제목	국문	임산부의 산소성 손상에 대한 유전적 감수성
	영문	Genetic susceptibility of term pregnant women to oxidative damage

저 자 및 소 속	국문	홍윤철¹ , 이관희¹, 이철호¹, 하은희², David C. Christiani³ 인하대학교 의과대학 산업의학과¹, 이화여자대학교 의과대학 예방의학교실², 하바드 보건대학원 환경보건과
	영문	Yun-Chul Hong¹ , Kwan-Hee Lee¹, Cheol-Ho Yi¹, Eun-Hee Ha², David C. Christiani³ *Department of Occupational and Environmental Medicine, Inha University College of Medicine¹, Department of Preventive Medicine, Ewha Women's University College of Medicine², Department of Environmental Health, Harvard School of Public Health³*

분야	역학 [유전역학]	발표자	홍윤철 [일반회원]	발표형식	구연

진행상황	연구완료

1. 목적

Pregnant women and developing fetuses are reported to be vulnerable to environmental pollutants, including polycyclic aromatic hydrocarbons (PAH) from the household sources. There is evidence that maternal PAH exposure is associated with an increased risk of adverse pregnancy outcomes, such as reduced birth weight and small-for-gestational-age. Because neonatal urinary 8-OH-dG concentrations increase with maternal exposure to environmental tobacco smoke, cellular oxidative stress is likely an important determinant of adverse pregnancy outcome. 8-OH-dG is a well-established measure of oxidative DNA damage and MDA is one of the main products of lipid peroxidation.

Generally, biomarker studies show variability between individuals, and genetic difference is a cause of this variability. Therefore, it is possible that genetic polymorphisms modulate the levels of oxidative injury biomarkers. Genetic polymorphisms have been detected in a variety of enzymes involved in the activation and detoxification of exogenous chemicals, and of enzymes involved in production and scavenging of reactive oxygen species.

To examine whether the levels of oxidative stress biomarkers, namely, urinary 8-hydroxydeoxyguanosine (8-OH-dG) and malondialdehyde (MDA), are modulated by genetic polymorphisms, we conducted a study upon pregnant women, at delivery, in Incheon, Korea. To evaluate genetic susceptibility to oxidative stress, we examined the influence of metabolism and oxidative stress-related genotypes. CYP1A1 (MspI and Ile-Val), CYP2E1 (PstI) polymorphisms for phase I enzyme activity and GSTM1 and GSTT1 polymorphisms for phase II detoxification enzyme, which are both associated with the metabolism of PAH, were analyzed. Myeloperoxidase (MPO) and manganese superoxide dismutase (MnSOD), which are associated with oxidative stress, were also analyzed.

2. 방법

The study included 81 pregnant women from Incheon, an industrialized urban area in Korea. Enrollment was restricted to women who had resided in Incheon and had not smoked during pregnancy. Initially, 105 pregnant women hospitalized for delivery volunteered to participate during 6 months of enrollment (January 1, 1999 to June 13, 1999). Twenty-four women were excluded from the final analysis because their

blood and urine samples proved to be unsuitable for laboratory analysis. Other than height, the general characteristics of excluded women were not different from the final study participants. Blood and urine samples were collected at admission. A questionnaire administered to the pregnant women at the blood sampling included questions on exposure to environmental tobacco smoke, residential and employment histories, alcohol consumption and diet patterns.

Urinary concentrations of biomarkers were adjusted to creatinine levels to control for variations in urine flow, and log-transformed concentrations were used to stabilize the variance. Geometric mean and geometric standard deviations of the urinary concentrations were used as measures of the data distribution. Associations between the levels of biomarkers and predictor variables were initially evaluated by the Student's t-test followed by multivariate analyses. Multiple regression analysis was then used to investigate the relationships between genetic polymorphisms and oxidative injury biomarkers, whilst controlling other covariates. The statistical analyses were performed using SAS (version 6.12) software. All statistical significance testing was two-sided.

3. 결과

The characteristics of the study participants are described in Table. The proportion reporting environmental tobacco smoke exposure was 54.3%. The homozygous wildtype frequencies of CYP1A1 MspI, CYP1A1 Ile-Val, CYP2E1 PstI, GSTM1, and GSTT1 were 46.3%, 57.5%, 69.1%, 60.5%, and 49.4%, respectively. The frequencies for wild-type MPO and MnSOD were 79.2% and 77.9%. Genotype distributions agreed with those predicted by the Hardy-Weinberg equilibrium (P>0.05). The homozygous and heterozygous allelic variants were combined in the analysis because of small numbers of homozygous variant genotypes.

The geometric mean (GSD) urinary concentrations of oxidative injury biomarkers of the study subjects were 2.47 mg/g creatinine (3.34) for 8-OH-dG and 0.22 mg/g creatinine (0.37) for MDA. 8-OH-dG levels were statistically significantly correlated with urinary MDA levels (Pearson's correlation coefficient 0.291, P

Genetic polymorphisms of metabolizing enzyme and oxidative stress-related enzyme changed the concentrations of urinary 8-OH-dG and MDA. When analyzed with other variables in the multivariate model, the concentrations of urinary 8-OH-dG were significantly elevated in the GSTM1 null type (P=0.02) and in the MnSOD mutant type (P=0.04). The concentrations of urinary MDA did not change significantly by genetic polymorphism. Age, height, weight, duration of pregnancy, exposure to environmental tobacco smoke, and diet did not significantly affect the level of either urinary biomarker. Because the polymorphisms in GSTM1 and MnSOD significantly affected the level of urinary 8-OH-dG, the combinations of polymorphisms of GSTM1 and MnSOD were evaluated. The concentration of urinary 8-OH-dG was highest in subjects with the GSTM1 null and MnSOD variant type.

4. 고찰

Our results show that urinary concentrations of 8-OH-dG and MDA are sensitive indicators of oxidative stress, and that these biomarkers are correlated with each other in term pregnant women. Moreover, the marker of oxidative DNA damage, urinary 8-OH-dG, was modified by some genetic polymorphisms, including polymorphisms in the metabolizing gene GSTM1 and in the oxidative stress-related gene MnSOD.