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PRELIMINARY REPORT

Calcium-to-Creatinine Ratio in Spot Urine Samples in Early Pregnancy and Its Relation to the Development of Preeclampsia

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We investigated the relation between an alteration in calcium (Ca) excretion in early pregnancy and the risk of preeclampsia in 1,147 pregnant women. We measured Ca and creatinine (Cr) concentrations in spot urine samples obtained at 12 weeks or less of gestation. Seventy-one (6.2%) had hypertension alone, nine (0.8%) developed superimposed preeclampsia, 39 (3.4%) developed proteinuria alone, and 13 (1.1%) developed preeclampsia; 1,015 women did not develop hypertension or proteinuria. The Ca/Cr ratio was significantly reduced in the 39 women who eventually developed proteinuria ($0.116 \pm .103$) and 13 who developed preeclampsia ($0.121 \pm .063$) compared with 1,015 women who had neither hypertension nor proteinuria ($0.158 \pm .239$). The relative risk of development of preeclampsia, proteinuria, or superimposed preeclampsia was 1.98 (95% confidence interval, 1.22 to 3.22) for women with a Ca/Cr ratio less than the 30th percentile (0.082) compared with women with a Ca/Cr ratio greater than the 30th percentile. These results suggest that preeclampsia may be related, in part, to a relative Ca intake deficiency. Determination of the Ca/Cr ratio in spot urine samples in the first trimester is of only limited clinical value for identifying women with an increased risk of preeclampsia.

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PREECLAMPSIA is the most common medical complication of pregnancy and is an important cause of maternal and fetal morbidity and mortality. Although preeclampsia is a multisystem disorder, elevated blood pressure is usually the first clinical sign. Women with established preeclampsia exhibit hypocalciuria,^{1,2} and calcium supplementation has been found to decrease the incidence of gestational hypertension.³⁻⁵ Studies have suggested that women who eventually develop preeclampsia exhibit hypocalciuria^{6,7} or a low urinary calcium (Ca) to creatinine (Cr) ratio⁸ in the second trimester of pregnancy. We investigated the usefulness of an alteration in calcium excretion in the first trimester of pregnancy as an early marker of the subsequent risk of preeclampsia.

SUBJECTS AND METHODS

We measured Ca and Cr concentrations in spot urine samples obtained at 12 weeks or less of gestation from 1,474 pregnant Japanese women at Jichi Medical School Hospital between June 1991 and December 1994. We excluded 148 women from analysis for the following reasons: 98 delivered at other hospitals; 43 had a miscarriage before 15 weeks' gestation; and seven, none of whom developed preeclampsia, underwent preterm delivery at less than 33 weeks' gestation. The remaining 1,326 women were evaluated prospectively at our clinic and gave birth after at least 33 weeks of gestation at Jichi Medical School Hospital. Urinary levels of Ca and Cr were measured by

a colorimetric technique (Iatrotect Ca, Dia-Iatron, Tokyo, Japan, for Ca; and Serotec CRE-L, Serotec, Sapporo, Japan, for Cr) with an automatic analyzer (Hitachi 7250; Tokyo, Japan). All but one of the investigators (H.M.) were unaware of the results until completion of the study. After delivery, the medical charts were reviewed by two of us (A.I. and T.K.) for evidence of hypertension and proteinuria. We excluded 179 women with underlying conditions such as diabetes mellitus, renal disease, and autoimmune disease from the evaluation. Proteinuria was defined as the presence of protein in urine as detected by dipstick determinations at least twice during the third trimester. Hypertension was defined as a systolic or diastolic blood pressure of at least 140 or 90 mm Hg, respectively, observed on at least two occasions at any stage of pregnancy. Preeclampsia was defined as the development of hypertension and proteinuria (protein loss > 0.3 g/d) in the second half of pregnancy. Superimposed preeclampsia was defined as the development of proteinuria in the presence of hypertension that occurred earlier than 20 weeks of gestation.

The odds ratio was used to estimate the relative risk of complications. Miettinen's method⁹ was used to compute the 95% confidence interval.

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Table 1. Clinical and Laboratory Findings

Group	Age (yr)	Duration of Pregnancy (wk)	Blood Pressure (mm Hg)*	Urinary Concentration				Ca/Cr Ratio	
				Ca (mg/dL)		Cr (mg/dL)		Mean \pm SD	Range
				Mean \pm SD	Range	Mean \pm SD	Range		
Control (n = 1,015)	29.4 \pm 4.6	39.2 \pm 1.4	115 \pm 12/70 \pm 9	16 \pm 12	1-91	131 \pm 84	3-607	0.158 \pm .239	.003-7.333
Hypertension (n = 71)	29.5 \pm 4.7	38.5 \pm 1.6§	132 \pm 14 /80 \pm 10	15 \pm 11	1-63	132 \pm 92	23-521	0.143 \pm .115	.015-.690
Superimposed pre-eclampsia (n = 9)	30.3 \pm 3.3	37.0 \pm 1.1	139 \pm 13 /85 \pm 8	23 \pm 19	2-58	186 \pm 126	25-336	0.132 \pm .070	.068-.273
Proteinuria only (n = 39)	29.5 \pm 3.7	39.2 \pm 1.2	115 \pm 13/71 \pm 10	14 \pm 10	2-34	140 \pm 67	26-272	0.116 \pm .103†	.015-.625
Preeclampsia (n = 13)	31.0 \pm 2.7	39.0 \pm 2.2	131 \pm 14 /81 \pm 8	18 \pm 11	3-40	146 \pm 48	58-213	0.121 \pm .063†	.033-.274

*Determined at 37 weeks' gestation or at the final antenatal visit in women who did not complete 37 weeks.

† $P < .05$, ‡ $P < .02$, § $P < .01$, and || $P < .001$: v control.

Student's t test was used to compare means. A P value less than .05 was accepted as statistically significant.

RESULTS

Of 1,147 women for whom data were analyzed, 71 (6.2%) developed hypertension alone, nine (0.8%) developed superimposed preeclampsia, 39 (3.4%) developed proteinuria alone, and 13 (1.1%) developed preeclampsia (Table 1). The remaining 1,015 women (88%) had neither hypertension nor proteinuria and served as the control group. Ca and Cr concentrations in spot urine samples and the Ca/Cr ratio varied widely in each group. Although urinary concentrations of Ca and Cr did not differ significantly among groups, the Ca/Cr ratio was significantly lower in groups with proteinuria and preeclampsia compared with the control group. The Ca/Cr ratio was less than the 10th percentile (0.043) in 10 (16%) of 61 women with proteinuria only, superimposed preeclampsia, or preeclampsia; less than the 30th percentile (<0.082) in 28 women (46%); and less than the 50th percentile (<0.121) in 38 women (62%). The best cutoff point for identifying the risk of complications was obtained by analyzing the receiver operating characteristic curve for the Ca/Cr ratio. The relative risk for development of complications for women with a Ca/Cr ratio less than 0.082 was 1.98 (95% confidence interval, 1.22 to 3.22), compared with women with a Ca/Cr ratio greater than 0.082. This best cutoff value had a sensitivity of 46%, a specificity of 71%, a positive predictive value of 8.1%, and a negative predictive value of 96%.

DISCUSSION

Women with a low urinary Ca/Cr ratio at 12 weeks or less of gestation were more likely to develop preeclampsia or proteinuria than women with a higher Ca/Cr ratio, suggesting that women with an increased risk of preeclampsia exhibited decreased urinary Ca excretion during the first trimester. Increased dietary Ca intake is associated with decreased blood pressure.¹⁰ The inverse relationship between Ca intake and gestational hypertension and eclampsia,¹¹ the beneficial effect of Ca supplementation on blood pressure during pregnancy,³⁻⁵ and the present results strongly suggest that a relative Ca intake deficiency contributes, in part, to the development of preeclampsia.

The best cutoff value for the Ca/Cr ratio had low sensitivity and low positive predictive value for identifying women at risk of proteinuria, superimposed preeclampsia, or preeclampsia, suggesting that the urinary Ca/Cr ratio in the first trimester is of limited clinical value for identifying women at increased risk of preeclampsia. This result is consistent with a previous report¹² indicating that determination of the Ca/Cr ratio in spot urine samples is not a useful screening test for pregnancy-induced hypertension or preeclampsia.

In the present study, urinary Cr tended to be higher in women with superimposed preeclampsia, proteinuria, or preeclampsia than in control women or women with hypertension. A similar phenomenon was also observed by Baker and Hackett.¹² Further studies are needed to clarify the significance of this observation.

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