

Gestation, Severity of Hypertensive Disorders and Serum, Urinary, Calcium

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Abstract

Studies have supported and negated hypothesis, that hypocalcaemia is associated with hypertensive disorders of pregnancy (HDsP), mechanism is probably cellular. So serum and urinary levels do not reveal facts.

Objective: Study was carried out to know relationship between serum calcium, urinary calcium, fetomaternal outcome, with early onset (EO), late onset (LO) HDsP.

Materials and methods: Study subjects with singleton pregnancy beyond twenty weeks, diagnosed as gestational hypertension (GH), preeclampsia, eclampsia, over two years, were divided into EO (≥ 20 to <34 weeks gestation), LO (≥ 34 weeks), subdivided, category A (≥ 20 to <28 weeks), B (≥ 28 to <34 weeks), C (≥ 34 to <37 weeks), D (≥ 37 weeks), serum calcium, 24 h urinary calcium were measured. Pregnancy outcome was recorded.

Results: In EO HDsP, 11.07% had mild GH, of them 53.3% and in LO 38.97% had mild GH, of them 27.48% had hypocalcaemia. Amongst severe PE, of category A 55%, B 58.33%, C 40%, D 41% had hypocalcaemia. Mean serum calcium in A was 8.13 mg/dl, B was 8.15 mg/dl, C was 8.25%, D was 8.28 mg/dl, low in EO, but insignificant difference. Mean 24 h calciuria in A was 114.5 mg/24 h, B, 110.6 mg/24 h, significantly more than LO, 101.34 mg/24 h in C, 89.45 mg/24 h in D. Mean 24 h calciuria was significantly low in LO. In A 36 (45.0%) of 80 patients had hypocalcaemia, 6 (16.8%) of them had spontaneous preterm births, in B, of 191 patients, 106 (55.50%) had hypocalcaemia, spontaneous preterm births in 16.9%. In LO of 475 of C, 190 (40.0%) had hypocalcaemia 6.8% had spontaneous preterm births, significantly less than EO, though had hypocalcaemia.

Conclusion: Serum calcium was lower in EO than LO but difference insignificant. Many HDsP had hypocalciuria, mean 24 h calciuria was significantly more in EO compared to LO, difference in A, D significant. Studies are required to investigate further.

Keywords: Hypertensive disorders of pregnancy; Early onset; Late onset; Hypocalcaemia; Hypocalciuria

Abbreviations: EO: Early Onset; LO: Late Onset; HDsP: Hypertensive Disorders of Pregnancy, MGH: Mild Gestational Hypertension

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Citation: Chhabra S, Singh A (2018) Gestation, Severity of Hypertensive Disorders and Serum, Urinary, Calcium. Insights Reprod Med Vol.2 No.1:4

Received: September 18, 2017; Accepted: February 05, 2018; Published: February 15, 2018

Introduction

Studies have supported as well as negated the hypothesis that hypocalcaemia is associated with hypertensive disorders of

pregnancy (HDsP). Ray et al. [1] reported that preeclampsia was associated with increased levels of intracellular calcium, lower calcium-dependent ATPase activity of erythrocytes and hypocalciuria. It is well established that the free intracellular

calcium is a major determinant of vascular smooth muscle tone and consequently of peripheral vascular status [2-7]. Kisters et al. [8] reported significantly low levels of plasma calcium concentration in women with preeclampsia compared to healthy pregnant women or non-pregnant controls. Also membranous calcium content was significantly more in the preeclampsia cases compared to healthy pregnant women and non-pregnant controls. Lou et al. [9] have reported significant difference in mean serum calcium, 8.97 ± 0.49 in normotensive, 8.70 ± 0.58 in preeclampsia cases. The researchers reported that the trace element of calcium was not involved in the pathogenesis of preeclampsia. Jafrin et al. [10] with a study of 32 women with preeclampsia reported, the mean serum calcium, 7.32 ± 0.28 mg/dl, significantly less compared to that of the normal pregnancy. Conversely, low levels of urinary calcium excretion have been described in women with preeclampsia, probably due to increased tubular reabsorption [11]. In an observational case-control study by Richards et al. [12], hair and serum calcium concentrations were compared between women with preeclampsia and normal pregnancies and no significant difference was reported. So research continues about significance of calcium, especially in women with early onset and late onset HDsP.

Objective

Present study was carried out to know the relationship between serum calcium and 24 h urinary calcium and fetomaternal outcome in cases of EO and LO HDsP.

Materials and Methods

A prospective study of serum and urinary calcium in women with EO, LO HDsP, was carried out in the Obstetrics and Gynecology department with the help of Biochemistry of a rural institute in Central India. Institute's ethics committee's approval was taken. Study subjects were women with singleton pregnancy beyond

twenty weeks, diagnosed as gestational hypertension (GH), preeclampsia or eclampsia. Consent was taken. Those with pre-pregnancy renal, hepatic disorders, diabetes, or other disorders, past or current smokers and those not willing to deliver at the place of study, were excluded. The study subjects, over two years, were divided into EO (≥ 20 to <34 weeks gestation) and LO HDsP ≥ 34 weeks. The EO cases were further divided into category A (>20 to <28 weeks of gestation) and B (≥ 28 to <34 weeks) and the LO category C (≥ 34 to <37 weeks) and D (≥ 37 weeks). Information was collected and recorded with the help of a predesigned tool. Serum calcium and 24 h urinary calcium were done and repeated. Three venous blood samples and 24 h urine samples were collected at weekly intervals in category A, B and C and one or 2 samples were done in category D. The specimens were kept at 4°C till assayed for further analysis. Serum calcium and urinary calcium were analyzed by enzymatic method using automated spectrophotometer.

Serum calcium value of <8.2 mg/dl was taken as hypocalcaemia and urinary calcium <120 mg/24 h as hypocalciuria in all the cases and maternal, foetal, neonatal outcome were recorded. The measures of the four groups were compared for significance, using unpaired student's t test and ANOVA test. P values of less than 0.05 were considered significant.

Results

In EO HDsP, 11.07% (30 of 271) had mild gestational hypertension (MGH), 53.3% (16 of 30) of them had hypocalcemia. In LO cases 302 (38.97%) out of 775 had MGH, 27.48% (83 of 302) had hypocalcaemia, significant difference (P value <4.05). Overall in cases with MGH 40% (4 of 10 with MGH) of category A, 60.0% (12 of 20 with MGH) in category B, 31.18% (53 of 170 with MGH) in category C and 22.73% (30 of 132 with MGH) in category D had hypocalcemia, significant difference between EO & LO (p <0.05) (Table 1).

Table 1 Serum calcium and hypertensive disorders of pregnancy.

Category	Serum Calcium (mg/dl)		Mild GH	Severe GH	Mild PE	Severe PE	Eclampsia	Total
A N=80	<8.2	N=	4	15	5	11	1	36
		%	40.0	42.86	35.71	55.0	100.0	45.0
	≥ 8.2	N=	6	20	9	9	0	44
		%	60.0	57.14	64.29	45.0	0.0	55.0
B N=191	<8.8	N=	12	42	18	28	6	106
		%	60.0	52.5	48.65	58.33	100.0	55.5
	≥ 8.2	N=	8	38	19	20	0	85
		%	40.0	47.5	51.35	41.67	0.0	44.5
C N=475	<8.2	N=	53	33	48	28	28	190
		%	31.2	39.8	32.9	60.9	93.3	40.0
	≥ 8.2	N=	117	50	98	18	2	285
		%	68.8	60.2	67.1	39.1	6.7	60.0
D N=300	<8.8	N=	30	20	30	23	4	107
		%	22.7	55.6	32.6	67.6	66.7	35.6
	≥ 8.2	N=	102	16	62	11	2	193
		%	77.3	44.4	67.4	32.4	33.3	64.3
Total			332	234	289	148	43	1046

GH: Gestational hypertension; PE: Pre-Eclampsia

Out of EO, in category A (second trimester HDsP cases) MGH 40.0%, SGH 42.86%, mild PE 35.71%, severe PE 55.0%, and eclampsia 100% had hypocalcemia. In category B, 60% with MGH, 52.5% with SGH, 48.65% of MPE, 58.33% of SPE, 100% of eclampsia had hypocalcemia compared to category C 29.41% in MGH, 39.8% SGH 32.9% MPE, 34.78% SPE 40.0% eclampsia and in category D 15.15% of MGH, 55.6% SGH 32.6% MPE, of SPE 41.18% and 33.33% eclampsia (p<0.05) had hypocalcemia. Numbers with hypocalcemia were less in LO cases in most categories but there were variations. The mean serum calcium in category A was 8.13 mg/dl, in B 8.15 mg/dl and in C and D was 8.25% and 8.28 mg/dl, respectively, though comparatively low in EO cases but insignificant difference.

Over all in second trimester HDsP (Category A), 50% (5 of 10) of mild GH cases, 45.71% (16 of 35) with severe GH, 57.14% (8 of 14) with mild PE, 55.0% (11 of 20) with severe PE and the single patient of eclampsia in category A had hypocalciuria, more with PE had hypocalciuria, but with variations. In category B 25% of

mild GH, 46% severe GH, 29.07% of mild PE, 64.6% severe PE and 100% eclampsia had hypocalcemia. In category C 29.41% of mild GH, 40.96% of severe GH 52.05% of mild PE, with severe PE 34.78%, 40.0% of eclampsia numbers less than category A but variable. In category D 15.15% in mild GH 52.78% severe GH 50.0% of mild PE, severe PE 41.18% and 33.33% in eclampsia had hypocalciuria) variable (**Table 2**). The mean 24 h urinary calcium in category A was 114.5 mg/24 h, in category B, 110.6 mg/24 h, significantly more than LO cases (p>0.05), with 101.34 mg/24 h in category C and 89.45 mg/24 h in category D.

In second trimester hypertensive disorders, category (A), 36 (45.0%) of 80 patients had hypocalcaemia, 6 (16.8%) of them had spontaneous preterm births, and only 5.5% (2 of 36) went to term. Forty four patients (55.0%) of this category had normal serum calcium, 6 of 44 (18.1%) had spontaneous preterm births (**Table 3**). In all categories of HDsP numbers of preterm births were lower in cases with hypocalcaemia compared to normal calcium.

Table 2 Urinary calcium gestational age at delivery.

Category	Urinary Calcium (mg/24 h)		Mild GH	Severe GH	Mild PE	Severe PE	Eclampsia	Total
A N=80	<120	N=	5	16	8	11	1	41
		%	50.0	45.7	57.1	55.0	100.0	51.2
	≥ 120	N=	5	19	6	9	0	39
		%	50.0	54.3	42.9	45.0	0.0	48.7
B N=191	<120	N=	5	37	11	31	6	90
		%	25.0	46.3	29.7	64.6	100.0	47.1
	≥ 120	N=	15	43	26	17	0	101
		%	75.0	53.7	70.3	35.4	0.0	52.8
C N=475	<120	N=	50	34	76	16	12	188
		%	29.4	41.0	52.1	34.8	40.0	39.6
	≥ 120	N=	120	49	70	30	18	287
		%	70.6	59.0	47.9	65.2	60.0	60.4
D N=300	<120	N=	20	19	46	14	2	101
		%	15.2	52.8	50.0	41.2	33.3	33.6
	≥ 120	N=	112	17	46	20	4	199
		%	84.8	47.2	50.0	58.8	66.7	66.3
TOTAL			332	234	289	148	43	1046

N: Numbers; GH: Gestational Hypertension; PE: Pre-Eclampsia

Table 3 Gestational age at delivery and serum calcium.

Category	Serum Calcium (mg/dl)	Gestational Age At Delivery (in weeks)										Total	%
		<28		≥ 28-32		≥ 32-34		≥ 34-37		≥ 37			
		S	I	S	I	S	I	S	I	S	I		
A n=80	<8.2	3	12	2	13	1	3	-	-	-	2	36	16.66
	≥ 8.2	-	-	1	2	1	13	6	21	-	-	44	18.18
B n=191	<8.2	-	-	12	25	1	26	5	20	1	16	106	15.09
	≥ 8.2	-	-	6	-	16	1	13	36	3	10	85	42.35
C n=475	<8.2	-	-	-	-	-	-	13	42	15	120	190	6.84
	≥ 8.2	-	-	-	-	-	-	50	44	60	131	285	17.54
D n=300	<8.2	-	-	-	-	-	-	-	-	17	90	107	15.88
	≥ 8.2	-	-	-	-	-	-	-	-	22	171	193	11.39
Total		3	12	21	40	19	43	87	163	118	540	1046	

S: Spontaneous; I: Induced

Table Gestational age at delivery and 24 hr urinary calcium.

Category	24 Urinary Calcium (mg/24 h)	Gestational Age At Delivery (in weeks)										Total	%
		<28		≥ 28-32		≥ 32-34		≥ 34-37		≥ 37			
		S	I	S	I	S	I	S	I	S	I		
A n=80	<120	1	8	2	12	2	5	2	7	-	2	41	17.07
	≥ 120	2	4	1	3	-	11	4	14	-	-	39	17.94
B n=191	<120	-	-	6	18	2	19	5	23	1	16	90	14.44
	≥ 120	-	-	12	7	13	10	13	33	3	10	101	37.62
C n=475	<120	-	-	-	-	-	-	13	53	10	112	188	6.91
	≥ 120	-	-	-	-	-	-	50	33	65	139	287	17.42
D n=300	<120	-	-	-	-	-	-	-	-	11	90	101	10.89
	≥ 120	-	-	-	-	-	-	-	-	28	171	199	14.07
Total		3	12	21	40	17	45	87	163	118	540	1046	

S: Spontaneous; I: Induced

In category B of 191 patients, 106 had hypocalcaemia (55.50%), spontaneous preterm births occurred in 16.9% of 106 cases. Of 85 (44.50% of 191) women with normal serum calcium 41.2% had preterm births.

In LO cases of 475 patients of category C, 190 (40.0%) had hypocalcaemia and 6.8% of them had spontaneous preterm births. Of 285 patients with normal serum calcium 17.5% had preterm births.

In category D, of 300 patients beyond 37 weeks, 107 had hypocalcaemia (35.67%), of which 15.89% (17 of 107) had spontaneous labour and the rest 84.11% had labour induced. And of 193 patients with normal serum calcium, 11.40% (22 of 193) had spontaneous labour and in 88.60% labour was induced.

Fetal growth restriction (FGR) cases were significantly associated with hypocalcaemia and no hypocalciuria in both EO and LO HDsP (Table 4).

Discussion and Conclusion

Outcome of some studies revealed that the pathogenesis of pre-eclampsia might be having linkage to calcium [1,13]. In the present study overall in second trimester HDsP, (A) 51.25% cases (41 of 80) (category A) and 47.12% (90 of 191) in category B had hypocalcaemia, but 39.58% (188 of 475) in category C and 33.67% (101 of 300) in category D had hypocalcaemia, numbers with hypocalcaemia decreasing in LO cases. Overall in second trimester HDsP (category A), MGH 50.0%, SGH 45.7%, MPE 57.1%, SPE 55.0% and Eclampsia 100.0% had hypocalcaemia. In category B 25% of MGH, 46.3% of SGH, 29.7 MPE, 64.6% of SPH and 100% of eclampsia cases had hypocalcaemia. In category C 29.41% with MGH, 41% with SGH, 52.1% with MPE, 34.78% with SPE and 40.0% with eclampsia and in category D 15.15% with MGH, 52.8% SGH, MPE 50%, 41.18% in SPE and 33.33% of eclampsia cases had hypocalcaemia, variable picture in EO and LO HDsP and with different severity of HDsP. The mean 24 h urinary calcium in category A was 114.5 mg/24 h, in category B 110.6 mg/24 h, significantly less than LO cases, 101.34 mg/24 h in category C and 89.45 mg/24 h in term cases. Overall numbers of women with hypocalcaemia decreased in LO cases. The mean value of 24 hours urinary calcium was significantly low in LO cases. Though all cases of HDsP had hypocalcaemia, the mean 24

h urinary calcium was significantly more in EO cases, category A 110.6 mg/24 h in category B 114.5 mg/24 h, in LO cases, 101.34 mg/24 h in category C and 89.45 mg/24 h in category D ($p>0.05$). Whether it was excretion difference or less absorption is not clear because serum calcium was on lower side in EO cases and a lot of research is needed.

It seems more studies are required to define cut off values and the relationship of serum calcium and urinary calcium to onset of disorder and severity of HDsP and also in depth role of calcium. Present study was mainly for differences in serum and urinary calcium in EO and LO HDsP. Serum calcium and urinary calcium were measured to have some understanding of relationship but finding did not reveal anything significant. Intracellular calcium might be playing a major role. A lot of research is needed, whether extra calcium will help or not because if the problem is cellular it may be something else.

Dasgupta et al. [14] studied the changes in calcium excretion in women with pre-eclampsia, eclampsia and reported that 24 h urinary calcium decreased progressively in patients who developed preeclampsia around 32nd to 40th week and this difference was significant and suggested, calciuria may be good tool for prediction of preeclampsia and its severity. Normally there is an increase in the intracellular calcium in pregnancy [15,16]. Kosch [17] reported that this effect is exaggerated in preeclampsia due to a significant increase in the membranous calcium content. Conversely Kisters et al. [8] reported that membranous and intracellular calcium concentrations were low in these patients. The reduced calcium release into the sera by the pre-eclamptic women was reported to be directly related to an inhibition of calcium influx as well and prevent calcium mediated relaxation of vessels [18,19]. Further in-depth studies are required to investigate these altered cellular mechanisms leading to altered calcium excretion in HDsP.

In the Cochrane Database of Systematic Reviews [20], 11 studies were included with a modest reduction in high blood pressure with calcium supplementation with no effect on the risk of preterm births. Although there was a reduction in risk amongst women at high risk of hypertension, some heterogeneity in the results could be associated with study subjects' size, with the small studies having the most positive results. As the small

studies tended to recruit high-risk women, at least some of the heterogeneity may be explained by calcium having a greater effect for high-risk women. The other factors affecting the findings of various studies may be because of timings of sample collection, numbers of samples collected, storage and processing, prior history of calcium intake and level of dietary calcium. Severity of disease at early gestation was believed to be related to calcium haemostasis and needs to be investigated further. Present study is about calcium in serum and urine in cases with EO and LO and there was heterogeneity in findings though in category A more women with severe HDsP had hypocalcemia but in B it was not so.

In category C, D much lower number of women had low calcium. In category A there was hardly any difference in numbers with hypocalcemia in relation to severity of HDsP. In B there was a lot of heterogeneity. In C and D overall fewer women had hypocalcemia, but there was heterogeneity. Even for preterm births there has heterogeneity in cases with hypocalcemia and hypocalcaemia. Overall number of patients with hypocalcaemia decreased in LO cases but the mean value of 24 h urinary calcium was also significantly lower in LO cases. In-depth studies are needed to investigate about calcium in HDsP before calcium can be recommended for prevention as a program.

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