

Serum parathyroid hormone and total serum calcium levels in mild & severe preeclampsia versus normal pregnancy

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Summary:

Background: Preeclampsia (PE) is a major cause of maternal morbidity and mortality, complicating 3-14% of all pregnancies. Although the etiology remains unknown, placental hypoperfusion and diffuse endothelial cell injury are considered to be the central pathological process; many endocrinological changes have been linked to the etiology of preeclampsia including parathyroid hormone and calcium level.

Objective: to compare serum parathyroid hormone and total serum calcium levels in mild and severe preeclampsia versus normal pregnancy.

Patients and methods: Serum parathyroid hormone (PTH) level and total serum calcium level were measured in thirty normotensive pregnant women and thirty women with mild preeclampsia and thirty women with severe preeclampsia using Enzyme Linked Immuno- Sorbent Assay (ELISA) test for parathyroid hormone & colorimetric test for total serum calcium. All pregnant women enrolled in the study had similar demographic background. Patient and control groups were matched for age, and gestational age.

Results: Total serum calcium level was decreased and parathyroid hormone level was elevated in preeclamptic women compared to normotensive women with significantly lower total serum calcium (7.43 ± 0.68) and higher level of parathyroid hormone (93.84 ± 10.63) in severe preeclampsia compared to mild preeclampsia group where total serum calcium was (8.02 ± 1.02) and parathyroid hormone was (79.34 ± 6.04). With p value < 0.005 between mild & severe preeclampsia groups.

Conclusion: Total serum calcium is significantly decreased & parathyroid hormone is significantly increased in severe preeclampsia in comparison to normal pregnancy.

Keyword: serum calcium, serum PTH, preeclampsia.

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Introduction:

High blood pressure with or without proteinuria is a major causes of maternal death and morbidity worldwide (1) as well as perinatal morbidity and mortality. Half of the women with hyper tension have pre-eclampsia (2). The incidence of preeclampsia in developed world is estimated to range from 2-6% in healthy nulliparous women (3). In developing world, the incidence is reported to be 4-18% (4) the disease is mild in 75% of cases and severe in 25 % (5). Of all cases of preeclampsia, 10% occur in pregnancies of less than 34 weeks' gestation. Eclampsia is estimated to occur in 1 in 200 cases of preeclampsia when magnesium prophylaxis is not administered (6). Preeclampsia account for up to 14% (50000-75000) maternal death annually (2, 7). For this reasons, strategies to reduce the risk of hypertensive disorders of pregnancy have received a considerable attention (8). An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980 (9). An association has been found between preeclampsia and hypocalciuria (10), lower urinary calcium to creatinine ratio (11), hypocalcaemia

(12), lower dietary milk intake (13) and between eclampsia and hypocalcaemia (14, 15).

Low calcium intake may cause high blood pressure by stimulating either parathyroid hormone or renin release, thereby increasing intracellular calcium in vascular smooth muscle and leading to vasoconstriction. A possible mode of action for calcium supplementation is that it reduces parathyroid hormone release and intracellular calcium, and so reduces smooth muscle contractility. By similar mechanism, calcium supplementation could also reduce uterine smooth muscle contractility and prevent preterm labour and delivery (16). Several studies revealed that preeclamptic women had lower serum ionized calcium than normotensive third trimester pregnant women and that the intact parathyroid hormone levels were significantly higher in preeclamptic women as compared to normotensive pregnant third trimester women and a significant inverse relationship was observed between parathyroid hormone and both urine and serum ionized calcium (17).

The purpose of this study is to determine the level of serum calcium & its effect on the level of PTH in normal pregnancy and in pregnancies complicated by preeclampsia.

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Patient and Methods

Prospective case control study was conducted in the Department of Obstetrics and Gynecology/ Baghdad Teaching Hospital/ Medical City/ Baghdad/ Iraq in the period from March 2010 to March 2011, which includes ninety patients (sixty patients with approved diagnosis of preeclampsia and thirty normotensive pregnant women as a control group). Patients and control groups were matched for the age (20 to 35 years) and gestational age (28 to 41 weeks). The gestational age was calculated on the basis of weeks of gestation since the last menstrual period and confirmed by early ultrasound. The blood pressure was measured twice 4 hours apart at rest, and the diastolic level was measured at korotkoff phase V. Blood sample (3ml) was drawn from antecubital vein or from the dorsum of the hand of each patient without using tourniquet and left to stand at room temperature for at least 30 minutes to allow the blood to clot and then centrifuged for 5 minutes frozen at -20C° and kept till the time of testing when serum parathyroid hormone level was measured by ELISA using DRG PTH EIZA kit according to the manufacturer’s instructions. Also serum calcium was measured using colorimetric test (O.cresolphthaleine). Urine sample were taken for proteinuria dipstick.

Preeclampsia group: This group was subdivided into two subgroups: First subgroup included 30 patients diagnosed with severe preeclampsia with blood pressure 160/110 mm Hg and proteinuria of 3+ or more on two random urine samples collected at least 4 hours apart. Second subgroup included 30 patients diagnosed with mild preeclampsia with blood pressure > 140/90 mm Hg but less than 160/110 mm Hg and without signs and symptoms that are associated with severe preeclampsia while proteinuria in this group was 1+ or 2+.

Control group: The control group included 30 pregnant women, all of whom were monitored at the Department of Obstetrics

and Gynecology of our hospital from the 1st trimester and who have an uncomplicated antenatal course. Blood pressure measurements in this group were normal. Control patients were matched for gestational age and had no history of illness, hypertension, Diabetes or renal disease.

Verbal consent was taken from the studied groups for participation in this study.

Statistical analysis:

Analysis of data was carried out using the available statistical package of SPSS-18 (statistical packages for social sciences- version 18 “PASW” statistics).

Data were presented in simple measures of frequency, percentage, mean, standard deviation, standard error of mean and range (minimum-maximum values). The significance of difference of different means (quantitative data from different preeclampsia groups and control group) was tested using analysis of variance (ANOVA) for more than two groups and using independent student-t-test for difference between two means, while different percentages (qualitative data from different preeclampsia groups and from control group) were tested using pearson chi-square test (X2-test). Pearson correlation was calculated for the correlation between two quantitative variables with its t-test for testing the significance of correlation. Statistical significance was considered whenever the P-value was less than 0.05.

Results:

A total of 90 women in their third trimester of pregnancy were included in our study.

The demographic characteristics of the three groups included in the study are shown in table 1 with no statistically significant difference in age, gestational age between mild & severe preeclampsia and normotensive patients.

Table 1: Demographic characteristics of 3 different groups included in the study.

	Severe PE		Mild PE		Control		P- Value	
	No.	%	No.	%	No.	%	Severe Versus control	Mild Versus control
Age(years) <20	4	13.3	3	10.0	3	10.0	0.890	0.869
20-24	9	30.0	9	30.0	12	40.0		
25-29	7	23.3	7	23.3	5	16.7		
30-34	7	23.3	5	16.7	6	20.0		
≥ 35	3	10.0	6	20.0	4	13.3		
Mean ± SD (Range)	26.17±5.88 (16-38)		27.30±6.67 (17-39)		26.50±6.27 (17-39)		0.833	0.634
GA(Weeks) Preterm	22	73.3	9	30.0	8	26.7	0.0001*	0.774
Full term	8	26.7	21	70	22	73.3		
Mean±SD(Range)	34.23±3.30 (28-40)		36.73±2.80 (28-40)		36.90±2.62 (28-40)		0.001*	0.813

Systolic, diastolic blood pressure (B.P) & albumin distribution in mild, severe PE and the control groups are shown in table 2 with statistically significant difference in blood pressure between the three groups.

Table2: Systolic, diastolic B.P & albumin distribution in 3 different groups included in study.

	Severe PE No. = 30	Mild PE No. = 30	Control No. = 30	P – Value	
				Severe versus Cont.	Mild versus Cont.
SBP Mean±SD(Range)	173.0±14.89 (150-200)	142.83±9.35 (130-160)	121.67±9.32 (110-135)	0.0001*	0.0001*
DBP Mean ±SD (Range)	118.50±8.22 (110-140)	94.17±4.56 (90-105)	76.67±4.97 (65-85)	0.0001*	0.0001*
Albumin in urine (++++)	7	23.3	-	-	-
(+++)	16	53.3	-	-	-
(++)	7	23.3	11	36.7	-
(+)	-	-	19	63.3	-
Nil	-	-	-	-	30 100.0

Significant using Pearson Chi-square test for difference between proportions or Students-t-test for difference between two independent means at 0.05 level of significance.

Blood samples show elevation in parathyroid hormone in preeclampsia group with mean ±SD of 93.84 ± 10.63, 79.34 ± 6.04 for severe & mild preeclampsia respectively while in control group it was (42.01 ± 18.29). Which was significantly higher (P < 0.05) in both mild & severe preeclampsia when compared to control group and it was highly significant with P-value of 0.0001 between mild and severe preeclampsia. The maximum level of parathyroid hormone was 113.00 pg/L, 100.20 pg/L, 70.00pg/L for severe, mild preeclampsia & control group respectively while the minimum level was 76.70 pg/L, 74.60 pg/L, 14.20 pg/L for severe, mild preeclampsia and control group respectively as shown in table 3.

Table 3: Parathyroid hormone levels in 3 different groups included in the study.

Parathyroid hormone(pg/L)	Severe PE	Mild PE	Control
No.	30	30	30
Mean	93.84	79.34	42.01
Standard Deviation	10.63	6.04	18.29
Standard Error of Mean	1.94	1.10	3.34
Mode	80.00	76.90	28.10
Minimum	76.70	74.60	14.20
Maximum	113.00	100.20	70.00
Percentile 5th	77.90	74.80	15.00
25th	80.40	75.50	28.10
50th (Median)	96.50	76.95	38.45
75th	100.50	80.00	60.00
95th	110.00	93.00	68.10
99th	113.0	100.2	70.0
P value compared to control	0.0001*	0.0001*	
P value between mild & severe	0.0001*		

Significant using Students-t-test for difference between two

independent means at 0.05 level of significance

Total serum calcium level was decreased in preeclampsia group with mean ±SD of 7.43 ± 0.68, 8.02 ± 1.02 for severe & mild preeclampsia respectively while in control group the level was 9.48 ±0.74 which was statistically significant with P-value of 0.0001 in both mild and severe preeclampsia when compared with control group, it was also statistically significant with P-value of 0.01 between mild and severe preeclampsia as shown in table 4.

Table 4: Serum Calcium levels in 3 different groups included in the study.

Parathyroid hormone(pg/L)	Severe PE	Mild PE	Control
No.	30	30	30
Mean	7.43	8.02	9.48
Standard Deviation	0.68	1.02	0.74
Standard Error of Mean	0.12	0.19	0.14
Mode	8.00	8.20	10.00
Minimum	6.00	6.70	8.10
Maximum	8.40	10.20	10.70
Percentile 5th	6.20	6.80	8.20
25th	7.00	7.20	8.90
50th (Median)	7.55	8.00	9.55
75th	8.00	8.40	10.00
95th	8.20	10.10	10.40
99th	8.4	10.2	10.7
P value compared to control	0.0001*	0.0001*	
P value between mild & severe	0.01*		

Significant using Studies-t-test for difference between two independent means at 0.05 level of significance

Discussion:

In our study the level of total serum calcium was decreased in preeclampsia group compared to the control group and this decrease was statistically significant with lower level in severe preeclampsia group than in mild preeclampsia group. While parathyroid hormone was increased to a significant level in preeclamptic as compared to control group with higher level in patients with severe preeclampsia as compared to those with mild preeclampsia.

Many studies was done previously explain the relation between serum calcium, parathyroid hormone and preeclampsia.

Jain S. et al (18) analyze and compare the concentration of calcium, magnesium, and zinc in the serum of women with pre-eclampsia and in normal pregnant women. They found that reduction in serum levels of calcium, magnesium, and zinc during pregnancy might be possible contributors in the etiology of pre-eclampsia, and supplementation of these elements to diet may be of value to prevent pre-eclampsia. Hultin H. et al. (19) investigate the association of parathyroid adenoma with subsequent preeclampsia in the first singleton pregnancy with adjustment for potential confounding factors. They found that parathyroid adenoma prior to delivery is significantly associated with preeclampsia. Herrera J.A et al (20) reported that preeclamptic women present with a reduction in extracellular calcium concentration with low level of serum ionized calcium & found that the concentration of ionized calcium is crucial for the synthesis of vasoactive substances in endothelium like prostacyclin & nitric oxide. Saleh F. et al (21) found that there was a significant association between both systolic and diastolic blood pressure and serum PTH. The urinary calcium/urinary creatinine increased with increasing blood pressure. However, the urinary calcium/urinary creatinine did not affect the association between blood pressure and serum PTH in a multiple linear regression model. The relationship between blood pressure and serum PTH was also seen in subjects with similar urinary calcium/urinary creatinine, and a negative association between serum PTH and the urinary calcium/urinary creatinine was found. In conclusion, there is significant association between PTH and preeclampsia. Shaarawy M. et al (17) had studied the levels of calcium in urine & blood & also measure serum PTH, & 1, 25 (OH) 2 Vitamin D in patients with preeclampsia and found a reduction in total serum calcium, 1, 25 (OH) 2 Vitamin D, hypocalciuria & increase PTH in preeclampsia. Indumati V. et al (22) who measured both total & ionized calcium level in normal pregnancies & in pregnancies complicated by preeclampsia & had found that significant decrease in both total & ionized calcium in preeclampsia group; Also he found that this decrease in total & ionized calcium lead to an increase in PTH. Thereby increasing the intracellular calcium

levels, which lead to an increase in vascular smooth muscle contraction & thus increase in blood pressure. Hofmery G. et al (1) who measured total serum calcium, urine calcium to creatinine ration in patient with preeclampsia & found that in preeclampsia there was hypocalcaemia, low urine calcium to creatinine ratio & concluded that these changes in serum calcium lead to increase in PTH in patient with preeclampsia. Malas N.O et al (23), and Jaramillo L.P. et al (24) studied the relationship between total, ionized serum calcium, & preeclampsia and found that both total & ionized serum calcium was significantly decrease in preeclampsia & concluded that this decrease in serum calcium have a role in pathogenesis of preeclampsia by stimulating the release of PTH. These findings are similar to that present in our study. In a study done by August, et al (25) to determine whether alteration in calcium regulatory hormones are present in preeclampsia revealed that PTH was higher, but not significantly, in those with preeclampsia and the ionized calcium was not significantly different between preeclampsia and normotensive women this may be probably due to uncategorization of patient with preeclampsia into mild & severe groups while we did this in our study & he did not use the same exclusion criteria (like calcium intake in pregnancy which was excluded in our study). Over loop B.V. et al (26) observed that a reduction in ionized serum calcium level, elevated serum parathyroid hormone in mild gestational hypertensive disorders in addition, parathyroid and extracellular calcium affect the synthesis of PG12 which participate in the etiopathogenesis of pregnancy induced hypertension. Seely E.W et al (27) who studied changes in calciotropic hormones in preeclampsia reported that preeclamptic women had lower serum ionized calcium than normotensive third trimester pregnant women and that intact PTH levels were significantly higher in preeclamptic women as compared to normotensive pregnant 3rd trimester women and significant inverse relationship was observed between PTH & both urine & serum ionized calcium.

Conclusion:

Total serum calcium is significantly decreased & parathyroid hormone is significantly increased in severe preeclampsia in comparison to normal pregnancy.

Author contribution:

Study conception: Dr. Maad M. Shalal

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Acquisition of data analysis: Dr. Inaam F. Mohammad

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Drafting of manuscript: Dr. Najmah M. Miran

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