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Environmental exposure and risk of uterine leiomyoma: an epidemiologic survey

Y. SHEN[1], Q. XU[2,3], J. XU[1,4], M.L. REN[1], Y.L. CAI[1]

[1]Department of Obstetrics and Gynecology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China
[2]Ministry of Education Key Laboratory of Environmental Medicine Engineering, Southeast University, Nanjing, China
[3]School of Public Health, Southeast University, Nanjing, China
[4]Department of Obstetrics and Gynecology, Zhangjiagang First People's Hospital, Zhangjiagang, China

Abstract. – AIM: The present study was undertaken to explore the relationship between environmental exposure and risk of uterine leiomyoma in women using an epidemiologic survey.

SUBJECTS AND METHODS: We conducted a case-control survey of premenopausal Han women aged 30-50 years in Nanjing. The subjects included 600 patients with uterine leiomyoma confirmed at the Affiliated Zhongda Hospital of Southeast University between February 2010 and June 2012 and 600 patients with non-uterine leiomyoma or healthy volunteers who presented to the above mentioned hospital for physical examination during the same period. We entered the results into a database and explored the relationship between risk factors and prevalence of uterine leiomyoma using univariate or multivariate non-conditional logistic regression analysis.

RESULTS: The results showed that patients aged 40-45 years had a high prevalence of uterine leiomyoma. The prevalence of uterine leiomyoma in subjects with an education beyond high school was higher than in those with a high school education or less. Exposure to plastic products (odds ratio [OR]: 1.481; 95% confidence interval [CI]: 1.046-2.097); exposure to cosmetics and other chemicals (OR: 1.954; 95% CI: 1.479-2.582); and consumption of soybean milk (OR: 2.518; 95% CI: 1.894-3.347), food additives, sweeteners, and preserved food (OR: 3.166, 95% CI: 2.247-4.461) had a significant effect on the occurrence of uterine leiomyoma ($p < 0.05$).

CONCLUSIONS: Exposure to plastic products, cosmetics, and other chemicals as well as intake of soybean milk, food additives, sweetener, and preserved foods may be risk factors for uterine leiomyoma.

Key Words:
Uterine leiomyoma, Environmental exposure, Epidemiologic survey.

Introduction

Uterine leiomyoma is the most common benign tumor in the female reproductive system, and it is most often found in women aged 30-50 years, i.e., in women of childbearing age. The prevalence of uterine leiomyoma in women aged more than 35 years is 20%, while the prevalence increases to 51.2%-60.0% in women aged 40-50 years. Among patients with uterine leiomyoma, 25% have clinical manifestations such as bradymenorrhea, menorrhagia, hypogastralgia, and acyesis[1-2]. Uterine leiomyoma is one of the main causes of hysterectomy, and although satisfactory non-surgical treatment methods are still lacking, surgical treatment can have significant effects on the physical and mental health of women. Recently, with the increased prevalence of uterine leiomyoma, prevention has become a greater concern.

Although the causes of uterine leiomyoma are not entirely clear, there is a consensus that it is an estrogen-dependent tumor. With the increasingly serious problem of environmental pollution, pollutants known as environmental endocrine disrupters (EEDs) have aroused widespread concern around the world. Environmental estrogens, an important class of EEDs, possess estrogen-like activities that imitate the physiological and biochemical effects of endogenous estrogen and have antagonizing androgen effects. The correlation between environmental estrogens and the occurrence and development of gynecological tumors has gradually become a concern; an experimental study found that some organochlorine pesticides could promote the proliferation of Eker rat uterine leiomyoma-derived cells, which could be inhibited by the estrogen antagonist ICI 182,780[3]. Accordingly, re-

Corresponding Author: Yang Shen, Ph.D; e-mail: shenyang0924@sina.cn

searchers have begun to consider the correlation between long-term exposure to these exogenous estrogens and the increased prevalence of uterine leiomyoma.

Subjects and Methods

Subjects

All subjects were premenopausal Han women aged 30-50 years from Nanjing. The subjects presented to the Department of Gynecology and Obstetrics at the Affiliated Zhongda Hospital of Southeast University between February 2010 and March 2012. Subjects with a diagnosis of uterine leiomyoma that was confirmed through imaging and/or pathological examinations were included in the case group (600 cases), and patients with non-uterine leiomyoma as well as healthy volunteers who presented at the Hospital during the same period were included in the control group (600 cases).

Formulation of the Questionnaire

We drafted a questionnaire and determined the risk factors associated with the onset of uterine leiomyoma based on relevant literature to formulate a unified epidemiologic survey.

Survey Contents, Methods, and Quality Control

The contents of the survey included the following: (1) general sociological characteristics such as age, name, height, weight, and education; (2) basic personal information such as marital and reproductive history as well as occupation; (3) present diseases including history and pathological report of the patient; (4) case history and family history including personal previous medical history and the onset of tumor in the immediate family; and (5) living habits including smoking, drinking, and exposure to environmental pollutants. The survey was conducted via face-to-face interviews by full-time investigators collecting premorbid data. To ensure the accuracy and reliability of the results, we checked the data of all samples, uniformly trained all the investigators, and double-blindly entered survey items into the database; the authenticity and accuracy of the survey data and the blood collection process were ensured. The confounding bias was controlled to match the major factors of sex, age, and habitat; we constructed the database with EpiData software and performed computer verification and logic checks on the entered data. In total, 1,200 patients, with 600 patients in each group, were eligible and completed the questionnaire.

Statistical Analysis

Data analysis was performed using SPSS software (SPSS Inc., Chicago, IL, USA). The relationships between environmental exposure factors, occurrence, and development of uterine leiomyoma were assessed using univariate non-conditional logistic analysis; the combined effects of various environmental exposures on uterine leiomyoma and its correlation were calculated using multivariable logistic regression analysis.

Results

Age Distributions in the Case and Control Groups

There were significant differences in the age composition of the case and control groups (Table I). The distribution by age group (30-33, 34-36, 37-39, 40-42, and 43-45 years) is shown in Figure 1.

General Demographic Characteristics

We enrolled premenopausal Han women from Nanjing according to the survey design. All subjects in the case group had a single disease and were in good physical condition before presenting at the hospital. Patients who had a history of chronic liver and kidney disease, endocrine diseases, and other forms of cancer were excluded. We found no significant difference in body mass index (BMI), marital status, education, and number of pregnancies (term, greater than 5 months) between the case and the control group ($p > 0.05$) (Table II).

Table I. Age distributions in the case and control groups.

Myoma	n	Mean ± SD (age)	t	p
1	600	38.68 ± 4.228	3.373	0.001
0	600	37.54 ± 4.025		

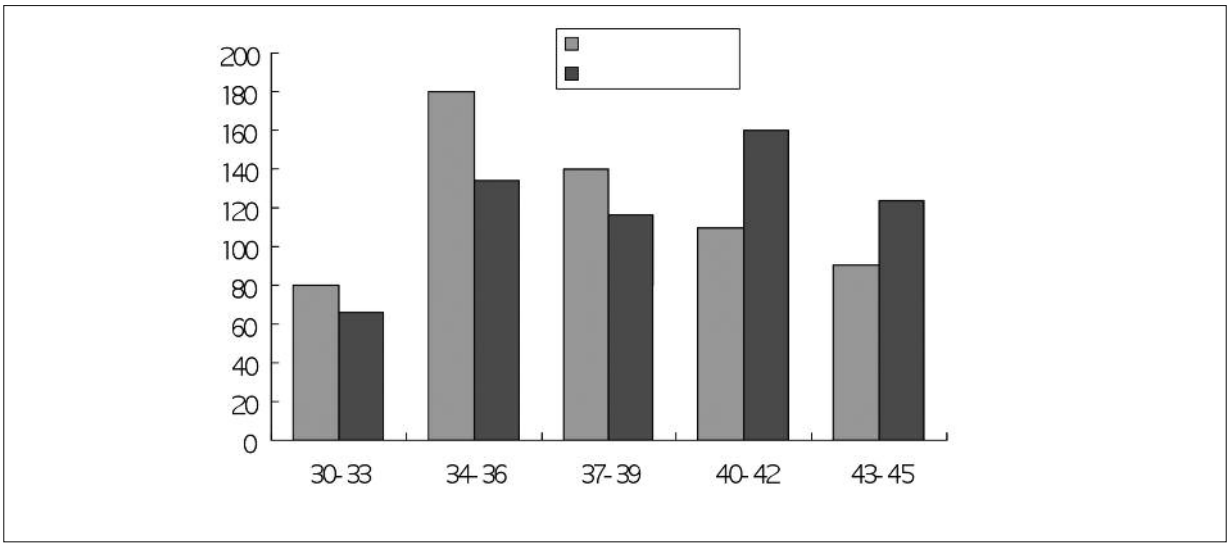

Figure 2. Age distributions in the case and control groups.

Living Habits, Psychological Factors, Environmental Exposure, and Uterine Leiomyoma

We performed non-conditional logistic regression analysis on survey results after evaluation. The onset of uterine leiomyoma in the case and control groups in terms of living habits, psychological factors, and environmental exposure is shown in Table III.

Multifactor Analysis

We performed multivariate non-conditional logistic regression analysis on environmental exposure factors and risk factors with significance, including age, BMI, number of births, and other confounding factors (Table IV). We found no significant difference in the prevalence of uterine leiomyoma among those exposed to farm products and physical activity or exercise ($p > 0.05$). How-

Table II. General demographic characteristics.

Factors	Case group (%)	Control group (%)	*p*	OR (95% CI)
BMI (kg/m^2)				
< 18	18 (3.0)	0 (0)	0.999	0.000 (0.000-0.000)
			0.999	0.000 (0.000-0.000)
			0.999	0.000 (0.000-0.000)
18-25	496 (82.7)	516 (86.0)		
25-30	86 (14.3)	60 (10.0)		
> 30	0 (0)	24 (4.0)		
Marital status				
Unmarried	6 (1.0)	16 (2.7)		
Separated/divorced/loss of spouse	10 (1.7)	34 (5.7)	0.127	2.832 (0.744-10.782)
Married	584 (97.3)	550 (96.7)	0.774	0.784 (0.149-4.124)
Education				
Beyond high school	318 (53.0)	252 (42.0)		
High school or less	282 (47.0)	348 (58.0)	0.007[a]	1.557 (1.128-2.150)
Pregnancy (> 5 months)				
None	48 (8.0)	36 (6)		
Once	492 (82.0)	528 (88)	0.998	0.000 (0.000-0.000)
Twice	0 (0)	36 (6.0)	0.998	0.000 (0.000-0.000)
Three times or more	60 (10.0)	0 (0)	0.997	0.000 (0.000-0.000)

Note: [a]There were significant differences in the prevalence of uterine leiomyoma between the population with an education level of high school or more and those with an education level of high school or less ($p < 0.05$; OR: 1.557; 95% CI: 1.128-2.150).

Table III. Living habits, psychological factors, and environmental factors.

Factors	Case group (%)	Control group (%)	p	OR (95% CI)
Physical activity or exercise				
Frequent	12 (2.0)	16 (2.7)		
Occasional	110 (18.3)	104 (17.3)	0.549	1.410 (0.458-4.341)
Never	478 (79.7)	480 (80)	0.605	1.328 (0.454-3.885)
Mental state				
Better	120 (20.0)	168 (28.0)		
Ordinary	386 (64.3)	336 (56.0)	0.017a	1.608 (1.088-2.377)
Poor	94 (15.7)	96 (16.0)	0.235	1.371 (0.814-2.308)
Passive smoking				
Frequent	158 (26.3)	192 (32.0)		
Occasional	54 (9.0)	50 (8.3)	0.390	1.312 (0.706-2.440)
No	388 (64.7)	358 (59.7)	0.134	1.317 (0.918-1.889)
Chemical substances				
No exposure	252 (42.0)	396 (66.0)		
Occasional	272 (45.3)	156 (26.0)	0.000b	2.740 (1.917-3.915)
Frequent	76 (12.7)	48 (8.0)	0.001c	2.488 (1.424-4.346)
Farm products				
No exposure	288 (48.0)	320 (53.3)		
Eat fruits with peel	310 (51.7)	280 (46.7)	0.206	1.230 (0.893-1.695)
Pesticides exposure	2 (0.3)	0 (0)	1.000	0.000 (0.000-0.000)
Soybean milk				
No consumption	136 (22.7)	216 (36.0)		
Occasional	264 (44.0)	324 (54.0)	0.184	1.294 (0.884-1.894)
Frequent	200 (33.3)	60 (10.0)	0.000d	5.294 (3.184-8.803)
Honey				
No consumption	156 (26.0)	204 (34.0)		
Occasional	426 (71.0)	396 (66.0)	0.058	1.407 (0.989-2.002)
Frequent	18 (3.0)	0 (0)	0.999	0.000 (0.000-0.000)
Food additives and so on				
No exposure	220 (36.7)	312 (52.0)		
Occasional	288 (48.0)	276 (46.0)	0.023e	1.480 (1.056-2.074)
Frequent	92 (15.3)	12 (2.0)	0.000f	10.873 (4.487-26.346)
Plastic products				
No exposure	160 (26.7)	168 (28.0)		
Occasional	374 (62.3)	408 (68.0)	0.837	0.963 (0.668-1.386)
Frequent	66 (11.0)	24 (4.0)	0.004g	2.887 (1.394-5.980)

Note: [a]There were significant differences between the population with an ordinary mental state and that with a poor mental state ($p < 0.05$; OR: 1.608; 95% CI: 1.088-2.377). [b]There were significant differences in the onset risk of uterine leiomyoma between the population occasionally exposed to cosmetics and other chemical substances and that with no exposure ($p < 0.05$; OR: 2.740; 95% CI: 1.917-3.915). [c]There were significant differences in the onset risk of uterine leiomyoma between the population frequently exposed to cosmetics and other chemical substances and that with no exposure ($p < 0.05$; OR: 2.488; 95% CI: 1.424-4.346). [d]There were significant differences in the onset risk of uterine leiomyoma between the population that frequently consumed soybean milk and that with no consumption ($p < 0.05$; OR: 5.294; 95% CI: 3.184-8.803). [e]There were significant differences in the onset risk of uterine leiomyoma between the population occasionally exposed to food additives and that with no exposure ($p < 0.05$; OR: 1.480; 95% CI:1.056-2.074). [f]There were significant differences in the onset risk of uterine leiomyoma between the population frequently exposed to food additives and that with no exposure ($p < 0.05$; OR: 10.873; 95% CI: 4.487-26.346). [g]There were significant differences in the onset risk of uterine leiomyoma between the population frequently exposed to plastic products and that with no exposure ($p < 0.05$; OR: 2.887; 95% CI: 1.394-5.980).

ever, exposure to cosmetics and other chemicals (odds ratio [OR]: 2.257; 95% confidence interval [CI]: 1.510-3.375) and consumption of soybean milk (OR: 3.336; 95% CI: 2.203-5.051), honey (OR: 2.257; 95% CI: 1.510-3.375), food additives, sweetener, and preserved foods (OR: 1.900; 95% CI: 1.220-2.959) had a significant effect on the prevalence of uterine leiomyoma ($p < 0.05$).

Discussion

Because of the various etiologic studies and epidemiologic investigations, researchers have found that the cause of uterine leiomyoma could not be explained by a single factor and that it may be the interaction of multiple factors. Estrogen may be one of the major contributing factors

Table IV. Logistic regression analysis on risk factors and uterine leiomyoma.

Risk factors	B	Wald	p	OR (95% CI)
Age	0.059	6.608	0.010	1.061 (1.014-1.110)
Education	–0.635	10.125	0.001	0.530 (0.358-0.784)
Plastic products	0.393	4.902	0.027	1.481 (1.046-2.097)
Chemical substances	0.670	22.195	0.000	1.954 (1.479-2.582)
Food additives	1.152	43.403	0.000	3.166 (2.247-4.461)
Soybean milk	0.923	40.417	0.000	2.518 (1.894-3.347)

in the occurrence and development of uterine leiomyoma. In addition to endogenous estrogen, increasing exposure to EEDs with the development of social industrialization is considered to be associated with the increase in the number of uterine leiomyoma cases every year. This study used an epidemiologic survey to analyze various factors (including natural, social, and psychological factors) and EED exposure to explore the correlation between environmental exposure and the occurrence of disease. A macro-epidemiologic study suggested the risk factors of uterine leiomyoma that have been described in the following text.

Age, Smoking, Drinking, and Exercise

Age is considered the most important risk factor for uterine leiomyoma, which may be attributable to increasing patient age, accumulation of endogenous estrogen, change in the patient's immune system function, or continuous exposure to exogenous risk factors[4]. However, smoking, drinking, and exercise are likely to affect the level of estrogen metabolism as well as growth factor and immune function, which then influences the susceptibility to uterine leiomyoma[5]. In this study, the number of cases involving active smoking and drinking was too small to be included in the statistical analysis. The results showed that there were significant differences in the age distribution between the 2 groups; the population aged 40-45 years had a higher prevalence of uterine leiomyoma, while there was no significant difference with respect to passive smoking and exercise.

Family History and Race

We found familial aggregation during the diagnosis of uterine leiomyoma in our clinical cases. This was supported by the Nurses' Health Study II, in which researchers confirmed the diagnosis of uterine leiomyoma by ultrasonography or pathological examination; the ages were standardized, and the prevalence of uterine leiomyoma was 30.6/1000 per year in black women and 8.9/1000 per year in white women. However, the prevalence could not be explained by the childbearing history, use of hormone drugs, BMI, and other factors. Meanwhile, education and occupation were similar among subjects; hence, these differences could not be influenced by the quality control deviation of the report or the differences in health care utilization[6]. In this study, we selected the Han population in Nanjing and inquired in detail whether family relatives had been diagnosed with uterine leiomyoma, other reproductive system cancers, or estrogen-dependent diseases. However, the survey results were not satisfactory and were not included in statistical analysis owing to a lack of cases and medical examination of subjects' relatives. For further statistical analysis, sample sizes should be increased.

Factors Influencing High Levels of Estrogen

Iatrogenic Factors

The relationship between the use of oral contraceptives and the onset risk of uterine leiomyoma is still unclear. It has been reported that subjects who did not take oral contraceptives for a long time had a lower risk of uterine leiomyoma[7]. Another study indicated that the risk of uterine leiomyoma was higher in those who took oral contraceptives for the first time at 13-16 years of age than that in those who never took oral contraceptives[8]. This may be attributable to the effects of early use of oral contraceptives on women. The number of subjects who took oral contraceptives on a long-term basis in the 2 groups was small and could not be compared.

Endogenous Estrogen

The risk of uterine leiomyoma onset has been reported to be higher in obese women[9], which is

considered by researchers to be attributable to high expression of aromatase in adipose tissue. We calculated the BMI for the subjects in our study, and the results showed no significant differences between the 2 groups.

Many studies have also reported that women who have given birth are less likely to have uterine leiomyoma than those who have not given birth; moreover, the prevalence of uterine leiomyoma tended to decline with increasing numbers of births[10]. Researchers have considered that pregnancy decreases the action time of estrogen; hence, we identified a pregnancy term of more than 5 months as a statistical indicator, whereas miscarriage or induced abortion for a pregnancy term of less than 5 months was not included in the statistical analysis. The results indicated that there was no significant difference between the 2 groups in regard to the effect of the number of pregnancies (> 5 months).

Exposure to Environmental Estrogen

Environmental estrogen can simulate the physiological and biochemical functions of endogenous estrogen. In human beings, it can disturb the synthesis, release, transportation, combination, and metabolism of normal endocrine compounds and change the normal function of the endocrine system; subsequently, it damages the stability as well as feedback and regulatory functions of the organism[11]. Environmental estrogens include synthetic compounds and natural phytoestrogen; they have been widely reported in the literature[12-13].

The phytoestrogens that we are exposed to regularly are mainly divided into 3 categories: isoflavones, lignans, and coumestans. They are abundant in soybeans, flaxseed, and other foods and can exert an estrogen effect by binding to the estrogen receptors. Some scholars have found that receptors for these compounds exist in the nucleus or the cell membrane and that they can disturb estrogen metabolism mediated by some specific enzymes leading to disruption of endocrine function[14]. In our epidemiologic survey, we compared the conditions of subjects who consumed soybeans and found that the prevalence of uterine leiomyoma was higher in those with a higher frequency of soybean consumption; these findings support the above mentioned report.

Although the chemical structure of the organic acid in royal jelly is completely different from that of estrogen, it can exert an estrogen effect by adjusting the estrogen receptors and improving the expression of the component gene in the receptor[15]. There was no significant difference in the frequency of honey consumption between the 2 groups in this study.

At present, some reports have confirmed that there are more than 70 chemicals, which may disturb endocrine function; these chemicals are common in the environment and have hormone-like effects[16-17]. These chemicals compounds include the following[18-19]: organochlorine pesticides such as DDT and polychlorinated biphenyls; chemical compounds, dioxin, and toxic gases released due to burning of garbage; pharmaceuticals such as diethylstilbestrol, which is used as a synthetic hormone for women; freon released from old models of refrigerators; all kinds of plastic products, especially plastic food utensils that can release considerable diphenol A, phthalate, polythene, etc; phenylketone, butyl hydroxyanisole, and oxybenzene in cosmetics; and various kinds of pigments and preservatives. Environmental estrogens exist everywhere and greatly increase the exposure to estrogen[20]. In this category, we have mainly investigated exposure to pesticides, cosmetics, food additives, and relevant plastic products. There was no significant difference in the exposure to farm products between the 2 groups. The subjects investigated in our study were local people in Nanjing and included a few farmers; hence, the minute quantity of pesticides on the surfaces of fruits was not enough to induce disease. Theoretically, sufficient amounts of environmental estrogen may be accumulated over a period of time, but the sample in our study is too small to draw positive results; a larger sample size and long-term follow-up are needed in the future.

There are many reports on the harmful effects of use of plastic products on women. Researchers have determined the content of phthalate metabolites in urine and found higher levels of dibutyl phthalate in patients with uterine leiomyoma[21]. This study showed that the prevalence of uterine leiomyoma in people who were regularly exposed to plastic products (including plastic cups, plastic lunch boxes, plastic food bags, preservative films) was higher than that in people who were not exposed to them. We previously surveyed a small sample of 300 cases with no positive results. Obvious differences were seen after increasing the sample size; however, there were certain problems. The design of this survey mainly focused on the macro-statistics of the frequen-

cy of plastic product use and formed ranked data. However, there was no accurate index available for measuring ethyl ethane sulfate levels in plastic products, the amount that permeates into food under heating, and the levels absorbed by the human body. This could be further explored by future studies.

Moreover, in this study, the prevalence of uterine leiomyoma was higher in those who like consuming food rich in food additives, such as snacks, beverages, or pickled food; moreover, patients with uterine leiomyoma used cosmetics and other chemicals more than patients in the control group. Exposure to food and chemicals with excessive additives has an influence on the prevalence of uterine leiomyoma.

Other Factors

Changes in stress levels influence the female endocrine system. An epidemiologic study reported that women with a higher level of education had a higher risk of uterine leiomyoma, which might be related to their levels of stress or differences in levels of health care obtained[22]. Psychological stress, cultural background, and other confounding factors were also analyzed statistically. The prevalence of uterine leiomyoma in a population with a moderate mental state is higher than that in those with a better mental state; the prevalence of uterine leiomyoma in a population with an education beyond high school is higher than that in those with a high school education or less. In the following multivariate logistic regression analysis, there are still differences in cultural backgrounds between the 2 groups. The influence of stress, cultural background, and other compounding factors is complex. Our study was not a special investigation on psychological factors lacking refinement and theoretical basis. In another study, we plan to quantify these factors and improve the overall experimental design for obtaining a credible conclusion.

Conclusions

Exposure to plastic products, cosmetics, and other chemical substances and the consumption of soybean milk, food additives, sweeteners, and preserved foods may be risk factors for uterine leiomyoma.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Parker WH. Etiology, symptomatology and diagnosis of uterine myomas. Fertil Steril 2007; 87: 725-736.
2) Levy G, Hill MJ, Beall S, Zarek SM, Segars JH, Catherino WH. Leiomyoma: genetics, assisted reproduction, pregnancy and therapeutic advances. J Assist Reprod Genet 2012; 29: 703-712.
3) Hodges LC, Bergerson JS, Huner DS, Walker CL. Estrogenic effects of organochlorine pesticides on uterine leiomyoma cells in vitro. Toxicol Sci 2000; 54: 355-364.
4) Rice KE, Secrist JR, Woodrow EL, Hallock LM, Neal JL. Etiology, diagnosis, and management of uterine leiomyomas. J Midwifery Womens Health 2012; 57: 241-247.
5) Nagata C, Nakamura K, Oba S, Hayashi M, Takeda N, Yasuda K. Association of intakes of fat, dietary fibre, soya isoflavones and alcohol with uterine fibroids in Japanese women. Br J Nutr 2009; 101: 1427-1431.
6) Marshall LM, Spiegelman D, Barbieri RL, Goldman MB, Manson JE, Colditz GA, Willett WC, Hunter DJ. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997; 90: 967-973.
7) Chiaffarino F, Parazzini F, La Vecchia C, Ricci E, Crosignani PG. Oral contraceptive use and benign gynecologic conditions: A review. Contraception 1998; 57: 11-18.
8) Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, Stampfer MJ, Hunter DJ. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 1998; 70: 432-439.
9) Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003; 188: 100-107.
10) Parazzini F, Negri E, La Vecchia C, Chatenoud L, Ricci E, Guarnerio P. Reproductive factors and risk of uterine fibroids.Epidemiology 1996; 7: 440-442.
11) Fucic A, Gamulin M, Ferencic Z, Katic J, Krayer von Krauss M, Bartonova A, Merlo DF. Environmental

exposure to xenoestrogens and oestrogen related cancers: reproductive system, breast, lung, kidney, pancreas, and brain. Environ Health 2012; 11(Suppl 1): S8.

12) Lorand T, Vigh E, Garai J. Hormonal action of plant derived and anthropogenic non-steroidal estrogenic compounds: phytoestrogens and Xenoestrogens. Curr Med Chem 2010; 17: 3542-3574.

13) Hunter DS, Hodges LC, Eagon PK, Vonier PM, Fuchs-Young R, Bergerson JS, Walker CL. Influence of exogenous estrogen receptor ligands on uterine leiomyoma: evidence from an in vitro/in vivo animal model for uterine fibroids. Environ Health Perspect 2000; 108(Suppl 5): 829-834.

14) Jeng YJ, Kochukov MY, Watson CS. Membrane estrogen receptor-α-mediated nongenomic actions of phytoestrogens in GH3/B6/F10 pituitary tumor cells. J Mol Signal 2009; 4: 2.

15) Moutsatsou P, Papoutsi Z, Kassi E, Heldring N, Zhao C, Tsiapara A, Melliou E, Chrousos GP, Chinou I, Karshikoff A. Fatty acids derived from royal jelly are modulators of estrogen receptor functions. PLoS One 2010; 5: e15594.

16) Van der Linden SC, Heringa MB, Man HY, Sonneveld E, Puijker LM, Brouwer A, Van der Burg B. Detection of multiple hormonal activities in wastewater effluents and surface water, using a panel of steroid receptor CALUX bioassays. Environ Sci Technol 2008; 42: 5814-5820.

17) Goksøyr A. Endocrine disruptors in the marine environment: mechanisms of toxicity and their influence on reproductive processes in fish. J Toxicol Environ Health A 2006; 69: 175-184.

18) Luzardo OP, Almeida-González M, Henríquez-Hernández LA, Zumbado M, Alvarez-León EE, Boada LD. Polychlorobiphenyls and organochlorine pesticides in conventional and organic brands of milk: occurrence and dietary intake in the population of the Canary Islands (Spain). Chemosphere 2012; 88: 307-315.

19) Cabrerizo A, Dachs J, Barceló D, Jones KC. Influence of organic matter content and human activities on the occurrence of organic pollutants in antarctic soils, lichens, grass, and mosses. Environ Sci Technol 2012; 46: 1396-1405.

20) Petro EM, Leroy JL, Covaci A, Fransen E, De Neubourg D, Dirtu AC, De Pauw I, Bols PE. Endocrine-disrupting chemicals in human follicular fluid impair in vitro oocyte developmental competence. Hum Reprod 2012; 27: 1025-1033.

21) Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA. Association of exposure to phthalates with endometriosis and uterine leiomyomata: Findings from NHANES, 1999-2004. Environ Health Perspect 2010; 118: 825-832.

22) Vines AI, Ta M, Esserman DA. The association between self-reported major life events and the presence of uterine fibroids. Womens Health Issues 2010; 20: 294-298.