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Original Research Article

Maternal serum selenium as a predictor of preeclampsia

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ABSTRACT

Background: Preeclampsia (PE) is a hypertension disorder condition occurring in 7-10% of all pregnancies. Preeclampsia if unidentified and left untreated is associated with poor maternal and fetal adverse outcomes. The objective of the present study was to characterize maternal serum selenium levels as a predictor of preeclampsia and to correlate dietary selenium intake with serum selenium levels in first trimester of pregnancy

Methods: A retrospective case-control study of 107 pregnant women was conducted over 1.5 years at St. John's Medical College Hospital. On screening for inclusion criteria, at baseline, information on maternal socio-demography, anthropometry, dietary intake and clinical examination was collected. A venous blood sample at baseline and 2nd or 3rd trimester of pregnancy was collected for estimation of selenium concentrations. Blood pressure was measured at baseline and followed up during pregnancy to select cases and controls. Pregnant women were termed 'cases' based on NHBPEP (National High Blood Pressure Education Program) classification and subsequent 22 women with normal blood pressure controlled for age were termed as 'controls'.

Results: No statistically significant differences were observed for baseline characteristics, biochemical parameters and blood pressure at recruitment among cases and controls. Cases had significant lower levels of energy ($P=0.032$) and micronutrients like zinc ($P=0.027$), selenium ($P=0.022$), magnesium ($P=0.047$) at first trimester. The serum selenium levels were significantly higher in cases as compared to the controls (69.2 ± 13.7 vs. 59.6 ± 12.9 ; $P=0.021$) at baseline.

Conclusions: Our findings suggest that serum selenium levels may not be an independent predictor of preeclampsia. Assessment of other micronutrients, oxidative stress markers and other complementary elements may be useful in predicting preeclampsia.

Keywords: First trimester, Predictor, Preeclampsia, Selenium status

INTRODUCTION

Hypertensive disorder of pregnancy remains a major concern in obstetric care, which has been a challenge to obstetricians and researchers since many decades. Preeclampsia occurs in nearly 7-10% of all pregnancies and is a condition which when not identified and left untreated is associated with poor maternal and fetal adverse outcomes. It is essential to diagnose and adequately treat the elevated blood pressure before 34

weeks of gestation as the trophoblastic invasion of the placenta occurs in the 2nd trimester and abnormality of it will affect the growth of the fetus.¹ About 10-25% of maternal death in developing countries is associated with preeclampsia and being complicated with seizures called as eclampsia.² Placental implantation with abnormal trophoblastic invasion of uterine vessels is one of the theories in etiopathogenesis of preeclampsia.³ A number of parameters have been studied as a predictor of preeclampsia, which are related to placental perfusion,

vascular resistance, fetal placental unit, endocrine dysfunction, renal dysfunction and oxidant stress.⁴ Though the risk factors are well known, there are no biomarkers that can predict and prevent the onset of preeclampsia.⁵

Selenium (Se) is an essential trace element found as a component of glutathione peroxidase (GPx), a selenoprotein, which protects the endothelium by scavenging on oxidation products of hydroperoxides and lipoperoxides.⁶ Selenium-dependent GPx's plays a key role in protection against oxidative damage, and have been shown to have reduced activity during pregnancy, with the lowest activity at delivery.⁷ Activity of the selenoproteins is determined by activity/ translation of the relevant genes, among which a number of single-nucleotide polymorphisms (SNPs) are described in non-pregnant subjects, including some with reported effects on gene expression, mRNA translation, or protein stability.⁸⁻¹⁰ Preeclampsia has a familial component, but it is not known whether these SNPs could, independently or in association with lower selenium status, be determinants of the putative impairment in antioxidant defence.¹¹

Utility of serum selenium lies in its ability to predict the onset of preeclampsia, which allows for screening of a subpopulation that is at a higher risk to end up with poor maternal and neonatal outcomes. Observational studies have shown an association of preeclampsia with low levels of serum selenium.¹² Although there is dearth of data, a randomised controlled trial in UK, SPRINT (Se in Pregnancy Intervention) was conducted to measure the effect of dietary selenium supplementation (i.e., 60µ/day) on the markers of preeclampsia, endothelial and placental function.¹³ A reduced incidence of preeclampsia was noted in the selenium supplemented group compared to the placebo group.¹⁴ This study was therefore conducted in a South Indian pregnant woman to evaluate the role of selenium status in early pregnancy on preeclampsia.

METHODS

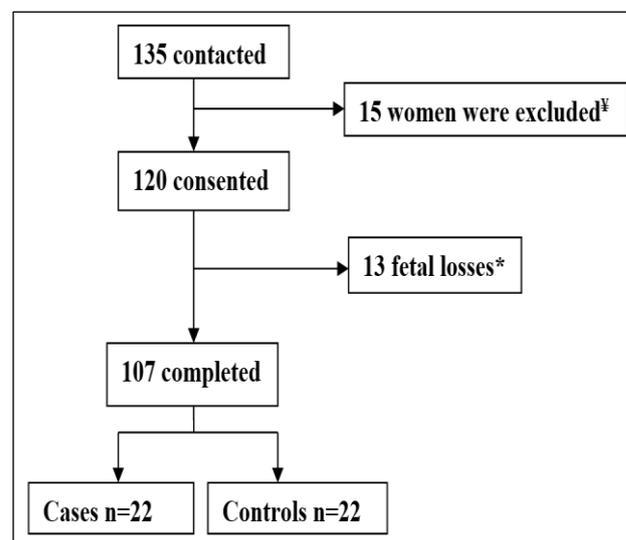
Study design

A retrospective case-control study was conducted at the out-patient unit of Obstetrics and Gynaecology department, St. John's Medical College Hospital, Bangalore, India, from December 2014 to May 2016. Pregnant volunteers were enrolled in early pregnancy (baseline) and followed up until delivery. At recruitment, information on socio-demography was collected by the trained researchers, maternal anthropometry, dietary intake, clinical status and venous blood sample was collected at baseline and during second or third trimester of pregnancy. Blood pressure was measured at baseline and followed up during the course of pregnancy to select cases and controls. Mean arterial pressure (MAP) is an average blood pressure in an individual during a single cardiac cycle. It was calculated using the following

formula i.e. $MAP = [(2 \times \text{diastolic}) + \text{systolic}] / 3$. Those women who met the classification of preeclampsia as per NHBPEP15 were categorized as cases and matched for age, parity and education (an index of socio-economic status) with control subjects. The study procedure was approved by the Institutional Ethical Review Boards at St. John's Medical College Hospital. A written informed consent was obtained from each study subject at enrolment.

Study subjects

All pregnant women aged 18–40 years who were between 12 to 14 weeks of gestation with singleton pregnancy and registered for antenatal screening were invited to participate in the study. Women with chronic hypertension, diabetes mellitus, peripheral vascular disease, thyroid disease, abnormal BMI (i.e., underweight, overweight or obese), sexually transmitted disease and having anomalous fetus (detected by anomaly scan) were excluded from the study Figure 1.



‡- 2 HBsAg positive, 4 abnormal TSH, 4 low BMI, 5 high BMI.
*- includes spontaneous abortion and missed abortion.

Figure 1: Flow diagram of recruitment and follow-up in the study cohort.

Socio-demographic and anthropometric information

At the first trimester visit, baseline information on socio-economic status (SES) such as age, education, parity, obstetric history and family composition was collected. Gestational age (in weeks) was calculated from the reported first day of the last menstrual period (LMP) which was subsequently confirmed by ultrasonographic measurement. All antenatal women were measured for weight to the nearest 100 g by a digital balance (Soehnle, Germany). They were also subjected for measurement of height using a stadiometer to the nearest 1 cm at baseline. Subsequently maternal body mass index (BMI) was calculated using weight and height at baseline (kg/m^2).

Biochemical parameters

Venous blood was drawn from all study subjects by venipuncture using trained personnel and collected in plain vacutainers (Beckton Dickinson), for the analysis of serum selenium 1 ml of serum was stored in a plain vacutainer at -80°C until analysis. As per the routine antenatal screening, whole blood was used for the measurement of haemoglobin and other baseline parameters like fasting blood sugar and TSH (Thyroid stimulating hormone) level were also estimated. Serum selenium was analyzed after preparation of the sample by diluting 1:1 (200 μL sample + 200 μL conc. Nitric acid). Then the sample was centrifuged at 500 rpm for 5 minutes. The supernatant was taken as sample for Selenium estimation on atomic absorption spectroscopy (AAS). The concentrations obtained on AAS were multiplied by a factor of 2.

Dietary methods

A validated food frequency questionnaire (FFQ) during pregnancy was administered at recruitment to obtain information on habitual dietary intake for the preceding 3 months. In brief, the questionnaire consisted of 108 items, along with portion sizes and frequency.

Standard measures were placed before the respondent to quantify the portion size of each food item when administering the questionnaire. Recipes for the food items were tested in the laboratory and raw ingredients

for each recipe were weighed, and volume to weight conversions measured for each cooked food item.

Statistical analysis

Continuous data was represented as mean \pm standard deviation (SD) and the categorical data as number (percentages). Chi square test of significance was applied for the categorical variables and independent t-test was applied for continuous variables to observe the differences between variables across cases and controls. Two-sided P-values of <0.05 were considered statistically significant. All analysis was performed on excel and SPSSv18.0 (PASW Statistics, SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the study subjects was around 26 years. Table 1 describes the socio-demographic, anthropometric and clinical parameters of the cases and control subjects. Maternal parameters such as parity and socio-economic status were compared between the two groups using Chi square test.

High number of cases were pregnant for the first time as compared to the controls (54.4 Vs 45.5%; $P < 0.382$). Further it was observed that higher percentage of cases belonged to lower SES as compared to the controls (54.0 Vs 59.0%, $p < 0.500$). However, statistically significant difference was not noted.

Table 1: Sociodemographic, anthropometric and clinical parameters.

Parameter	Cases (mean \pm SD) n=22	Controls (mean \pm SD) n=22	P value
Age	25.9 \pm 4.1	25.9 \pm 4.1	1.000
Parity			
Nulliparous	12 (54.4%)*	10 (45.4%)*	0.382
Multiparous	10 (45.4%)*	12 (54.4%)*	
Socioeconomic status			
Upper	10 (45.4%)*	9 (40.9%)*	0.500
Lower	12 (54.4%)*	13 (59.09%)*	
BMI (kg/m^2)	22.4 \pm 1.8	21.2 \pm 2.2	0.06
Blood pressure in 1st trimester			
Systolic	114.4 \pm 9.8	113.5 \pm 7.9	0.763
Diastolic	73.9 \pm 6.8	72.5 \pm 5.8	0.450
Mean arterial pressure	87.4 \pm 6.9	86.2 \pm 5.6	0.515
Blood pressure in 2nd/ 3rd trimester			
Systolic	153.2 \pm 8.3	122.1 \pm 7.3	0.000
Diastolic	96.1 \pm 2.1	72.8 \pm 4.3	0.000
Mean arterial pressure	115. \pm 3.9	89.2 \pm 4.4	0.000
Proteinuria			
1+	17 (77.27%)*		
2+	2 (9.09%)*		
3+	3 (13.63%)*		

*Number (%)

All the subjects at recruitment had anthropometrical measurements such as height and weight to estimate their body mass index (BMI). Maternal BMI was higher in the cases although was not statistically significant. However, the anthropometrical measurements did not show statistically significant difference between the 2 groups. The mean systolic, diastolic and mean arterial pressures of both cases and controls were equivalent with no significant difference in the first trimester.

Mean arterial pressure of 86.2 ± 5.6 and 87.4 ± 6.9 was noted in the controls and cases group respectively. This depicts that to begin with there was no difference between the controls and cases. Whereas, the mean systolic,

diastolic and mean arterial pressures of the cases were significantly elevated in second/third trimester. Mean arterial pressure was 89.2 ± 4.4 mmHg in controls and 115.1 ± 3.9 mmHg in cases with $P=0.000$. This indicates that the cases had significantly elevated blood pressure in the second or third trimester after diagnosis of preeclampsia. Further, the cases were categorized into mild and severe preeclampsia by assessing their urine protein levels by dipstick method at diagnosis. It was observed that 77.2% of the cases had mild preeclampsia and 22.7% progressed to severe preeclampsia. The dietary patterns of the subjects were assessed using a validated 24 hr dietary recall and the diet intake of macro- and micronutrient was compared (Table 2).

Table 2: Dietary pattern and intake of micro/ macronutrients.

Parameter	Cases (mean \pm SD) n=22	Controls (mean \pm SD) n=22	P value
Diet			
Vegetarian	2 (9.09%)*	3 (13.63%)*	0.500
Non-Vegetarian	20 (90.9%)*	19 (86.3%)*	
Micro/Macronutrients			
Energy (kCal/day)	1504 \pm 457.06	1839 \pm 542.8	0.032
Protein (g/day)	42.3 \pm 15.13	52.8 \pm 15.8	0.030
Fat (g/day)	38.7 \pm 16.6	51.6 \pm 17.8	0.017
Carbohydrate (g/day)	246.7 \pm 69.1	291.0 \pm 84.8	0.065
Copper (mg/day)	1.5 \pm 0.51	1.8 \pm 0.6	0.053
Manganese (mg/day)	4.4 \pm 1.91	5.9 \pm 2.7	0.052
Zinc (mg/day)	6.5 \pm 2.1	8.0 \pm 2.4	0.027
Selenium (μ g/day)	45.3 \pm 15.5	65.1 \pm 35.8	0.022
Magnesium(mg/day)	362.4 \pm 115.8	441.2 \pm 138.5	0.047
Vitamin E (mg/day)	9.2 \pm 3.5	12.5 \pm 4.3	0.008
Vitamin C (mg/day)	125.2 \pm 85.4	119.5 \pm 81.87	0.824

*Number (%)

It was observed that majority were non-vegetarians 88.6% (i.e., those who consumed meat and egg) whereas only 11.3% were noted to be vegetarians (i.e., those who consumed milk and did not consume egg). The control subjects had significantly higher macro nutrient intakes such as energy, protein and fats as compared to the cases (1839 vs. 1504 kcal/d, 52.8 vs. 42.3 g/d, and 51.6 vs. 38.7 g/d respectively). Of the micronutrients, intakes of zinc, selenium and magnesium were significantly lower in control subjects as compared to the cases (8.0 vs. 6.5 mg/d, 65.1 vs. 45.3 μ g/day and 441.2 vs. 362.4 mg/d; all $p < 0.05$ respectively). In-addition to the micronutrients, intake of Vitamin E; an antioxidant was significantly lower in the cases (9.2 vs. 12.5 mg/d) although vitamin C did not show similar lower trend in the cases (125.5 vs. 119.5 mg/d).

The average serum selenium levels for the total population at baseline was 64.4 ± 13.9 μ g/L, however the cases showed significantly higher levels when compared to the controls (69.2 vs. 59.6; $p=0.021$) (Table 3).

Table 3: Serum Selenium levels of the subjects in first trimester.

Parameter	Cases (mean \pm SD) n=22	Controls (mean \pm SD) n=22	P value
Selenium	69.2 \pm 13.7	59.6 \pm 12.9	0.021

Table 4: Correlation of selenium intake with selenium status.

Selenium intake with selenium status	Cases n=22	Controls n=22
	$r = -0.145$, $P = 0.519$	$r = -0.141$, $P = 0.533$

However, all subjects' selenium intake negatively correlated with the selenium status; $r = -0.213$, $P = 0.165$ (Table 4). There was no significant correlation observed between intake and selenium status neither in cases nor in controls with $r = -0.145$, $P = 0.519$; $r = -0.141$, $P = 0.533$

respectively. No significant correlation was observed with selenium intake or status at recruitment and blood pressure in 2nd trimester among cases and controls.

DISCUSSION

This case control study was conducted to evaluate the utility of serum selenium as a predictor of preeclampsia and to correlate the dietary selenium levels with the first trimester selenium levels. Number of maternal factors such as age, parity, BMI, dietary pattern etc are identified as determinants of preeclampsia. Therefore, present study focused on evaluating maternal factors that included matched cases of preeclampsia with normotensive women for age and further at secondary level of matching with parity and socioeconomic status. Also, anthropometric measures of the study subjects were similar to that of other studies.¹¹⁻¹² The first trimester mean systolic, diastolic and mean arterial pressures of both controls and cases were statistically not different in the first trimester indicating that apparent healthy women were recruited in the study. The study subjects were followed up until delivery and those women who developed preeclampsia were observed to have had a rise of systolic blood pressure of 30 mmHg, diastolic blood pressure of 24mmHg and MAP of 26 mmHg compared to the normotensive women in 2nd or 3rd trimester with $P=0.000$. Among the cases, 77.3% had mild preeclampsia and 22.7% progressed to severe preeclampsia.

Selenium levels are thought to be higher in non-vegetarian diet and hence a protective measure against preeclampsia in women consuming non-vegetarian diet. In this population, the overall percentage of non-vegetarian consumers was high, however equal numbers of non-vegetarians were observed in cases and controls. This observation of higher non-vegetarians is similar to the findings by Rayman et al.¹⁷ The authors on examining the selenium levels showed no difference in Selenium status across the 2 groups of vegetarians and non-vegetarians' population. Our finding of similar dietary pattern was noted with predominance of non-vegetarian diet. We also studied the first trimester dietary pattern including macro and micronutrient intake, including correlation of dietary selenium intake with serum selenium levels of the subjects. We found significant difference in the macro and micronutrient including antioxidant like vitamin E between the 2 groups. It was observed that cases had significant lower levels of energy, selenium, zinc, magnesium and vitamin E as compared to the controls.

Cases had lower absolute intake of macro and micronutrients per day, assessed by validated FFQ (food frequency questionnaire) as compared to controls. The key observation was on selenium intake which was almost 20µg/day lower in cases, although, this trend was not observed in the selenium levels as a biomarker. We observed significantly lower levels of serum selenium at baseline in controls than the cases in these apparent

healthy pregnant women. While evidences suggest that preeclamptic women in their third trimester tend to have lower levels in comparison to the normotensive pregnant women.¹² Mistry et al further has shown association with micronutrients and antioxidant enzymes during early second trimester in preeclamptic women.¹¹ However, they did not find reduced levels of selenium or selenoproteins. Although studies show directional changes of selenium concentrations among women with preeclampsia, these changes are well captured once the disease is set in, either in the 2nd or 3rd trimester as measured by the previous groups. In the anticipation of their role in preeclampsia it is observed that reduced selenium levels in third trimester is seen when the disease has already set in with oxidative stress playing its role, leading to excessive consumption of selenium by scavenging the oxidative products and protecting the fetus from free radical damage. This is not observed in first trimester sample as oxidative stress and second wave of placental angiogenesis occurs in 2nd trimester. Hence it leads to ambiguity whether the difference in serum selenium levels is due to the preeclampsia condition and selenium alone not an appropriate predictor marker especially for identification of preeclampsia in the 1st trimester, prior to the onset of its pathogenesis.

CONCLUSION

Findings from present study suggest that serum selenium levels may not be an independent early predictor of preeclampsia. A cumulative assessment of other micronutrients, oxidative stress markers and other complementary elements along with selenium may be used for predicting preeclampsia.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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