeclampsia

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ABSTRACT

Background: Gestational hypertension and preeclampsia is one of the leading causes of maternal and fetal morbidity and mortality. The objective of this study was to study prediction of gestational hypertension/preeclampsia by using first trimester serum vitamin D and hs-CRP and second trimester uterine artery diastolic notching.

Methods: It was an observational study conducted in the departments of obstetrics and gynaecology, clinical biochemistry and radiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India. All pregnant women with 11 to 14 weeks gestational age attending antenatal clinic between October 2012 and June 2013 were enrolled in the study. A detailed history including history of the duration of sun exposure was taken and a general physical examination including obstetrical examination was done at every visit. Serum sample were taken for hs-CRP and vitamin-D levels at 11-14 weeks. Uterine artery colour doppler study was done between 22-24 weeks for uterine artery diastolic notching. The main outcome measures were development of gestational hypertension/ preeclampsia/ eclampsia.

Results: The mean vitamin D levels were significantly lower and mean hs-CRP levels were significantly higher in the hypertensive group as compared to the normotensive group, p=0.001 and p=0.004, respectively. Significant number women who developed hypertension had unilateral (46.2%) or bilateral (20.4%) uterine artery diastolic notching, p=0.005 and p=0.000, respectively. Crude’s odds ratio of uterine artery diastolic notching for prediction of hypertension in pregnancy was high, 9.894, 95% CI, 3.273-29.907 as compared to vitamin D (<13.5 ng/ml) and hs-CRP (>9.15 mg/L), 2.859, 95% CI, 1.418-5.763 and 7.16, 95% CI, 3.33-15.397.

Conclusions: Uterine artery diastolic notching in the early second trimester is found to be the best predictor of PE followed by first trimester hs-CRP and vitamin D.

Keywords: Gestational hypertension, hs-C reactive protein, Preeclampsia, Prediction, Uterine artery doppler, Vitamin D

INTRODUCTION

Gestational hypertension and preeclampsia (GHT/PE) complicate approximately 5-10% of pregnancies, incidence of it, in India is 8-10%.¹² It is one of the leading causes of maternal and fetal complications.³ It also directly or indirectly contributes to a significant number of maternal deaths.⁴ Even with advancements in the obstetric care, it is not possible to accurately predict which women can develop this complication, in spite of
being healthy in the first half of pregnancy. Starting low dose aspirin early in pregnancy can avert preeclampsia; therefore, it is important to find out women at risk of developing hypertensive disorders in pregnancy.5

Placenta in normal pregnancy produces a number of factors that are released into the maternal circulation. Alterations in the concentration of these factors in the maternal blood have been used to predict fetal outcome especially in terms of fetal anomalies and aneuploidy. Various authors have studied changes in the maternal serum concentration of these factors but the results so far have not been encouraging. Various other serum biomarkers in the early trimester have been studied to predict preeclampsia developing later in the pregnancy but till date no biomarker either single or in combination has been successfully able to predict the development of hypertension in low risk women.5

Normal levels of vitamin D are thought to play role in optimum placentalion. Vitamin D has been suggested to mediate immune response at the feto-maternal interface and helps in increasing maternal immunological tolerance and reduces production of inflammatory mediators.7,8 Two meta-analysis have suggested possible role of low levels of vitamin D in development of PE.9,10

Development of preeclampsia is related to poor placentation and leads to increase in release of the markers of oxidative stress and inflammation from the placenta. hsCRP is one of the markers of systemic inflammation and it’s levels are found to be high in women with PE.11,12 This biomarker has gained significance as it is easily available and is less costly as compared to other markers of inflammation.

Abnormalities in the placental implantation are also responsible for the high resistance flow in the uterine circulation. Hence, in women who develop hypertension later in pregnancy, there is failure of disappearance of uterine artery diastolic notching around midgestation.13-16 Previous studies have reported that combining biochemical markers of inflammation with uterine artery Doppler is more sensitive in predicting preeclampsia.17,18

The present study was planned to find out the association of first trimester maternal serum vitamin D and hsCRP levels, and second trimester uterine artery doppler with development of GHT and preeclampsia. It was also aimed to study prediction of subsequent development of GHT/PE by using these parameters.

METHODS

This was a prospective cross-sectional study conducted in the department of obstetrics and gynaecology in collaboration with department of clinical biochemistry and department of radiology, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi. Before starting the study, permission was taken from the Institutional ethical committee. All pregnant women attending antenatal clinic between October 2012 and June 2013, with 11 to 14 weeks gestational age, singleton pregnancy, willing to participate in the study and deliver at Safdarjung Hospital were recruited. Before starting the study, the procedure was explained to the women in a language understood by them and informed consent was taken.

A detailed history including history of the duration of sun exposure was taken and a complete physical examination including obstetrical examination was done at every visit to note maternal and foetal wellbeing. Besides, routine antenatal investigations, serum sample were taken for hs-CRP and vitamin-D levels at 11-14 weeks. Serum hs-CRP and vitamin-D levels estimation was done by enzyme linked immunosorbert assay (ELISA) technique.

Uterine artery Doppler study was done between 22-24 weeks with colour Doppler ultrasonography machine model Philips HD11 XE, Delhi by Philips Health Care. The probe was placed approximately two to three cm inside the iliac crests and the beam was directed downward and inward around 2 cm above the midpoint of inguinal ligament. Normally uterine arteries have strong forward diastolic flow due to low resistance in the uterine vessels. Diastolic notching seen on Doppler flow study of uterine artery on one or both sides was noted.

Follow up of all women was done until delivery for the development of gestational hypertension and preeclampsia.

For the analysis of results, the study population was divided into 2 groups on the basis of subsequent development of hypertension. Hypertensive group comprised of women who subsequently developed gestational hypertension or preeclampsia and normotensive group comprised of women who remained normotensive till delivery. Gestational hypertension was defined as BP >140/90 mmHg for the first time in pregnancy without proteinuria, after 20 weeks of gestation. Preeclampsia without severe features was defined as the presence of hypertension (BP ≥ 140/90 mmHg) with proteinuria on 2 occasions, at least 6 hours apart, but without evidence of end-organ damage, in a woman who was normotensive before 20 weeks' gestation. Severe preeclampsia was defined as the presence of 1 of the following symptoms or signs in the presence of preeclampsia: Systolic BP ≥ 160 mmHg, Diastolic BP ≥ 110 mmHg on 2 occasions with evidence of end-organ damage.19

Statistical analysis

A master chart was created using MS-EXCEL. The descriptive statistics in term of mean, median, SD, range of all the parameters was calculated for hypertensive and for normotensive groups separately. SPSS 16 was used to analyse the data and Pearson Chi square test, t test,
Fischer’s test and Anova one-way were used to compare various parameters; p value was kept <0.05 as cut off for significance. The receiver operating characteristic curve (ROC) curve was used to choose the cut off value of Vitamin D and hs-CRP. The logistic regression model was used for causal effect relationship. The effects of these predictors were measured in terms of Odds Ratio (OR) and its confidence intervals (C.I.).

RESULTS

A total of 153 women were included in the study, one woman was lost to follow up, therefore data of 152 women was analysed. The age and serum levels of vitamin D and hs-CRP in hypertensive and normotensive groups are shown in Table 1.

### Table 1: Distribution of study parameters in normotensive and hypertensive women.

| Parameters                        | Normotensive (N=103) | GHT/PE (N=49) | p value |
|-----------------------------------|----------------------|---------------|---------|
| Mean age±SD (years)               | 24.47±3.64           | 25.16±3.72    | 0.474   |
| Nulliparous                       | 44.1%                | 71.3%         | 0.530   |
| Sun exposure < 30 minutes         | 22.11%               | 22.45%        | 0.996   |
| Mean vitamin D (ng/ml)            | 18.97±14.28          | 12.28±7.08    | 0.001   |
| Mean hs-CRP (mg/l)                | 8.39±7.39            | 19.32±12.74   | 0.004   |
| Unilateral uterine artery diastolic notching | 4.8%                | 46.2%         | 0.005   |
| Bilateral uterine artery diastolic notching | 0%                  | 20.4%         | 0.000   |

### Table 2: Comparison of vitamin D, hs-CRP levels and uterine artery Doppler as predictors of P.E./GHTN.

| Variable                          | Sensitivity (%) | Specificity (%) | PPV† (%) | NPV‡ (%) | Accuracy (%) | p value |
|-----------------------------------|-----------------|-----------------|----------|----------|--------------|---------|
| Vitamin D (< 30 ng/ml)            | 98              | 10.6            | 34       | 91.7     | 38.6         | 0.067   |
| Vitamin D (< 13.5 ng/ml)          | 61.2            | 64.44           | 44.8     | 77.9     | 63.4         | 0.003   |
| hs-CRP (> 5 mg/l)                 | 89.8            | 36.5            | 40       | 88.4     | 53.2         | 0.001   |
| hs-CRP (> 9.15 mg/l)              | 73.5            | 72.12           | 55.4     | 85.2     | 72.5         | 0.000   |
| UA Diastolic notching             | 38.8            | 95.2            | 79.2     | 76.7     | 77.17        | 0.001   |
| Vitamin D + hs-CRP⁕               | 87.8            | 43.3            | 42.2     | 88.2     | 57.5         | 0.000   |
| Vitamin-D + hs-CRP⁕ + Abnormal UA doppler | 34.7            | 95.2            | 77.3     | 75.6     | 75.8         | 0.000   |

†positive predictive value ‡negative predictive value ⁕serum vitamin D < 30 mg/ml and serum hsCRP > 5 mg/L.
The mean vitamin D levels were significantly lower and mean hs-CRP levels were significantly higher in the hypertensive group as compared to the normotensive group, \( p=0.001 \) and \( p=0.004 \), respectively. Significant number women who developed hypertension had either unilateral or bilateral uterine artery diastolic notching, \( p=0.005 \) and \( p=0.000 \), respectively.

Serum vitamin-D and hs-CRP cut off levels of 13.5 ng/ml and 9.15 mg/l, respectively were calculated from receiver operating characteristic curve (ROC Curve), Figure 1 and 2. The comparison of sensitivity, specificity, positive predictive value and negative predictive value of serum vitamin D, hs-CRP and abnormal uterine artery Doppler done in early pregnancy was calculated for prediction of development of hypertension during pregnancy is shown in Table 2.

The sensitivity of hs-CRP was highest for prediction of hypertension during pregnancy whereas abnormal uterine artery doppler had highest positive predictive value. Crude’s odds ratio of abnormal uterine artery for prediction of hypertension in pregnancy was high, 9.894, (95% CI, 3.273-29.907) as compared to vitamin D and hs-CRP, Table 3.

### Table 3: Crude odds ratio for maternal serum markers and uterine artery doppler for prediction of P.E./GHTN.

| Variable | Cut off | \( p \) value | OR | 95% C.I. |
|----------|---------|--------------|----|---------|
| Vitamin-D (ng/ml) | 13.5 | 0.003 | 2.859 | 1.418-5.763 |
| Vitamin-D (ng/ml) | 30 | 0.112 | 4.667 | 0.584-37.305 |
| hs-CRP (mg/L) | 9.15 | 0.000 | 7.16 | 3.33-15.397 |
| hs-CRP (mg/L) | 5 | 0.005 | 4.011 | 1.458-11.033 |
| Diastolic notch | - | 0.000 | 9.894 | 3.273-29.907 |

### DISCUSSION

Hypertensive disorders complicate 8-10% of the pregnancies and are responsible for 8% maternal mortality.\(^1,4\) The placental dysfunction associated with the pathology starts early in pregnancy. If we can identify women at risk of developing GHT/PE early in pregnancy, timely interventions can reduce maternal and fetal severe morbidity and mortality. Low levels of vitamin D, high levels of hsCRP which is a marker of inflammation along with early pregnancy uterine artery notching are associated with development of placental dysfunction and are hence been studied as markers for identifying women at risk of developing GHT/PE. The present study was planned to find out the association of first trimester vitamin D and hsCRP taking conventional and ROC cut offs and presence of second trimester uterine artery diastolic notching with risk of development of GHT/PE in women attending a tertiary care hospital.

The present study found the prevalence of GHT/PE to be 32.24% which is higher than reported by other authors.\(^1,2\)

The higher prevalence of GHT/PE in the present study was because the study was conducted in a tertiary care hospital. There was no significant difference in the age and parity of women in the study and control group. Although there was no difference in the duration of sun exposure in women with and without GHT/PE, the vitamin D levels of women in the study group were lower than the control group, \( p=0.001 \). The accuracy of predicting GHT/PE in women with hypovitaminosis D (\(<\) 30 ng/ml) was 38.6%, \( p=0.67 \) but when the cut off was calculated from ROC, vitamin D levels of less than 13.5 ng/ml were able to predict GHT/PE with accuracy of 63.4%, \( p=0.003 \), OR 2.859; 95% CI 1.418-5.763.

Our findings are consistent with the reports of previous authors who also observed significantly lower levels of vitamin D in women who subsequently developed pre-eclampsia and significant correlation of vitamin D levels with maternal mean arterial pressure.\(^20,22\) A meta-analysis by Tabesh et al also showed significant association of vitamin D deficiency with risk of developing pre-eclampsia.\(^23\)

The mean first trimester serum hsCRP in the present study was found to be higher in the women who developed GHT/PE than the control group, 19.32±12.74 mg/L and 8.39±7.39 mg/L respectively, \( p=0.004 \). The hsCRP of >5 mg/L were associated with predictive accuracy of 53.2% but with the value of >9.15 mg/L, calculated by ROC, the accuracy of prediction was 72.5%, \( p <0.001 \). The risk developing GHT/PE with first trimester hsCRP levels >9.15 mg/L was significantly high, OR 7.16; 95% CI 3.33-15.397, \( p=0.000 \), risk calculated by taking the conventional cut-off of <5 mg/L was also high OR 4.011, 95% CI 1.458-11.033, \( p=0.005 \).

Various studies have reported higher levels of serum hsCRP in the first trimester.\(^11,24,25\) A recent study by Elkady et al, also found higher first trimester hsCRP levels in women with pre-eclampsia as compared to the control group, 7.86±0.99 and 2.71±1.69, respectively, \( p < 0.001 \).\(^26\)
In the present study, the accuracy of uterine artery diastolic notch in predicting the development of GHT/PE was 77.17%, P=0.001, crude OR was 9.894, 95% CI-3.273-29.90, P=0.000. Kurdi et al, reported bilateral uterine artery diastolic notching in 12.4% of their cases and found OR of 12.8 for development of PE.23 Espinoza et al also found bilateral uterine artery notching to be associated with risk of developing PE later during pregnancy OR 2.1; 95% CI 1.28-3.36, early onset PE OR 4.47; 95% CI 1.50-13.35, and GHT OR 1.50; 95% CI 1.02-2.26. They concluded that bilateral uterine artery diastolic notching between 23-25 weeks of gestation is an independent risk factor for the development of early onset PE and GHT.24

The main limitation of our study was that it was a hospital-based study done at a tertiary care centre; therefore, the incidence of GHT/PE in our study was high. Most of these women may be at high risk of development of hypertensive disorder during pregnancy and the results may not be applicable to the low risk women. Another limitation was that risk assessment of the participants on the basis of history was not done.

The main strength of our study is that we were able to follow most of the enrolled women till delivery; only one woman was lost to follow up. If a woman missed her scheduled visit, she was contacted telephonically and counseled to continue to be the part of study.

CONCLUSION

Early screening for risk of PE would benefit in identifying patients who are at high risk for maternal and perinatal complications due to GHT/PE developing later in the course of pregnancy. Uterine artery diastolic notching in the early second trimester is found to be the best predictor of PE. By taking ROC cut off hsCRP is better predictor for calculating risk of developing GHT/PE. However, taking conventional cut offs for hsCRP and vitamin D, combination of hsCRP and Vitamin D levels with uterine artery doppler are observed to yield better prediction of GHT/PE.

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