

# Estrogen receptor 1, Glutathione S-transferase P1, Glutathione S-transferase M1, and Glutathione S-transferase T1 Genes with Dysmenorrhea in Korean Female Adolescents

Hee-Yeon Woo, M.D.<sup>1</sup>, Kye-Hyun Kim, M.D.<sup>2</sup>, and Se-Won Lim, M.D.<sup>3</sup>

Departments of Laboratory Medicine<sup>1</sup>, Obstetrics and Gynecology<sup>2</sup>, and Psychiatry<sup>3</sup>, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea

**Background** : Dysmenorrhea is the most common gynecologic complaint among adolescent females. We investigated the association between genetic polymorphisms and dysmenorrhea.

**Methods** : A total of 202 postmenarcheal Korean female adolescents 16-17 yr old participated in this study. Genotyping for glutathione S-transferase mu 1 (*GSTM1*), glutathione S-transferase theta 1 (*GSTT1*), glutathione S-transferase pi 1 (*GSTP1*), and estrogen receptor 1 (*ESR1*) was performed using PCR-based methods.

**Results** : The PP+Pp genotype of the *ESR1* gene was more frequent than pp genotypes in subjects with dysmenorrhea than in subjects without dysmenorrhea (odds ratio=2.440; 95% confidence interval, 1.036-5.753; *P*=0.040) using an unadjusted univariate logistic regression analysis. The relationship between dysmenorrhea and *ESR1* gene polymorphisms remained significant after adjustment for premenstrual syndrome, years elapsed after menarche, and family history of dysmenorrhea. No significant difference was observed between subjects with dysmenorrhea and subjects without dysmenorrhea for polymorphisms of *GSTM1*, *GSTT1*, and *GSTP1* genes.

**Conclusions** : Our results suggest that *ESR1* gene polymorphisms may be associated with dysmenorrhea. (*Korean J Lab Med* 2010;30:76-83)

**Key Words** : Adolescent, Dysmenorrhea, Estrogen receptor 1, Glutathione S-transferase, Polymorphism

## INTRODUCTION

Dysmenorrhea is the most common gynecologic complaint among adolescent females and it is characterized by symptoms ranging from lower abdominal cramping and back pain to nausea, vomiting, and diarrhea. Dysmenorrhea is categorized as primary (in the absence of organic pelvic pathology) or secondary (in the presence

of organic diseases such as endometriosis and adhesive disease). It is prevalent in 60–93% female adolescents [1, 2]. Pelvic abnormalities, such as endometriosis or uterine anomalies, are identified only in approximately 10% of female adolescents with severe dysmenorrheal symptoms [3].

The cause of dysmenorrhea is not completely understood, but its major biological pathways are believed to involve endocrine, myometrial, and prostaglandin factors [2]. A variety of gene polymorphisms have been investigated, but only a few have shown an association with dysmenorrhea. Epidemiologic studies have shown a link between dysmenorrhea and several environmental factors, including smoking and alcohol intake [4, 5]. It is thought that an association exists between the detoxification activi-

Received : September 14, 2009

Manuscript No : KJLM09-113

Revision received : November 13, 2009

Accepted : November 20, 2009

Corresponding author : Kye-Hyun Kim, M.D.

Department of Obstetrics and Gynecology, Kangbuk Samsung Hospital, 108 Pyeong-dong, Jongno-gu, Seoul 110-746, Korea  
Tel : +82-2-2001-2457 Fax : +82-2-2001-2187  
E-mail : khmd.kim@samsung.com

\*This study was supported by a Samsung Biomedical Research Institute Grant, #SBRI C-A7-301-1.

ty of endogenous or exogenous substances and adverse reproductive outcomes [6]. Several studies have shown the relationship between the risk of dysmenorrhea and metabolic gene polymorphisms, such as the glutathione S-transferase (GST)-related genes or cytochrome P450 genes that are associated with the detoxification process [7, 8]. However, other studies have reported no significant association between GST-related genes and dysmenorrhea [9, 10]. Dysmenorrhea does not occur during anovulatory cycles but occurs in the process of ovulation, and the effects of progesterone and estrogen on the endometrium and myometrium appear to constitute a primary mechanism. In the uterus, a strong estrogen receptor 1 (ESR1) immunoreactivity has been detected in the nuclei of epithelial, stromal, and muscle cells [11]. Endometriosis, the most common secondary dysmenorrhea, is considered an estrogen-dependent disorder, and although its association with *ESR1* gene polymorphisms has been discussed, it remains controversial [12, 13]. Three polymorphisms in the *ESR1* gene, i.e., intron 1 polymorphisms involving PvuII and XbaI and (TA)<sub>n</sub> repeat allelic variants in the 5-prime upstream of exon 1, have mainly been investigated. The *ESR1* PvuII polymorphism has been analyzed and reported most frequently, and the PvuII polymorphic site is known to abolish an activator-protein 4 (AP-4) transcription factor binding site, as determined by homology with the DNA consensus sequence [14]. A polymorphism in a protein-coding region, G229A in exon 1 of the *ESR1* gene, has also been analyzed, but no relationship between this polymorphism and dysmenorrhea was observed [13].

Investigating the relationship between genetic polymorphisms and dysmenorrhea will be helpful in elucidating the pathophysiology of dysmenorrhea and in finding solutions to provide clinical care for adolescents with dysmenorrhea. However, no study has addressed the association between genetic polymorphisms and dysmenorrhea in a homogenous adolescent population. In this study, we investigated the association between *GST mu 1* (*GSTM1*), *GST theta 1* (*GSTT1*), *GST pi 1* (*GSTP1*), and *ESR1* gene polymorphisms and dysmenorrhea in Korean female adolescents.

## MATERIALS AND METHODS

### 1. Subjects

We recruited 333 postmenarcheal Korean female adolescents aged 16–17 yr from 2 all-girls high schools in Seoul, South Korea, and 205 (61.6%) girls participated in this study. We obtained informed consent from all subjects and their parents. Participants who had undergone surgery, chemotherapy, radiation therapy, or treatment for obstetric/gynecologic diseases, and had been pregnant or were consuming exogenous hormones during the preceding 3 months were excluded from the study population. We also excluded participants who were suspected of having organic pelvic diseases according to the presence of any of the following criteria: 1) both heavy menstrual blood flow ( $\geq 7$  pads/day) and irregular menstrual cycle length, 2) no response to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), or 3) pain episodes unassociated with menstruation. On the basis of above exclusion criteria, 3 participants were eliminated from the study. Therefore, the final number of participants was 202. A detailed questionnaire was completed by each participant to gather demographic data (age, height, and body weight); past medical history; and health-related behavior such as alcohol consumption, smoking, and menstruation-related information. Body mass index (BMI) was calculated as weight divided by square of height ( $\text{kg}/\text{m}^2$ ), and participants were divided into 4 groups according to the BMI cut-offs suggested for Korean girls aged 17 yr [15]. The ethics committee of the Kangbuk Samsung Hospital approved this study.

### 2. Menstrual data

We obtained menstrual data, including age at menarche, menstrual cycle regularity, duration of menstrual bleeding, amount of menstrual bleeding, dysmenorrhea, premenstrual syndrome (PMS), and first-degree family history of dysmenorrhea. Dysmenorrhea was defined as pelvic or lower abdominal pain associated with menstruation

during every period.

### 3. DNA extraction

Peripheral blood was drawn from each subject and collected in a tube in which ethylenediaminetetraacetic acid (EDTA) was added. Genomic DNA was extracted from leukocytes using the QIAamp blood kit (Qiagen, Hilden, Germany) according to the instructions of the manufacturer.

### 4. Genotyping

#### 1) *ESR1* genotyping

Genotyping of the PvuII polymorphism in intron 1, which is 0.4 kb upstream of exon 2 of the *ESR1* gene (rs2234693), was determined by PCR–restriction fragment length polymorphism (RFLP) analysis, essentially as described previously [16]. The sequences of the primers are listed in Table 1. Genotypes were defined as PP, Pp, and pp. Upper-case letters represent the absence of restriction sites, and lower-case letters represent the presence of restriction sites.

#### 2) *GSTM1* and *GSTT1* genotyping

*GSTM1* and *GSTT1* genotyping for gene deletions were carried out by PCR as described by Lin et al. [17] with minor modifications. The sequences of the primers are listed in Table 1. Amplification of the beta-actin gene was used as an internal control. If the study subject was null for the gene, no PCR product was present.

**Table 1.** Primer sequences for PCR in this study

Gene	Primer sequence	PCR product (bp)
<i>ESR1</i>	(F) 5'-TTTCACGCAGTCTGGAGTTG-3' (R) 5'-ACCACACTCAGGGTCTCTGG-3'	496
<i>GSTM1</i>	(F) 5'-GAACTCCCTGAAAAGCTAAAGC-3' (R) 5'-GTTGGGCTCAAATATACGGTGG-3'	219
<i>GSTT1</i>	(F) 5'-TCACCGGATCATGGCCAGCA-3' (R) 5'-TTCTTACTGGTCCTCACATCTC-3'	459
<i>GSTP1</i>	(F) 5'-ACCCCAGGGCTCTATGGGAA-3' (R) 5'-TGAGGGCACAGAAGCCCCT-3'	176

#### 3) *GSTP1* genotyping

An A to G transition in codon 105 (exon 5) of the *GSTP1* gene (rs1695) resulting in an Ile to Val amino acid substitution was determined by PCR–RFLP according to the method of Harris et al. [18]. The sequences of the primers are listed in Table 1. Electrophoresis of the digested PCR products showed a homozygous (Ile/Ile) *GSTP1* BsmAI polymorphism as one 176-bp DNA band. A heterozygous (Ile/Val) polymorphism showed 3 bands of 176, 91, and 85 bp. Homozygotes (Val/Val) showed 2 bands of 91 and 85 bp each.

### 5. Statistical analysis

This study was designed to have 80% power at the 5% significance level to detect the odds ratio (OR) of 2.0, assuming that risk genotype rate is 60% [19] and the prevalence of the dysmenorrhea genotype is 75% in general adolescent population [20].

Statistical significance of differences between groups was determined using the Fisher's exact test. Using a 95% confidence interval (CI), we first estimated the ORs for the association of genetic polymorphisms with the risk of dysmenorrhea using a univariate logistic regression analysis. We then developed a second model adjusting for variables that might confound the relationship between genetic polymorphisms and dysmenorrhea and calculated adjusted ORs. We adjusted for the variables, which showed significant associations with dysmenorrhea using Fisher's exact tests.

The presence of Hardy–Weinberg equilibrium for genotype frequencies was calculated using the Chi-square ( $\chi^2$ ) test. All of the analyses were performed using SPSS statistical software (SPSS, Inc., Chicago, IL, USA), with the cutoff point for statistical significance set at  $P < 0.05$ .

## RESULTS

The baseline characteristics of the subjects enrolled in this study are shown in Table 2. The mean age at menarche was 13.4 yr (range, 11–16 yr). Among 202 girls, 172

girls (85.1%) had dysmenorrhea during every period. The statistical power of the analysis, which was calculated from the prevalence of dysmenorrhea seen in this study, was 57% at the 5% significance level.

We analyzed the association between BMI, menstrual factors, first-degree family history of dysmenorrhea, smoking, and alcohol intake and dysmenorrhea. In a two-by-two  $\chi^2$  analysis, presence of PMS ( $P=0.000$ ), an early age at menarche ( $P=0.005$ ), and a first-degree family history ( $P=0.000$ ) were significantly related to an increased risk of dysmenorrhea (a portion of this menstrual data was previously published in a local Korean journal) [21].

The genotype frequencies of PP, Pp, and pp for the *ESR1* gene were 19.8% (40/202), 48.0% (97/202), and 32.2% (65/202), respectively. The genotype distributions for the dysmenorrhea group ( $\chi^2=0.06$ ,  $df=1$ ,  $P=0.799$ ) and dysmen-

orrhea-free group ( $\chi^2=1.88$ ,  $df=1$ ,  $P=0.171$ ) were in Hardy-Weinberg equilibrium. The allele frequencies of P and p were 43.8% and 56.2%, respectively. The genotype frequencies of the *GSTM1* null mutation and *GSTT1* null mutation were 54.0% (109/202) and 52.0% (105/202), respectively. The genotype frequencies of *GSTP1* Ile/Ile, Ile/Val, and Val/Val were 66.8% (135/202), 30.7% (62/202), and 2.5% (5/202), respectively. The genotype distributions for the dysmenorrhea group ( $\chi^2=0.97$ ,  $df=1$ ,  $P=0.325$ ) and dysmenorrhea-free group ( $\chi^2=0.54$ ,  $df=1$ ,  $P=0.461$ ) were also in Hardy-Weinberg equilibrium. The association of the genotypes of *ESR1*, *GSTM1*, *GSTP1*, and *GSTT1* genes with dysmenorrhea is indicated in Table 3. Fisher's exact tests did not indicate a significant association between *ESR1* genotype and dysmenorrhea under a recessive model (PP vs Pp+pp,  $P=0.806$ ). However, a significant association was observed under a dominant model (PP+Pp vs pp,  $P=0.033$ ); this result was not adjusted for other factors. We also estimated ORs with 95% CI for the association of each genetic polymorphism with dysmenorrhea using a univariate logistic regression analysis. The PP+Pp genotype of the *ESR1* gene was more frequent in subjects with dysmenorrhea than was the pp genotype compared to subjects without dysmenorrhea (OR=2.440; 95% CI, 1.036–5.753;  $P=0.040$ ). In a multivariate logistic regression analysis, the relationship between dysmenorrhea and *ESR1* gene polymorphisms remained significant after adjustment for PMS, years elapsed after menarche, and family history of dysmenorrhea, which showed significant associations with dysmenorrhea using Fisher's exact tests. No significant difference was observed between subjects with dysmenorrhea and subjects without dysmenorrhea for the polymorphisms of the *GSTM1*, *GSTT1* and *GSTP1* genes under both the dominant and recessive models. We also analyzed the relationship between combined genotypes and dysmenorrhea (Table 4). We presumed that the PP or Pp genotypes of *ESR1*, null mutations of *GSTM1*, *GSTT1*, and *GSTP1* Val/Val polymorphisms were putative high-risk alleles for dysmenorrhea based on the association of the individual genotypes with the risk of dysmenorrhea. Subjects carrying all presumptive low-risk genotypes were

**Table 2.** Characteristics of participants (N=202)

Factors	Number (%)
Body mass index (kg/m <sup>2</sup> )	
<18.20	26 (12.9)
18.20-22.69	135 (66.8)
22.70-24.67	22 (10.9)
≥ 24.68	19 (9.4)
Years elapsed after menarche	
<2 yr	55 (27.2)
≥ 2 yr	147 (72.8)
Menstrual cycle	
Regular	132 (65.3)
Irregular	70 (34.7)
Menstrual duration	
Normal	171 (84.7)
Abnormal	28 (13.9)
Pre-menstrual syndrome	
Absent	65 (32.2)
Present	137 (67.8)
Dysmenorrhea	
Absent	30 (14.9)
Present	172 (85.1)
Family history of dysmenorrhea	
Absent	70 (34.7)
Present	122 (60.4)
Smoking	
No	200 (99.0)
Yes	2 (1.0)
Alcohol intake	
No	190 (94.1)
Yes	12 (5.9)

**Table 3.** Association between genotypes of *ESR1*, *GSTM1*, *GSTP1*, and *GSTT1* genes and dysmenorrhea among 202 Korean female adolescents

Genotypes	N of group without dysmenorrhea (%)	N of group with dysmenorrhea (%)	Odds ratio (95% CI, <i>P</i> value*)	Adjusted odds ratio <sup>†</sup> (95% CI, <i>P</i> value*)
<i>ESR1</i> genotypes				
Dominant model				
PP & Pp	15 (50.0)	122 (70.9)	2.440 (1.036-5.753, 0.040)	3.381 (1.393-8.209, 0.007)
pp	15 (50.0)	50 (29.1)	1.0	1.0
Recessive model				
PP	5 (16.7)	35 (20.3)	1.277 (0.456-3.576, 0.641)	1.470 (0.492-4.392, 0.490)
Pp & pp	25 (83.3)	137 (79.7)	1.0	1.0
<i>GSTM1</i>				
Present	11 (36.7)	82 (47.7)	1.0	ND
Null	19 (63.3)	90 (52.3)	0.599 (0.262-1.373, 0.226)	
<i>GSTP1</i>				
Ile/Ile	23 (76.7)	112 (65.1)	1.0	ND
Ile/Val	6 (20.0)	56 (32.6)	1.953 (0.737-5.174, 0.178)	
Val/Val	1 (3.3)	4 (2.3)	0.420 (0.040-4.414, 0.469)	
<i>GSTT1</i>				
Present	16 (53.3)	81 (47.1)	1.0	ND
Null	14 (46.7)	91 (52.9)	1.322 (0.593-2.948, 0.495)	

\**P* value <0.05 is statistically significant; <sup>†</sup>Odds ratios analyzed after adjusting for PMS, years elapsed after menarche, and family history of dysmenorrhea. Abbreviations: ND, not done; CI, confidence interval.

**Table 4.** Association between combined genotype subgroups and dysmenorrhea

N of high-risk genotypes	Genes				N (%)	Odds ratio	95% CI	<i>P</i> value <sup>†</sup>
	<i>ESR1</i>	<i>GSTM1</i>	<i>GSTP1</i>	<i>GSTT1</i>				
0	pp	Present	ile/ile, ile/val	Present	17 (8.4)	1.0	0.469-6.961	0.389
1	PP, Pp	Present	ile/ile, ile/val	Present	55 (27.2)	1.808	0.514-6.460	0.353
	pp	Absent	ile/ile, ile/val	Present				
	pp	Present	val/val	Present				
	pp	Present	ile/ile, ile/val	Absent				
2	PP, Pp	Absent	ile/ile, ile/val	Present	90 (44.6)	1.822	0.514-6.460	0.353
	PP, Pp	Present	val/val	Present				
	PP, Pp	Present	ile/ile, ile/val	Absent				
	pp	Absent	val/val	Present				
	pp	Absent	ile/ile, ile/val	Absent				
	pp	Present	val/val	Absent				
3	PP, Pp	Absent	val/val	Present	40 (19.8)	2.154	0.500-9.282	0.303
	PP, Pp	Absent	ile/ile, ile/val	Absent				
	PP, Pp	Present	val/val	Absent				
	pp	Absent	val/val	Absent				
4	PP, Pp	Absent	val/val	Absent	0 (0)	–	–	–

\*Proportion of subjects with dysmenorrhea among subjects with each genotype; <sup>†</sup>*P* value <0.05 is statistically significant. Abbreviation: CI, confidence interval.

used as a reference. Statistically significant risk of dysmenorrhea was not observed according to the number of high-risk alleles.

## DISCUSSION

In this study, the prevalence of dysmenorrhea was 85.1%. This frequency was a little higher than that reported in

other Korean community-based studies [20, 22]. The findings in this study support the results of other studies indicating that dysmenorrhea is common among adolescents.

Only few studies have investigated genetic susceptibility to dysmenorrhea [7, 8, 23], and most epidemiological studies did not include questions about family history in the questionnaires provided to subjects. We found a significant relationship between the first-degree family history and dysmenorrhea, suggesting a genetic predisposition toward dysmenorrhea. In addition, there was a significant association between *ESR1* gene polymorphisms and dysmenorrhea. This relationship remained significant even after adjustment for PMS, years elapsed after menarche, and family history of dysmenorrhea (which showed significant associations with dysmenorrhea in participants using two-by-two  $\chi^2$  analyses). It is unclear how the anonymous intronic polymorphism of the *ESR1* gene influences protein function. However, tamoxifen, a selective estrogen-receptor modulator, was reported to exert a direct effect on uterine contractile activity, and this finding may explain the decrease in menstrual pain and cramps noted in the subjects with dysmenorrhea [24]. Several studies have shown that the PP genotype of the *ESR1* gene is associated with subjects with a higher bone mineral density [25, 26], a higher risk of premenopausal hysterectomy, and an earlier onset of menopause due to menorrhagia and fibroids [27]. These findings suggest that local estrogenic action is more potent in women carrying the PP genotype. However, some studies have reported contradictory findings in which the PP genotype frequency was low in patients with endometriosis, a well-known estrogen-dependent disease [12, 28]. These opposite results may reflect the possibility that most of the subjects with dysmenorrhea in our study had primary dysmenorrhea rather than a secondary dysmenorrhea such as endometriosis. Therefore, we believe that primary dysmenorrhea may partially result from local estrogenic action, but that the detailed estrogen-mediated pathway involved in primary dysmenorrhea may be different from that in secondary dysmenorrhea. Kitawaki et al. have also suggested that the endometrial estrogen metabolism of patients with endometrio-

sis is remarkably different from that of women without gynecological disease [12, 29]. Thus, the biological mechanism by which an *ESR1* polymorphism modifies the risk of dysmenorrhea remains to be determined. It will also be important to analyze other gene polymorphisms associated with dysmenorrhea such as the *RsaI* (exon 5) and *AluI* (exon 8) polymorphisms of the *ESR2* gene in future research [30].

We did not observe any significant association between GST-related genes and dysmenorrhea. This is in contrast to another study in which it was reported that the *GSTM1* genotype was associated with an increased risk of dysmenorrhea [23]. However, more recent studies have reported results similar to our findings, although these studies focused on the association of GST-related genes with endometriosis [9, 10, 31, 32]. Nevertheless, the possibility of a false-negative result due to the low statistical power of our analysis cannot be excluded, and further study with a larger sample size will be necessary. We also found no trend of increasing risk for dysmenorrhea in association with the number of putative GST-related and *ESR1* high-risk genotypes in our analysis of the combined genotype subgroups.

This study is the first to investigate the relationship between *ESR1* genotypes and dysmenorrhea in adolescents. Another strength of this research is that the study subjects were all 16 to 17-yr-old adolescent female students, whereas the age ranges of subjects included in most other dysmenorrhea studies varied widely. The adolescent period is a transitional period, and the disease features of adolescents are very different from those of other age groups in the clinical field of obstetrics and gynecology [33]. A previous study showed that dysmenorrhea occurs most commonly among young women, and its prevalence tends to decrease after the age of 25 yr [34]. Therefore, the association of dysmenorrhea with many factors was well defined in our study. One limitation of this study is that we did not confirm the presence of organic diseases such as endometriosis since we did not perform an endometrium biopsy or pelvic ultrasonography. However, we excluded subjects who were diagnosed with or received treatment

for obstetric/gynecological diseases as well as subjects who were suspected of having organic pelvic disease on the basis of their clinical characteristics. The second limitation of this study is the small number of subjects without dysmenorrhea, which was due to a higher prevalence of dysmenorrhea than expected. Although we used nonparametric statistical methods to analyze the association of dysmenorrhea with *ESR1* gene polymorphisms, the positive association might be less precise due to the small number of subjects without dysmenorrhea.

In summary, our results suggest that *ESR1* gene polymorphisms may be associated with a risk for dysmenorrhea. Further study using a larger population would be necessary to exclude the possibility of a causal relationship between the *ESR1* genotype and dysmenorrhea. This further research will provide a better understanding of the pathogenesis of dysmenorrhea and estrogen-dependent uterine disease.

## REFERENCES

- Andersch B and Milsom I. An epidemiologic study of young women with dysmenorrhea. *Am J Obstet Gynecol* 1982;144:655.
- Dawood MY. Primary dysmenorrhea: advances in pathogenesis and management. *Obstet Gynecol* 2006;108:428-41.
- Harel Z. Dysmenorrhea in adolescents. *Ann NY Acad Sci* 2008;1135:185-95.
- Harlow SD and Park M. A longitudinal study of risk factors for the occurrence, duration and severity of menstrual cramps in a cohort of college women. *Br J Obstet Gynaecol* 1996;103:1134-42.
- Parazzini F, Tozzi L, Mezzopane R, Luchini L, Marchini M, Fedele L. Cigarette smoking, alcohol consumption, and risk of primary dysmenorrhea. *Epidemiology* 1994;5:469-72.
- Hirvonen A. Genetic factors in individual responses to environmental exposures. *J Occup Environ Med* 1995;37:37-43.
- Lei L, Ye L, Liu H, Chen C, Fang Z, Wang L, et al. Passive smoking, cytochrome P450 gene polymorphisms and dysmenorrhea. *Eur J Epidemiol* 2008;23:475-81.
- Wu D, Chen D, Liu X, Ni J, Jin Y, Xu X. Analysis on associations of cytochrome P450 1A1-Hinc II and glutathion S-transferase-theta with primary dysmenorrhea. *Zhonghua Yi Xue Yi Chuan Xue Za Zhi* 2001;18:47-50.
- Baxter SW, Thomas EJ, Campbell IG. GSTM1 null polymorphism and susceptibility to endometriosis and ovarian cancer. *Carcinogenesis* 2001;22:63-5.
- Hur SE, Lee JY, Moon HS, Chung HW. Polymorphisms of the genes encoding the *GSTM1*, *GSTT1*, and *GSTP1* in Korean women: no association with endometriosis. *Mol Hum Reprod* 2005;11:15-9.
- Pelletier G and El-Alfy M. Immunocytochemical localization of estrogen receptors alpha and beta in the human reproductive organs. *J Clin Endocrinol Metab* 2000;85:4835-40.
- Kitawaki J, Obayashi H, Ishihara H, Koshiba H, Kusuki I, Kado N, et al. Oestrogen receptor-alpha gene polymorphism is associated with endometriosis, adenomyosis and leiomyomata. *Hum Reprod* 2001;16:51-5.
- Renner SP, Strick R, Oppelt P, Fasching PA, Engel S, Baumann R, et al. Evaluation of clinical parameters and estrogen receptor alpha gene polymorphisms for patients with endometriosis. *Reproduction* 2006;131:153-61.
- Hu YF, Luscher B, Admon A, Mermod N, Tjian R. Transcription factor AP-4 contains multiple dimerization domains that regulate dimer specificity. *Genes Dev* 1990;4:1741-52.
- Kim E, Hwang JY, Woo EK, Kim SS, Jo SA, Jo I. Body mass index cutoffs for underweight, overweight, and obesity in South Korean schoolgirls. *Obes Res* 2005;13:1510-4.
- Yaich L, Dupont WD, Cavener DR, Parl FF. Analysis of the PvuII restriction fragment-length polymorphism and exon structure of the estrogen receptor gene in breast cancer and peripheral blood. *Cancer Res* 1992;52:77-83.
- Lin DX, Tang YM, Peng Q, Lu SX, Ambrosone CB, Kadlubar FF. Susceptibility to esophageal cancer and genetic polymorphisms in glutathione S-transferases T1, P1, and M1 and cytochrome P450 2E1. *Cancer Epidemiol Biomarkers Prev* 1998;7:1013-8.
- Harris R, Stubbins M, Forman D, Howard GC, Wolf CR. Identification of genetic polymorphisms at the glutathione-S-transferase Pi locus and association with susceptibility to bladder, testicular and prostate cancer. *Carcinogenesis* 1997;18:641-4.
- Kim SH, Choi YM, Jun JK, Kim SH, Kim JG, Moon SY. Estrogen receptor dinucleotide repeat polymorphism is associated with minimal or mild endometriosis. *Fertil Steril* 2005;84:774-7.
- Cho SH, Kim KD, Kim SR, Cho SH, Hwang YY. Adolescent menstrual disorders: Comparison between 1998 and 1999. *Korean J Obstet*

- Gynecol 1999;42:2043-7.
21. Kim HO, Lim SW, Woo HY, Kim KH. Premenstrual syndrome and dysmenorrhea in Korean adolescent girls. *Korean J Obstet Gynecol* 2008;51:1322-9.
  22. Jung HM and Kim YS. Factors affecting dysmenorrhea among adolescents. *J Korean Acad Child Health Nurs* 2004;10:196-204.
  23. Wu D, Wang X, Chen D, Niu T, Ni J, Liu X, et al. Metabolic gene polymorphisms and risk of dysmenorrhea. *Epidemiology* 2000;11:648-53.
  24. Pierzynski P, Swiatecka J, Oczeretko E, Laudanski P, Batra S, Laudanski T. Effect of short-term, low-dose treatment with tamoxifen in patients with primary dysmenorrhea. *Gynecol Endocrinol* 2006; 22:698-703.
  25. Kurabayashi T, Tomita M, Matsushita H, Yahata T, Honda A, Takakuwa K, et al. Association of vitamin D and estrogen receptor gene polymorphism with the effect of hormone replacement therapy on bone mineral density in Japanese women. *Am J Obstet Gynecol* 1999; 180:1115-20.
  26. Willing M, Sowers M, Aron D, Clark MK, Burns T, Bunten C, et al. Bone mineral density and its change in white women: estrogen and vitamin D receptor genotypes and their interaction. *J Bone Miner Res* 1998;13:695-705.
  27. Weel AE, Uitterlinden AG, Westendorp IC, Burger H, Schuit SC, Hofman A, et al. Estrogen receptor polymorphism predicts the onset of natural and surgical menopause. *J Clin Endocrinol Metab* 1999; 84:3146-50.
  28. Georgiou I, Syrrou M, Bouba I, Dalkalitsis N, Paschopoulos M, Navrozoglou I, et al. Association of estrogen receptor gene polymorphisms with endometriosis. *Fertil Steril* 1999;72:164-6.
  29. Kitawaki J, Noguchi T, Amatsu T, Maeda K, Tsukamoto K, Yamamoto T, et al. Expression of aromatase cytochrome P450 protein and messenger ribonucleic acid in human endometriotic and adenomyotic tissues but not in normal endometrium. *Biol Reprod* 1997;57: 514-9.
  30. Wang Z, Yoshida S, Negoro K, Kennedy S, Barlow D, Maruo T. Polymorphisms in the estrogen receptor beta gene but not estrogen receptor alpha gene affect the risk of developing endometriosis in a Japanese population. *Fertil Steril* 2004;81:1650-6.
  31. Lin J, Zhang X, Qian Y, Ye Y, Shi Y, Xu K, et al. Glutathione S-transferase M1 and T1 genotypes and endometriosis risk: a case-controlled study. *Chin Med J* 2003;116:777-80.
  32. Kihara M, Kihara M, Noda K. Lung cancer risk of the *GSTM1* null genotype is enhanced in the presence of the *GSTP1* mutated genotype in male Japanese smokers. *Cancer Lett* 1999;137:53-60.
  33. Shin SY, Lee YY, Yang SY, Yoon BK, Bae D, Choi D. Characteristics of menstruation-related problems for adolescents and premarital women in Korea. *Eur J Obstet Gynecol Reprod Biol* 2005;121:236-42.
  34. Dawood MY. Dysmenorrhea. *J Reprod Med* 1985;30:154-67.