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RESEARCH ARTICLE

Impact of maternal serum calcium levels on severity of hypertensive disorder of pregnancy: A cross sectional study

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ABSTRACT

Objectives: Assess relationship between maternal serum calcium levels, severity of disease and overall perinatal and maternal outcome in women with hypertensive disorders of pregnancy. **Methods**: Present prospective cross sectional study was conducted in the Obstetrics and Gynaecology department of rural tertiary care centre of Northern India after proper Institution ethical committee approval and informed written consent from the participants over a period of seven months (October 2016-May 2017). A total of 110 childbearing women admitted at ≥34 weeks of gestation were divided into three groups; Gestational hypertension (n=35), Pre-eclampsia (n=49) and Eclampsia (n=26). Maternal serum calcium levels and its correlation with severity of disease and overall maternal and perinatal outcome were assessed in each group. **Results**: Of 110 childbearing women, cases with gestational hypertension had mean serum calcium 8.83 ± 0.55 mg/dl, in pre-eclampsia 8.55 ± 0.89 mg/dl and in eclampsia group 8.41 ± 0.76 mg/dl. Of total 66 term births, 31(88.57%) occurred in gestational hypertension group, 26(53.06%) in pre-eclampsia and 8(30.77%) in eclampsia group. Maximum maternal and perinatal morbidity and mortalities were observed in women with eclampsia having minimum serum calcium levels followed by pre-eclampsia and least in women with gestational hypertension having near normal serum calcium levels. **Conclusion**: Significant correlation was observed between maternal serum calcium and severity of hypertensive disorder of pregnancy, adverse perinatal and maternal outcome.

Keywords: Blood pressure, calcium, hypertension, pregnancy, perinatal.

Hypertension during pregnancy with or without proteinuria is one of the leading causes of maternal and perinatal morbidity and mortality all over the world [1-4], accounting for more than 40,000 maternal deaths annually[5]. Worldwide hypertensive Disorder of Pregnancy (HDP) affects around 10% of all pregnancies with pre-eclampsia and eclampsia together accounting for 10-15% of all direct maternal deaths [1] and major burden of perinatal morbidity and mortality [6-9]. There is worldwide regional variation in distribution of maternal deaths due to HDP with 16.1% occurring in developed countries, 9.1% in Africa, 9.1% in Asia, and around 25.7% in Latin America and the Caribbean [2].

Till date the only proven way to prevent development as well as severity of HDP is calcium supplementation [1]. Calcium supplementation during pregnancy is known to decrease incidence as well as severity of gestational hypertension, pre-eclampsia, eclampsia and also neonatal

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morbidity and mortality, as well as pre-term births, especially in developing countries [10-12], although the impact varies according to the baseline calcium intake and other prevailing risk factors in the population [13, 14]. The underlying mechanism can be explained by reduction in parathyroid calcium release and intracellular calcium concentration, in woman taking calcium supplementation during pregnancy, thereby reducing smooth muscle contractility and promoting vasodilatation and hence, decreasing the risk and or severity of HDP [10,15,16]. Calcium also increases magnesium levels causing indirect effect on smooth muscle function [13]. Furthermore, studies have shown a strong association between HDP and decreased calcium excretion in urine [17]; lower urinary calcium to creatinine ratio [18], hypocalcaemia [19], decreased plasma and higher intra-membranous calcium [20] and lower dietary intake of milk [13, 21]. Also pregnant women with severe HDP have significantly lower dietary calcium intake as compared to normotensive women [22]. Calcium is the most abundant mineral in the body and is essential for many diverse processes, including bone formation, muscle contraction, and enzyme and hormone functioning [23]. A dietary intake of 1200 mg/day of calcium for pregnant women is recommended by WHO and the Food and Agriculture Organization of the United Nations (FAO) [23], whereas in pregnant women with low dietary calcium intake the recommended calcium is 1.5 g to 2 g daily [24]. Inadequate consumption of this nutrient by antenatal women can lead to adverse effects in both mother and fetus, including muscle cramping, osteopenia, tremors, paraesthesia, tetanus, intra-uterine fetal growth retardation, low birth weight, preterm delivery and poor fetal mineralization [5].

Hence, the present study was conducted with the aim of having information about the impact of maternal serum calcium levels on severity of HDP and its effect on overall outcome of pregnancy. The results of proposed study will help in future in formulating policies for prevention of disease, its severity and fatality to at least some extent.

Materials and Methods

Type of study: Cross sectional study

Study population: Hundred and ten childbearing women ≥34 weeks of gestation admitted in the Obstetrics and Gynaecology department of a rural tertiary care centre of Northern India with Hypertensive Disorders of pregnancy over a period of seven months (October 2016 to May 2017) were enrolled as study subjects.

Exclusion criteria: Childbearing women < 34 weeks of gestation or with history of medical disorders like Type II diabetes mellitus, renal or liver pathology, hyperuricemia, cardiovascular diseases, acute infections, endocrinal disorders, auto-immune disorders, genital malignancies, blood discrasias etc. were excluded from the study. Also childbearing women with history of substance abuse or smoking were excluded.

Definitions: Hypertension during pregnancy is defined as diastolic blood pressure ≥90 mm Hg or a systolic blood pressure ≥ 140 mmHg or both on two occasions more than 4 hours apart [25]. Gestational Hypertension is defined by new onset of hypertension with systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg at ≥20weeks gestation in absence of proteinuria or new signs of end-organ dysfunction and usually resolves by 3 months postpartum [26]. Pre-eclampsia is defined as blood pressure ≥140/90 mm Hg on two occasions each 6 hours apart with proteinuria of at least 300 mg per 24 hours or at least 1+ on dipstick testing. Severe pre-eclampsia is defined as a blood pressure of 160/110 mm Hg or above measured on two occasions each 6 hours apart [25, 27]. Eclampsia is a convulsive condition associated with pre-eclampsia [25].

Data Collection: The present prospective cross sectional study was conducted in the department of Obstetrics and Gynaecology of a rural tertiary care centre of Northern India over a period of seven months from October 2016 to May 2017 after proper Institutional Ethical Clearance and informed written consent from the participants. Every effort was made not to disclose the identity of participants. A detailed family and medical history of all the childbearing women with gestational age 34 weeks or more admitted with the features of HDP was recorded followed by a thorough clinical examination. Systolic and diastolic blood pressure of all the participants was carefully recorded every four hourly. Blood pressure was measured using manual device with well applied sphygmomanometer placed an inch above the cubital fossa with patient sitting in a chair with feet flat on the floor and back supported. The size of the blood pressure cuff was such that the inflatable bladder covered 75-100%

of the circumference of upper arm of the patient. Blood pressure was measured in both arms and one with higher value was taken as the blood pressure of record. Korotkoff phase V readings were used for diastolic readings. Urine analysis was done in all subjects to measure the degree of proteinuria and to differentiate patients with gestational hypertension from pre-eclampsia. The degree of proteinuria was measured by dipstick and graded as Trace to 4+ (Trace, 0.1gm/L;1+, 0.3gm/L;2+, 1gm/L;3+, 3.0gm/L;4+, 10gm/L). At the same time blood was taken from the ante-cubital vein using a sterile needle and syringe early in the morning after overnight fasting for serum calcium measurement. Blood samples were allowed to clot and then centrifuged at 3000 revolutions per minute for 10 minutes. Serum calcium levels were measured by the O- Cresol Phthalein Complexone (OCPC) method. The reference levels of normal total serum calcium levels considered were [28] (Table 1)-

Table 1: Total Serum Calcium Levels

Unit	First Trimester	Second Trimester	Third Trimester
mg/dl	8.8 - 10.6	8.2 – 9	8.2 - 9.7
mmol/l	2.2 - 2.65	2.05 - 2.25	2.05 - 2.43

All the participants were then divided into 3 groups (on the basis of presence and absence of proteinuria and convulsions); Group I: Childbearing women with Gestational hyp-ertension, Group II: Childbearing women with preeclampsia and Group III: women with features of eclampsia. All the cases were followed until birth of the baby for final maternal and perinatal outcomes, which were recorded.

Statistical Analysis : The data was validated and analysed with the help of statistical software SPSS version 20. Categorical variables were presented in number and percentage (%) and continuous variables as mean ± SD and median. The quantitative variables were compared using unpaired t-test/Mann-Whitney Test between the two groups and ANOVA/ Kruskal Wallis test between more than two groups whereas the qualitative variables were correlated using Chi-Square test /Fisher's exact test. P value of <0.05 was considered statistically significant.

Results

Of total 110 childbearing women; 35 (31.81%) had Gestational hypertension, 49 (44.54%) Pre-eclampsia and remaining 26 (23.63%) had Eclampsia. The mean age of presentation in all the three groups was 26.51 ± 3.82 years, 27.14 ± 3.64 years and 24.73 ± 4.01 years respectively. Of 35 women with gestational hypertension, 13 (37.14%) were preterm (>-34-<37 weeks); 22 (62.86%) term (>-37-≥40 weeks) at the time of admission. Of 49 women with Pre-eclampsia 23 (46.94%) were preterm (>-34-<37 weeks) and 26(53.06%) term (>-37-≥40 weeks). Of these 49 women with pre-eclampsia 31(63.26%) had mild disease and 18 (36.73%) had severe pre-eclampsia. Similarly in eclamptic group of 26 women; 18 (69.23%) were preterm (>-34-<37 weeks) and eight (30.77%) were term (>-37-≥40 weeks). Demographic

Table 2: Demographic profile and perinatal outcome

Categories	Gestational Hypertension	Pre-eclampsia	Eclampsia	P value
Age (years)	26.51 ± 3.82	27.14 ± 3.64	24.73 ± 4.01	**<0.004**
(Mean± SD)	(Min-Max: 21-38)	(Min-Max: 22-35)	(Min-Max: 19-32)	
Gravidity				
Primigravida	10 (28.57%)	12 (24.49%)	17 (65.38%)	
Multigravida	25 (71.43%)	37 (75.51%)	9 (34.61%)	
Gestation (weeks)				
Preterm(<37)	13 (37.14%)	23 (46.94%)	18 (69.23%)	**<0.0001**
Term (>37)	22 (62.86%)	26 (53.06%)	8 (30.77%)	
Perinatal outcome				
Healthy	28 (77.78%)	14 (28.57%)	1 (3.85%)	
Oxygen support	5 (13.89%)	14 (28.57%)	12 (46.15%)	
Ventilatory support	1 (2.78%)	6 (12.24%)	7 (26.92%)	**<0.0001**
IUD[a]	1 (2.78%)	14 (28.57%)	4 (15.38%)	
Still Birth	1 (2.78%)	1 (2.04%)	2 (7.69%)	

a. IUD: Intrauterine death

features are depicted in Table 2. The mean ± SD values for serum calcium levels were 8.83 ± 0.55 mg/dl (Minimum to Maximum value: 7.8-9.9 mg/dl) in women with Gestational Hypertension; 8.55 ± 0.89 mg/dl (6.4 - 10.6 mg/dl) in women with Pre-eclampsia and 8.41 ± 0.76 mg/dl (6.7-9.7 mg/dl) in eclamptic group. Of 35 childbearing women with Gestational hypertension, nine out of thirteen women with gestation <37 weeks were induced at term (>37 weeks), accounting for 31(88.57%) term births [25(80.64%) vaginally and six (19.35%) by LSCS], and four (11.43%) preterm births [three (75%) vaginally and one (25%) by LSCS]. In Pre-eclmapsia group, 26(53.06%) cases gave birth at term [17(65.38%) vaginally and 9(34.62%) by LSCS], and 23(46.94%) cases at <37 weeks of gestation [15(65.22%) vaginally, six (26.09%) by LSCS and two (8.69%) by Vaginal birth after caesarean section]. Of 26 women with eclampsia, eight (30.77%) gave birth at term [five (62.5%) vaginally and three (37.5%) by LSCS], whereas 18 (69.23%) prematurely at <37 weeks [eight (44.44%) vaginally, one (5.55%) by forceps and nine (50%) by LSCS]. The relation between maternal age, serum calcium levels and mode of birth is depicted in Table 3.

Table 3: Relation of maternal serum calcium levels and modes of delivery

Group	Mode of Birth				P value
	VD[a]	LSCS[b]	Instrumental	VBAC[c]	
Gestational HTN	22(61.11%)	14(38.89%)	-	-	
S.Calcium (Mean±SD) (Min-Max) mg/dl	8.87 ± 0.47 (7.9-9.8)	8.78 ± 0.68 (7.8-9.9)	-	-	
Pre-eclampsia	21(42.86%)	26(53.06%)	-	2(4.08%)	0.539
S.Calcium (Mean±SD) (Min-Max) mg/dl	8.51 ± 0.94 (6.9-10.6)	8.64 ± 0.88 (6.4-10)	-	7.95 ± 0.35 (7.7-8.2)	
Eclampsia	8(30.77%)	17(65.38%)	1(3.85%)	-	
S.Calcium (Mean±SD) (Min-Max) mg/dl	8.26 ± 0.85 (7-9.4)	8.46 ± 0.75 (6.7-9.7)	8.7 ± 0 (8.7-8.7)	-	

a: Vaginal Delivery, b: Lower Segment Caesarean Section, c: Vaginal Birth After Caesarean

Of total 111 neonates (including one twin gestation) delivered to all women with HDP, 45 (40.54%) [4(8.88%) in gestational hypertension group; 23(51.11%) in pre-eclampsia group and 18(40%) in eclampsia group] were born prematurely and the remaining 66 (59.46%) [32(48.48%) in gestational hypertension group; 26(39.39%) in pre-eclampsia group and 8(12.12%) in eclampsia group] were born at term.

Table 4: Relationship between maternal serum calcium levels and perinatal outcome

Serum Levels (mg/dl)	Gestational Hypertension		Pre-eclampsia		Eclampsia		P value
	APGAR>7 N=28	APGAR<7 N=8	APGAR>7 N=14	APGAR<7 N=35	APGAR>7 N=1	APGAR<7 N=25	
S. Calcium (Mean± SD) (Min-Max)	8.91 ± 0.54 (8-9.9)	8.57 ± 0.53 (7.8-9.2)	8.69 ± 0.83 (6.9-9.8)	8.5 ± 0.92 (6.4-10.6)	8.2±0 (8.2-8.2)	8.42 ± 0.77 (6.7-9.7)	0.03

Of 36 neonates delivered from women in gestational hypertension group, 28(77.77%) were born healthy (APGAR score >7) and 8 (22.22%) neonates had APGAR score <7 at birth, of which 5(62.5%) had mild respiratory distress and were put on oxygen therapy by hood; one (12.5%) had severe birth asphyxia and was put on ventilator support, but later the baby was discharged under satisfactory condition. There was one (12.5%) intrauterine death and one (12.5%) fresh still birth in this group. In second group; of 49 neonates born to women with pre-eclampsia; 14(28.57%) were born healthy (APGAR >7) and 35(71.43%) had APGAR score <7 at birth, of which 14(40%) required oxygen by hood due to mild respiratory distress; 6(17.14%) developed severe birth asphyxia and

Table 5: Relation of maternal serum calcium levels and neonatal birth weight

Categories	Gestational Hypertension	Pre-eclampsia	Eclampsia
Serum Calcium (mg/dl) (Mean± SD)	8.83 ± 0.55	8.55 ± 0.89	8.41 ± 0.76
Birth Weight (Kg) (Mean± SD)	2.956±0.273	2.475±0.324	2.177±0.282
P value	0.4371	0.3418	0.2932

Table 6: Maternal outcome in relation to serum calcium level

Categories			Serum calcium	P – Value
Gestational hypertension	Healthy (N=34)		8.86±0.53 (7.9-9.9)	0.0001
	Morbid (N=1)	On ventilator (N=1)	7.8±0 (7.8-7.8)	
		Without ventilator (N=0)		
	Dead (N=1)			
Pre-eclampsia	Healthy (N=27)		8.89±0.74 (6.9-10)	
	Morbid (N=22)	On ventilator (N=5)	8.14±0.91 (6.4-10.6)	
		Without ventilator(N=17)		
	Dead (N=3)			
Eclampsia	Healthy (N=1)		6.7±0 (6.7-6.7)	
	Morbid (N=25)	On ventilator (N=10)	8.48±0.69 (7-9.7)	
		Without ventilator(N=15)		
	Dead (N=7)			

were put on ventilatory support, but all these six neonates survived and were discharged in good condition. Of remaining 15 (42.85%) neonates in this group; 14(40%) were intra-uterine deaths and one (2.85%) still birth. In the last group of 26 neonates delivered to women with eclampsia; only one (3.84%) was delivered healthy (APGAR score >7) and remaining 25 (96.15%) had poor APGAR score (<7) at birth, of which 12 (48%) required oxygen therapy for respiratory distress; seven (28%) neonates suffered severe birth asphyxia and were put on ventilator, of which two (28.57%) died on day 3 and five (71.43%) neonates were discharged in good condition after 20-25 days. Of remaining six (24%) neonates in this group; four were intra-uterine deaths and two still births. The relation between mean serum calcium levels and perinatal outcome is depicted in Table 4. Hence, of total 111 babies born to women with HDP; 43 (38.74%) were born healthy, 31(27.93%) suffered some degree of respiratory distress and required oxygen support, 14(12.61%) neonates suffered severe birth asphyxia and required ventilator support, of which two had neonatal deaths, 19(17.12%) babies died in-utero and there were a total of four (3.60%) still births (Table 2).

The maximum number of perinatal deaths were observed in eclampsia group where the maternal serum calcium levels were very low, followed by preeclampsia and lastly in gestational hypertension group where the calcium levels were near normal. Hence, it was found that lower maternal serum calcium levels were associated with poor perinatal outcome (p<.05).

Of 36 neonates born to women with Gestational Hypertension, the mean (±SD) birth weight was 2.956±0.273 Kg, in 49 neonates of Pre-eclmapsia the mean birth weight was 2.475±0.324 Kg, whereas in eclampsia group it was 2.177±0.282 Kg. No significant relation was observed between neonatal birth weight and maternal serum calcium (p>.05) as shown in Table 5.

Of 110 women with HDP, 34(97.14%) in gestational hypertension group, 27(55.10%) with pre-eclampsia and one (3.85%) with eclampsia remained healthy in their immediate post-partum period. Around 17 (34.69%) women with severe pre-eclampsia and 15 (57.69%) women with eclampsia required intensive care in immediate postpartum period in intensive care unit (ICU) and one (2.86%) women with gestational hypertension, five (10.20%) with pre-eclmapsia and ten (38.46%) with eclampsia required ventilator support and high dependency unit (HDU) care for management of critical maternal condition. Of these 16 women with severe disease, ten could not be revived and died due to complications of disease. A significant relationship was observed between maternal serum calcium levels and severity of disease and maternal outcome (p<.0001) as depicted in Table 6.

Discussion

The present study was conducted to assess the effect of maternal serum calcium levels on severity of HDP as well as on overall maternal and perinatal outcomes. The mean ± SD levels of serum calcium in women with gestational hypertension, pre-eclampsia and eclampsia were 8.83 ± 0.55, 8.55 ± 0.89 and 8.41 ± 0.76 mg/dl respectively, indicating that maternal hypocalcaemia was associated with more severe disease. This was similar to the results of study, which also reported that hypocalcaemia was significantly associated with HDP and calcium level shows strong association with severity of disease [29].

Similar results were reported by other studies also, which found lower levels of maternal serum calcium in women suffering from pre-eclampsia and gestational hypertension as compared to normotensive women [30-32]. Another study also reported that the maternal serum calcium levels were significantly lower in women with severe pre-eclampsia (8.7 +/- 0.59 mg/dl vs. 8.99 +/- 0.31 mg/dl, p = 0.045; and 9.05 +/- 0.52 mg/dl, p = 0.014) as compared to normal pregnant women and those with mild pre-eclampsia [16].

Furthermore, in the present study it was found that the risk of adverse perinatal outcome was more in women with lower serum calcium levels. There were a total of 45 preterm births of which 11.43% were in gestational hypertension group, 46.94% in women with pre-eclampsia and 69.23% in eclampsia group. Only one neonate in eclampsia group was born healthy (APGAR>7). Also the maximum number of perinatal mortalities was observed in women with eclampsia (30.77%) followed by pre-eclampsia (30.61%) and minimum in gestational hypertension (5.55%) group, indicating that low maternal serum calcium levels are a poor predictor of fetal outcome. This was supported by a recent meta-analysis which found that calcium supplementation during pregnancy was associated with decreased risk of pre-eclampsia by 52%-55% and gestational hypertension by 35% in developing countries. Furthermore they observed that calcium supplementation during pregnancy was associated with a significant fall in neonatal mortality and risk of pre-term births by 24% [33].

In our study no significant relation was observed between neonatal birth weight and maternal serum calcium levels in all three groups (p>0.05). Similar results were reported by other studies also who observed a non-significant effect of calcium supplementation on neonatal birth weight [10, 34].

In the present study a significant correlation was found between maternal serum calcium levels and severity of disease as well as maternal outcome. Maximum patients (97.14%) with gestational hypertension having near normal serum calcium levels (mean ± SD: 8.83 ± 0.55) remained healthy in their immediate post-partum period whereas 34.69% women with pre-eclampsia and 57.69% women with eclampsia required intensive care in immediate postpartum period and 10.20% with pre-eclmapsia and 38.46% with eclampsia required ventilator support and high dependency unit (HDU) care. This was supported by a recent meta-analysis which reported that women receiving calcium supplements during pregnancy were less likely to die or have serious problems related to HDP [11, 24]. Another meta-analysis concluded that calcium supplementation, though does not prevent preeclampsia but does reduce its severity, associated maternal and neonatal morbidity and mortality [35].

Conclusion

Low maternal serum calcium levels were significantly associated with severity of HDP and adverse maternal and perinatal outcome. It can be concluded that maternal serum calcium levels can be used as a predictor of maternal and perinatal outcome in women with hypertensive disorders of pregnancy. Hence, calcium supplementation can prevent development and severity of HDP as well as overall maternal and perinatal morbidity and mortality.

Limitation

The present study was conducted on a small group of childbearing women with hypertensive disorder of pregnancy. In future we can think of conducting the study on larger group and also we can give supplemental calcium to all childbearing women from the first trimester onwards till delivery and can look for development, severity of HDP and overall maternal and perinatal outcome.

Conflict of interest: None. **Disclaimer:** Nil.

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