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Case-control Study on Serum Calcium and Magnesium Levels in Women Presenting with Preeclampsia

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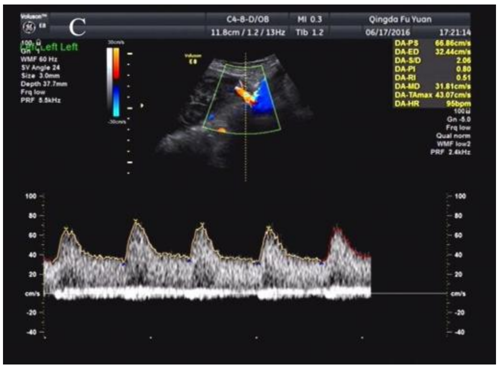
Abstract: **To study the difference of serum calcium (Ca^{2+}) and magnesium (Mg^{2+}) levels between preeclampsia (PE) pregnant women and normal pregnancy, and the effects on uterine artery blood flow resistance. This case-control study was conducted on 360 pregnant women (≥20 weeks gestation) received antenatal care at Affiliated Hospital of Qingdao University. The cases include 80 pregnant women with mild preeclampsia (MPE), 120 women with severe preeclampsia (SPE). The control group has 160 healthy and age matched pregnant women who were not received mineral during pregnancy. Demographic, anthropometric, clinical and obstetric data were gathered by an interview-based questionnaire. Venous blood samples were drawn for the measurement of serum Ca^{2+} and Mg^{2+} level. Doppler ultrasound was used to reflect the dynamic change of uterine artery. Pregnant women with SPE have significantly lower serum Ca^{2+} and Mg^{2+} levels than control group and pregnant women with MPE (OR=39.67, P<0.05). The uterine artery blood flow resistance in SPE is higher than others (P<0.05). This study shows that hypocalcemia and hypomagnesemia are the risk factors of SPE. Uterine artery blood flow resistance may be related to the decreased concentration of serum Ca^{2+} and Mg^{2+} levels.**



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1. Introduction

Preeclampsia (PE) is the human-pregnancy-specific disease that was defined as a blood pressure of at least 140/90 mmHg measured on two occasions each 6h apart, accompanied with proteinuria of at least 300mg per 24h, or at least 1+ on dipstick testing [1,2]. That is a disorder of widespread vascular endothelial malfunction and vasospasm. The global incidence of preeclampsia has been estimated at 5-14% of all pregnancies. In developing nations, the incidence has been reported as 4-18% [3]. The hypertensive disorders have been the second most common obstetric cause of stillbirths and early neonatal deaths. Risk factors for preeclampsia include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders, age >35 years at first pregnancy, smoking, and African American race [4]. The pathophysiology of preeclampsia involves both maternal and fetal factors. The developed abnormalities of placental vasculature in early pregnancy may lead to relative placental under perfusion. Hypoxia and ischemia could lead to body releases antiangiogenic enzyme into the maternal circulation that will alter maternal systemic endothelial function and cause hypertension and other manifestations of the PE disease.

Recently, many clinical studies shown that the relationship between aggravation of hypertension and the changes in maternal serum level of various minerals during pregnancy [5,6]. Serum Ca^{2+} and Mg^{2+} levels are very important for metabolism at the cellular level and are vital for cell death, muscle contraction and neuronal activity [7]. The observation of low serum Ca^{2+} and Mg^{2+} levels is agreed with other studies on hypertensive disorders complicating pregnancy [8,9]. Mg^{2+} as a kind of massive intracellular cation has been identified the cofactor in over 300 enzymatic reactions involving nucleic acid synthesis, energy metabolism and protein [10]. The essential trace element metabolism disturbance like calcium and magnesium play an important role in the development of PE disease [11]. Insufficient intaking of calcium is the contributory of the pathogenesis of hypertension. And the hypomagnesaemia will increase the incidence risk of PE disease [12]. And related studies show that serum Ca^{2+} and Mg^{2+} levels have significant role in pathophysiological regulation of blood pressure due to the effects of contractility and tone of blood vessels [13]. These reveal that serum Ca^{2+} and Mg^{2+} levels are related to the PE disease [14]. Considering the physiological serum Ca^{2+} and Mg^{2+} levels may be the risk predisposing factors to preeclampsia, further investigations should be carried out in preeclampsia pathogeny. The present study was aimed to find the possible role of serum Ca^{2+} and Mg^{2+} in preeclampsia etiopathogenesis and the link between their change and uterine artery resistance.

2. Methods

2.1. Study design

Total 380 participants (≥20 weeks gestation) were involved in the study. The cases group includes 120 pregnant women with mild preeclampsia and 100 pregnant women with severe preeclampsia. A total of 160 pregnant women with normal blood pressure and without proteinuria were selected to control group, who were age-matched with cases group only the gestational age 20 weeks or more were eligible participants for this study.

The matching criterion is that all gravitas have the same origin, maternal age±3 years and gestational age±2 weeks. PE was defined as blood pressure >140/90mmHg occurring after 20 weeks of gestation with previously normal blood pressure, associated with proteinuria >0.3g in a 24-hour urine specimen. Severe PE was defined according to the American College of Obstetricians and Gynecologists criteria as the presence of at least one of the following: (1) blood pressure >160/110mmHg in 2 measurements 4h apart while the patient was on a bed rest; proteinuria >5g in a 24h urine specimen; (2) oliguria of less than 25mL per hour; (3) cerebral or visual disturbances; (4) pulmonary edema or cyanosis; (5) epigastric pain; (6) impaired liver function defined as serum aspartate aminotransferase concentrations >70IU/L; (7) thrombocytopenia defined as platelet count lower than 100 Giga/L; (8) fetal growth restriction (FGR). Pregnant women with chronic hypertension, on antihypertensive therapy, eclampsia, diabetes, autoimmune disease and renal disease were excluded from the study.

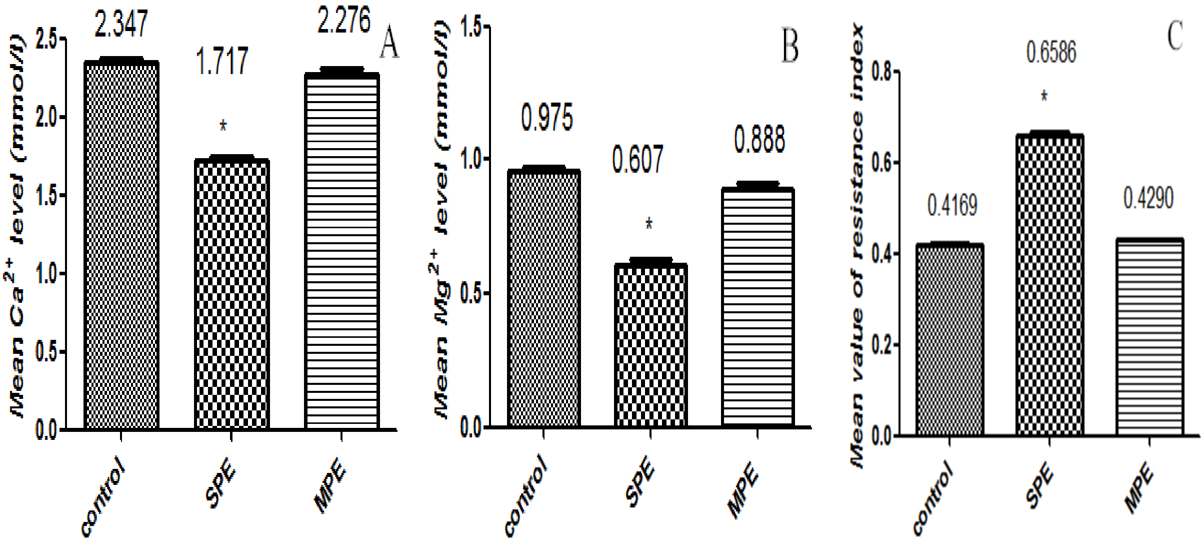

Figure 1. A and B: Mean Ca2+ and Mg2+ levels in the control group, SPE and MPE. C: uterine artery blood flow resistance, using MRI for this parameter. SPE: Severe preeclampsia, MPE: Mild preeclampsia, Ca2+: Calcium, Mg2+: Magnesium. P < 0.05 was considered significant for statistical comparisons using the t-test.

2.2. Blood pressure and proteinuria measurements

Blood pressure of all subjects was measured by the sphygmomanometer in two times with interval 6h. For diagnosing proteinuria, the protein content of 24h urine sample was measured routinely or 2 midstream urine samples collected in morning and evening showing albumin "±" in reagent stripe.

2.3. Biochemistry test of serum Ca^{2+} and Mg^{2+}

Serum Ca^{2+} is tested by O-Cresolphthalein complex one method without deproteinization. Calcium with O-Cresolphthalein complex one will form a violet complex in alkaline medium. Serum Mg^{2+} is tested by xylidyle blue. Magnesium ions could react with xylidyl blue in alkaline medium to form a water soluble purple red chelate. Color intensity of chelate is proportional to the concentration of magnesium ion in the sample. Calcium is excluded from the reaction by complexing with EGTA.

2.4. Detection of uterine artery resistance

The uterine artery resistance of the 380 participants was observed with HP4500 color doppler ultrasonic diagnostic apparatus. Before checking, all pregnant women should drink a little water in order to make bladders filling. The each side of uterine artery was visualized at the point distal to the crossover with the iliac artery. And then, 3 stable and consistent patterns of uterine artery blood flow spectrum were saved in their inspection report. The resistance index was calculated to reflect the blood flowing resistance of uterine artery.

2.5. Statistical analysis

Statistical analysis was performed by SPSS 23.0. Student's t-test was used to reveal the differences between each group. P < 0.05 shows existing statistical significant difference.

3. Results

As shown in Table 1, there was no significant difference in gestational and maternal ages between the three groups. Compared with control group, the mean blood pressure was significantly lower than women with MPE (P <0.05) and SPE (P <0.05).

There is a significantly lower mean serum Ca^{2+} (Figure 1A) and Mg^{2+} (Figure 1 B) levels of pregnant women with SPE than that in control group (P<0.001). And there are significant difference in the mean serum Ca2+ (P<0.05) and Mg2+ (P<0.05) levels between women with MPE and SPE, respectively. But, there is no difference in serum Ca^{2+} and Mg^{2+} between the MPE and control group.

Figure2B shows uterine artery diastolic flow of SPE group is significantly less and the systolic peak is relatively steep. From Figure2A and Figure2C can see, the uterine artery blood flow resistance of SPE group is higher than control group and MPE group. MRI maging examination also shows uterine artery blood flow resistance of SPE group is significantly higher than MPE (P<0.05) and control group (P<0.05), Figure1 C. But there is no significant difference in the uterine artery blood flow resistance between women with MPE and control group.

Table 1 Demographic, clinical and obstetric related characteristics of the study population

Variables	Control (n=160)	$^{\alpha}$P	SPE (n=120)	$^{\beta}$P	MPE (n=80)	$^{\gamma}$P
Age(years)	28.60 ±2.83	0.090	29.80	0.281	29.70	0.056
SBP (mmHg)	112.50 ±8.40	< 0.001	155.17	0.293	152.60	< 0.001
DBP (mmHg)	65.25±6.40	<0.001	101.63	0.513	102.24	< 0.001
BMI (kgm−2)	28.25 ±5.67	0.482	29.70	0.938	29.04	0.448
Gestational age (weeks)	31.92 ±4.69	0.632	31.40	0.499	30.72	0.251
Gravidity (%)						
Primigravida	88 (55)	0.962	77 (64.2)	0.894	53(66.2)	0.788
Multigravida	72(45)	0.113	43(35.8)	0.248	27 (33.8)	0.936
Contraceptive use (%)						
Yes	68 (42.5)	0.392	32 (26.7)	0.910	34 (42.5)	0.698
History of Abortion (%)						
Yes	40 (25.0)	0.279	12 (10.0)	0.9723	10(8.0)	0.443

Values are in mean ± SD and frequency (proportion) where appropriate. Comparison between proportions was using Fischer's exact test. One-way ANOVA coupled with Dunnett multiple comparisons was used to compare multiple groups. $^{\alpha}$P: comparison between control & SPE; $^{\beta}$P: comparison between SPE& MPE; $^{\gamma}$P: comparison between controls & MPE. SPE: Severe preeclampsia; PE: Pre-eclampsia, MPE: Mild preeclampsia; DBP: Diastolic blood pressure. Data in boldface indicate statistical significance.

As shown in Table 2, all women with SPE had hypocalcaemia (100%each). The proportion of women with SPE with hypomagnesaemia was 87.5% (OR=39.67, P=0.000), respectively. We found that serum calcium and magnesium reduced is the absolute risk factors for the occurrence of SPE. 160 pregnant women in the control group had hypocalcaemia 8(5%) and hypomagnesaemia 24(15%). And 80 pregnant women in the MPE group had hypocalcaemia 13(16%) (OR=3.68, P=0.000) and hypomagnesaemia 17(21%) (OR=1.5, P=0.000). A risk factor for the decline in blood calcium and magnesium is MPE. Compared with normal pregnant women, incidence rates were increased by 3.68 times and 1.5 times. 174 pregnant women (48.3%) of the total population were overweight. Of this, 39 were from the control group, 73 pregnant women are with SPE and 62 pregnant women are with MPE.

4. Discussion

PE is associated with increased morbidity and mortality, especially during delivery [1]. Our study' aim is that to study the difference of serum Ca^{2+} and Mg^{2+} levels between preeclampsia (PE) pregnant women and normal pregnancy, and the effects on uterine artery blood flow resistance. It also can help identify the factors that may contribute to the increased incidence of PE. Our results showed that: (1) levels of serum Ca^{2+} and Mg^{2+} was significantly reduced in women with SPE; (2)serum Ca^{2+} and Mg^{2+}in SPE lower than MPE; (3)serum Ca^{2+} and Mg^{2+} decline was associated with a higher risk of developing PE; (4)uterine artery blood flow resistance was significantly increase in women with SPE. The present study could add to cognition on the causes of PE and may influence prevention and treatment through mineral supplementation during the antenatal period.

PE is a severe disease as it is usually has significant unhealthy outcomes and can increase the maternal and perinatal mortality. However, although a large number of screening tests for preeclampsia have been put forward over the past few decades, no test has been able to properly screen for the disease and no completed measurement for initial prevention has been designed [15,16]. A probable theory to our survey is that PE is always accompanied by serum Ca^{2+} levels reduced, the levels of intracellular Ca^{2+} increased, the increased vascular resistance [17,18], the culminating in a peaked systolic and diastolic blood pressure. Furthermore, previous research has shown that altered Ca^{2+} homoeostasis, as exhibited by increased Ca^{2+} excretion, is connected with higher blood pressure levels [19]. Low serum Ca^{2+} levels may also increase blood pressure by irritating parathyroid hormone and rennin release, which could increase intracellular calcium in smooth muscle and lead to blood vessel contraction, eventually [20]. The research is further supported by the 2011 WHO recommendation, which found a higher risk of preeclampsia in fetation women with low dietary intake of calcium [21].

Mineral deficiencies like calcium, magnesium, have been identified to cause significant unhealthy problems for women of reproductive age, especially in developing countries owing to inadequate dietary intake. The risk of absence becomes increased during pregnancy due to the increased need of the growing fetus for many nutrients [22]. The changes of these trace elements could affect pregnancy. One of the problems that influenced by nutrient deficiencies is preeclampsia. Recently, more emphasis has been laid on the relationship between maternal serum level of elements and occurrence of preeclampsia [23,24].

The observed low levels of Mg^{2+} in women with PE could be caused by the decreased dietary intake, increased excretion by the kidneys, haemodilution of the extracellular clearance and increased consumption of minerals by the growing baby [25]. The lower serum Ca^{2+} and Mg^{2+} levels play an key role in the development of PE. Other researchers have found that a reduction in the level of extracellular Mg^{2+} could cause partial membrane depolarization. The decreased repolarisation with the opening of Ca^{2+} membrane channels will result in an intracellular Ca^{2+} gathering constantly-increasing. Furthermore, the existing increase in the foetal Ca^{2+} demand may also block bone resorption of Ca^{2+} with a concurrent intracellular pull [26,27]. The higher blood pressure and the increased uterine artery blood flow resistance are the regular clinical manifestation of PE disease.

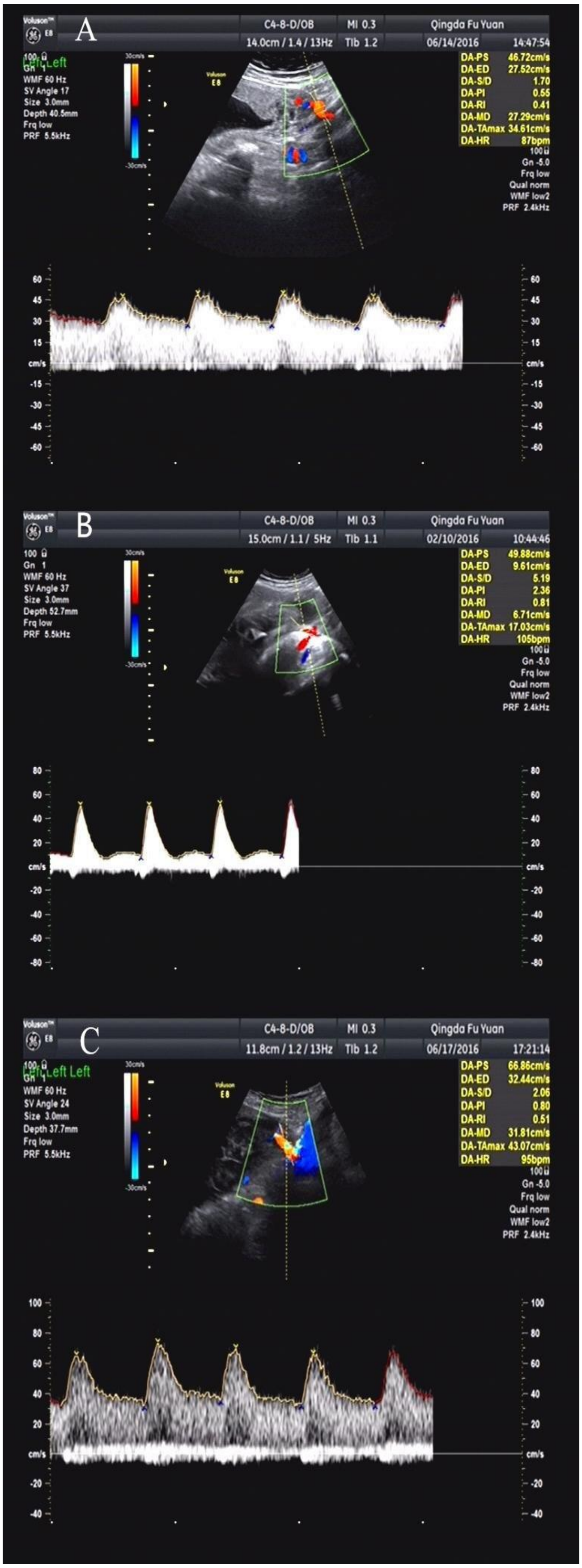

Figure2. The spectrum of uterine artery. A: Control group; B: SPE group, C: MPE group.

Table 2 Prevalence of overweight, obesity, hypocalcaemia and hypomagnesaemia amongst study participants

Variables	Controls(n=160)	SPE(n = 120)	MPE (n = 80)	Total(Prevalence)
BMI (kg/m2)				
BMI >25	36 (24.3%)	73(60.8%)	62 (77.5%)	174 (48.3%)
BMI <25	124 (75.7%)	47 (39.2%)	18(22.5%)	186 (51.7%)
Ca2+ (mmol/l)				
Low (<2.11)	8 (5.0%)	120 (100.0%)	13 (16%)	141 (39.0%)
Normal(2.11-2.52)	152 (95.0%)	0 (0.0%)	67(84%)	219(61.0%)
Mg2+ (mmol/l)				
Low (<0.75)	24 (15.0%)	105 (87.5%)	17(21.0%)	146 (40.5%)
Normal(0.75-1.02)	136 (85.0%)	15 (12.5%)	63 (79%)	214 (59.5%)

BMI = Body Mass Index, Ca^{2+} = Calcium, Mg^{2+} = Magnesium, PIH: Pregnancy-induced hypertension; PE: Pre-eclampsia.

5. Conclusion

In conclusion, according to the results from our research, the level of calcium and magnesium should be considered as a predicting factor of preeclampsia during the major evaluation of pregnancy. Our study suggested that lack of serum calcium and serum magnesium is a risk factor for the occurrence of preeclampsia. Uterine artery blood flow resistance may be related to the decreased concentration of serum Ca^{2+} and Mg^{2+} levels. So routine maintaining the levels of serum Ca^{2+} and Mg^{2+} should be used as a preventive method to allow the large sector of the developing countries population to maximize the use of the limited resources in the best way.

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Conflict of interests

There is no conflict of interest in this article. This multicenter case-control study with consecutive sampling was conducted in the Affiliated Hospital of Qingdao University, Qingdao, China, from August 2014 to June 2015. The study was approved by the Affiliated Hospital of Qingdao University ethics committee and authorities of the selected hospitals. Participations were voluntary and the written informed consents were obtained from each participant.

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