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Association between uterine leiomyoma and metabolic syndrome in parous premenopausal women

A case–control study

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Abstract

Previous studies have reported that uterine leiomyoma (UL) may share pathogenic features with obesity and hypertension, which are components of metabolic syndrome (MetS). We examined the association between UL and MetS in premenopausal parous women.

This 1:1 case–control study was conducted on 615 asymptomatic women with UL and 615 women without UL that were matched for age, reproductive history, and hormonal use, who underwent a comprehensive health examination. UL was diagnosed by a gynecologist based on transvaginal ultrasonography findings. Blood pressure (BP), body composition, fasting plasma glucose, lipid profiles, insulin, and HOMA-IR were checked.

Median age of the 1230 study subjects was 44 (40–47) years and 7% had MetS. Women with UL had significantly higher waist circumferences and body fat, BP, and low-density lipoprotein cholesterol (LDL-C) than women without UL. Although nonsignificant, the prevalence of MetS was higher in the UL group than in the non-UL group (9.3% vs 5.7%). In addition, the prevalence of UL increased as the number of abnormal metabolic components increased and was higher than in women without UL. Conditional logistic regression analysis, after adjustment for confounding factors, showed that hyperglycemia was significantly associated with an increased risk of UL (odds ratio = 1.45; 95% confidence interval, 1.10–1.89).

Prevalence of abnormal metabolic component was higher in premenopausal women with UL than in normal controls, regardless of age or reproductive history. Furthermore, the study suggests that UL may share pathogenic features with the components of MetS and that women with UL be considered eligible for the early screening of metabolic abnormalities.

Abbreviations: BMI = body mass index, BP = blood pressure, CI = confidence interval, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, HDL-C = high-density lipoprotein cholesterol, HTN = hypertension, IGF-1 = insulin-like growth factor-1, IQR = interquartile range, IR = insulin resistance, IUD = intrauterine device, LDL-C = low-density lipoprotein cholesterol, MetS = metabolic syndrome, OR = odds ratio, SD = standard deviation, SHBG = sex hormone–binding globulin, TG = triglyceride, TVUS = transvaginal ultrasonography, UL = uterine leiomyoma, WC = waist circumference.

Keywords: gynecology, insulin resistance, metabolic syndrome, premenopause, uterine leiomyoma, women

Editor: Perbinder Grewal.

Author's contribution: All authors were responsible for the study concept and design. YJT, SYL, SKP, and YJK collected and analyzed the data. JKL, DWJ, and YHY supervised the study. SYL analyzed the data statistically. SCK and IJK contributed to the analysis with suggestions and advice. YJT prepared the manuscript.

The work was supported by clinical research grant from Pusan National University Hospital 2016.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:46(e5325)

Received: 29 July 2016 / Received in final form: 12 October 2016 / Accepted: 13 October 2016

http://dx.doi.org/10.1097/MD.0000000000005325

1. Introduction

Uterine leiomyoma (UL) is a common gynecologic tumor in women of reproductive age.[1] Despite its widespread prevalence, little attention was paid to the pathogenesis or etiology of UL, until fairly recently, due to the rarity of malignant transformation.[2] The mass effect of UL is the main cause of hysterectomy, because it causes pressure upon adjacent organs, excessive uterine bleeding, or problems related to pregnancy, including infertility and repetitive pregnancy loss.[3]

Although pathophysiology of UL is not completely understood, ovarian hormones have been reported to play a key role.[4] From the hormonal aspect, age, premenopausal status, menarche age, parity, age at first birth, and use of oral contraceptives or intrauterine device (IUD) have been related to the risk of its development.[5] However, unfortunately, these variables are difficult to correct or prevent. Recently, published evidence has indicated central obesity, a component of metabolic syndrome (MetS), is associated with the risk of UL.[6,7] One possible explanation is that excessive body fat may influence the occurrence of UL by changing steroid hormone metabolism and insulin resistance (IR) and decreasing sex hormone–binding globulin (SHBG) levels in premenopausal women.[8] Furthermore, hyperinsulinemia induced by IR, another major component of MetS is associated with the upregulations of serum insulin-like growth factor-1 (IGF-1) and epidermal growth factor levels, and these agents could influence the development of UL by enhancing ovarian hormone secretion or directly promoting myometrial smooth muscle cell proliferation.[9,10] Interestingly, in a recent animal study, it was found IR induced by sugar- and fat-rich diets enhanced the effect of sexual hormones on myometrial growth in female rats.[11]

The majority of human studies conducted on the direct association between MetS and UL had small sample sizes and included only women diagnosed by hysterectomy due to gynecologic diseases.[12,13] However, the majority of UL patients do not present specific symptoms, and thus, UL is often detected incidentally at health checkup.[1,2] In our opinion, parous women with asymptomatic UL also should be included in studies that seek to identify metabolic risk factors in premenopausal parous women with UL. Unlike established risk factors of UL, such as, old age, younger menarche age, and parity, metabolic components are correctable and preventive variables. In addition, the evaluation of the risk of MetS development in women with UL is clinically important because it is the most serious risk factor of diabetes and cardiovascular disease.[14] We hypothesized that metabolic risk factors are probably related to UL in premenopausal parous women. To investigate this hypothesis, we studied the association between UL and metabolic risk in premenopausal parous women using a case–control study design.

2. Methods

2.1. Study subjects

The 1230 study subjects were recruited among premenopausal women checked for UL at a health promotion center at Pusan National University Hospital between March 2012 and February 2014. Eligible subjects were parous women who had undergone a comprehensive health examination, which included transvaginal ultrasonography (TVUS). Premenopausal was defined as the last menstruation and regular menstrual cycles and the final menstruation within 3 months before this health checkup. Women who met any of the following conditions were excluded: postmenopausal stage defined by 12 months or more of amenorrhea, any cancer, receipt of medication that might affect ovarian hormone metabolism within 12 months before health examination, and previous gynecological surgery such as hysterectomy, bilateral oophorectomy. Women with UL were matched in a 1:1 ratio with women without UL by age, menarche age, age at first birth, parity, and use of oral contraceptives and IUD. This study was exempted from ethics approval from our institutional review board and the requirement for informed consent (number of exempt review is E-2015030), because according to the Korean Good Clinical Practice, our retrospective chart review study was conducted using existing data and subjects were not identifiable directly or indirectly.

2.2. Data collection

All study subjects underwent ultrasonography and a fasting blood test during a comprehensive health examination. In addition, detailed medical histories and anthropometric measurements were collated.

Subjects also completed a questionnaire that contained items on the following: demographics, medical history (diagnosis or prescription drug use for hypertension [HTN], diabetes, or dyslipidemia), reproductive history (menarche age, age at first birth, parity, use of oral contraceptives, or IUD), and health-related habits (smoking, alcohol drinking, and regular exercise). For the analysis, subjects were classified as nondrinkers (0–98 g/wk) or drinkers based on alcohol consumption,[15] and as nonsmokers or current smokers. Frequency of exercise was assessed using number of times per week, and regular exercise was defined as ≥3 sessions/wk.

Blood pressure (BP) was measured 3 times while seated after a 15-minute rest and averaged; measurements were made automatically using a BP-203 RV II (Colin Corp., Komaki, Aichi, Japan). Body weight and height were measured using a digital scale, while wearing a light gown without shoes. Body mass index (BMI) was defined as weight (kg) divided by height squared (m^2). Trained examiners measured waist circumference (WC) at the midpoint between the lower costal margin and the iliac crest using a tape measure to the nearest millimeter. Percentage body fat and muscle mass were assessed by bioelectric impedance analysis (Inbody 720; Biospace Co. Ltd., Seoul, South Korea).

Blood samples were extracted from an antecubital vein into evacuated plastic tubes after an overnight fast (08:00 PM–10:00 AM). Samples were subsequently analyzed at a certified laboratory in Pusan National University Hospital. Lipid profiles were measured using an autoanalyzer (Hitachi 747, Hitachi Corp., Tokyo, Japan) and an enzymatic colorimetric method. Fasting plasma glucose (FPG) levels were measured using a glucose oxidase method and a Synchron LX 20 (Beckman Coulter, Fullerton, CA). IR was determined by homeostasis model assessment (HOMA-IR).

$$\text{HOMA} - \text{IR} = \frac{\text{FPG(mmol/L)} \times \text{fasting insulin(mU/mL)}}{22.5}$$

2.3. Definition of metabolic syndrome

MetS was diagnosed using the harmonizing definition proposed in 2009 by the American Heart Association-International Diabetes Federation,[16] that is, as the presence of 3 or more of the following 5 components:

(1) Central obesity; WC of ≥85 cm.

(2) Hyperglycemia; FPG ≥ 100 mg/dL or the use of antidiabetes medication.
(3) High BP; systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg or the use of antihypertensive medication.
(4) Hypertriglyceridemia; fasting plasma triglyceride (TG) ≥ 150 mg/dL or the use of lipid-lowering medication.
(5) Reduced high-density lipoprotein cholesterol (HDL-C); fasting plasma HDL-C < 50 mg/dL.

Central obesity was defined as a WC of ≥85 cm, as was suggested by the Korean Society for the Study of Obesity.[17]

2.4. Assessment of uterine leiomyoma

UL was diagnosed by a gynecological specialist using a TVUS (VOLUSON 730-Pro; General Electric Medical Systems, Zipf, Austria). Although histological confirm is the gold diagnostic standard for UL,[18] it is invasive, expensive, and unsuitable in asymptomatic premenopausal women. In addition, TVUS has high sensitivity (99%) and specificity (91%), which are comparable to histology. Total numbers and sizes of UL lesions were determined individually. If there were ≥2 UL lesions, the size of the largest UL lesion was recorded.

2.5. Statistical analysis

Women with UL were matched to women without UL by propensity score, age, age at menarche, age at first birth, parity, and use of oral contraceptives and IUDs. Propensity-score matching was conducted using IBM SPSS Statistics 20 using the SPSS R Essentials plug-in (IBM Corp, Somers, New York, USA). Logistic regression was performed to calculate propensity scores. Nearest neighbor 1:1 matching was implemented and the caliper was set at 0.05 of the standard deviation (SD) of the logit of the propensity score. Values are given as means ± SDs for normally distributed data or medians (interquartile ranges [IQRs]) for non-normally distributed data. The paired *t* test and McNemar test were used to detect differences between metabolic variables in the UL and non-UL groups. Metabolic parameters, except body fat and muscle mass, were non-normally distributed after log-transformation. To assess linearity of UL quartile size (first Q < 1.5 cm, 1.5 cm ≤ second Q < 2.3 cm, 2.3 cm ≤ third Q < 3.3 cm, fourth Q ≥ 3.3 cm) and metabolic variables, Pearson partial correlation coefficients were calculated after adjusting for age. UL number was classified as 1, 2, or ≥3 and comparisons between variables in these 3 groups were performed using the general linear model (GLM). Because age was only variable that showed a statistical significance, GLM adjusted for age was used to detect differences in metabolic profiles between patients with different UL numbers. Conditional logistic regression was performed to determine whether components of MetS contributed to the risk of UL. Covariates were included in the multivariable analyses if they had been previously established to be risk factors of UL. Thus, the multivariable model controlled for age, age at first birth, ever use of an oral contraceptive or IUD, parity, smoking, alcohol consumption, and regular exercise. The analysis was performed using SPSS ver. 20.0 (SPSS Inc., Chicago, IL), and statistical significance was accepted for a P value <0.05.

3. Results

3.1. Clinical characteristics of the study subjects

The median age (IQR) of the 1230 subjects was 44 years (40–47). Eighty-six (7%) women were diagnosed with MetS, 192 (15.6%) with central obesity, 236 (19.2%) with elevated BP, 90 (7.3%) with hyperglycemia, 142 (11.5%) with hypertriglyceridemia, and 303 (24.6%) with a low HDL-C. In the UL group (N = 615), median UL size (IQR) was 2.3 cm (1.5–3.3), and 93 (15.1%) women had UL > 4 cm and 176 (28.6%) women had multiple ULs (≥2).

3.2. Relations between metabolic components and the prevalence of uterine leiomyoma

Distributions of age and reproductive characteristics in the UL and non-UL groups were similar (Table 1). Regarding metabolic profiles, women in the UL group had significantly higher WCs, body fat levels, systolic BPs, diastolic BPs, and LDL-C levels than women in the non-UL group. In addition, the prevalence of DM was more frequent in the UL group compared with the non-UL group. Although not statistically significant, FPG, fasting insulin, TG, and TC were slightly higher in the UL group. Table 2 shows differences in the prevalence of metabolic abnormalities in the 2 groups. More women in the UL group had hyperglycemia (4.5% vs 10.1%, $P < 0.001$) and a low HDL-C (21.9% vs 27.3%, $P = 0.033$). The prevalence of MetS tended to be higher in the UL group (5.7% vs 8.3%, $P = 0.052$).

3.3. Associations between metabolic components and the sizes and numbers of uterine leiomyomas

In the UL group, UL size by quartile showed a positive linear correlation with age ($R = 0.146$, $P < 0.001$), BMI ($R = 0.143$, $P < 0.001$), and FPG ($R = 0.085$, $P = 0.035$) (Table 3). After adjusting for age, a positive correlation remained between UL size and BMI ($\gamma = 0.121$). Regarding the number of ULs, the prevalence of MetS was higher in women with multiple UL than in women with a single UL (10.8% vs 7.3%) (Fig. 1).

Women with ≥3 ULs had greater BMIs, body fat levels, higher systolic BP, and FPG and TG levels, but lower HDL-C levels than women with a single UL after adjusting for age (Table 4).

3.4. Odds ratios for uterine leiomyoma with respect to metabolic components

Conditional logistic regression analysis showed that hyperglycemia was significantly associated with an increased risk of UL (odds ratio [OR] = 1.45; 95% confidence interval [CI], 1.10–1.89) after adjusting for confounders (Table 5). Of the 5 metabolic components, only hyperglycemia was found to be significantly associated with UL.

4. Discussion

This study was designed to investigate the prevalence of MetS according to the existence of UL as diagnosed by ultrasonography in premenopausal parous women. Comparatively few reports have addressed the relationship between UL and MetS. Takeda et al[13] compared the prevalence of MetS characterized by obesity, HTN, and hyperglycemia in 213 women with UL and 159 without UL, and found that UL was significantly associated with obesity and HTN and that the presence of several metabolic risk factors increased the risk of UL. However, only women that underwent hysterectomy for a gynecological disease were included, and MetS was diagnosed based on BMI, not WC, which is the accepted index of abdominal adiposity. Furthermore, no data were presented on HDL-C or UL size or number.

Table 1

Characteristics of the 1230 premenopausal women by prevalence of UL.

Variables	Without UL N = 615	With UL N = 615	*P*
Age, y	44 (41–47)	44 (41–47)	0.364
Age group—no., %			0.242
≤39	128 (20.8)	121 (19.8)	
40–49	426 (69.2)	436 (70.8)	
≥50	62 (10.1)	58 (9.4)	
Menarche age, y	14.3 ± 1.5	14.2 ± 1.5	0.226
Age at first birth, y	26.5 ± 3.2	26.4 ± 3.6	0.797
Parity	1.75 ± 0.5	1.71 ± 0.5	0.088
Use of oral contraceptives or IUD, %	21 (3.4)	21 (3.4)	0.999
Current smoking, %	40 (6.5)	37 (6.0)	0.820
Alcohol drinking, %	180 (29.3)	161 (26.2)	0.597
Regular exercise, %	188 (30.6)	159 (26.0)	0.099
Diabetes mellitus, %	18 (2.9)	38 (6.2)	0.009
Oral antidiabetic agent user, %	15 (2.4)	15 (2.4)	0.999
Insulin user, %	2 (0.3)	4 (0.7)	0.687
HTN, %	39 (6.3)	51 (8.3)	0.228
Antihypertensive agent user, %	24 (3.9)	26 (4.2)	0.885
Lipid-lowering agent user, %	25 (3.9)	34 (5.5)	0.226
BMI, kg/m^2	22.8 (21.0–24.6)	22.8 (21.1–24.8)	0.371
WC, cm	76 (71–81)	77 (72–83)	0.010
Body fat, %	27.9 ± 4.8	28.6 ± 4.6	0.027
Muscle mass, kg	38.9 ± 3.9	38.7 ± 3.8	0.612
Systolic BP, mm Hg	113 (103–124)	115 (106–126)	0.008
Diastolic BP, mm Hg	70 (64–77)	71 (66–78)	0.037
TGs, mg/dL	74 (56–104)	78 (59–107)	0.215
HDL-cholesterol, mg/dL	59 (51–68)	58 (49–68)	0.277
Total cholesterol, mg/dL	185 (166–208)	184 (167–208)	0.657
LDL-cholesterol, mg/dL	110 (92–130)	111 (96–132)	0.040
FPG, mg/dL	84 (80–89)	85 (81–90)	0.075
Fasting insulin, μIU mL	4.09 (2.88–6.00)	4.27 (3.20–5.99)	0.632
HOMA-IR	0.85 (0.57–1.27)	0.88 (0.66–6.00)	0.293

Values are presented as means ± standard deviations or medians (interquartile ranges). *P* values were obtained using the paired *t* test for continuous variables or using McNemar test for categorical variables after log transformation except body fat and muscle mass. BMI = body mass index, BP = blood pressure, HDL = high-density lipoprotein, IUD = intrauterine device, LDL = low-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, UL = uterine leiomyoma, HTN = hypertension, WC = waist circumference, FPG = fasting plasma glucose, TG = triglyceride.

On the other hand, in the present study, asymptomatic women with no history of hysterectomy were included and information about body composition (both BMI and WC), metabolic profiles (HDL-C), UL size and number, was considered. More importantly, we included a control group by propensity score matching to reduce bias due to confounding. The present study shows that the OR for the prevalence of hyperglycemia, a component of MetS, was higher in women with UL after adjusting for confounders. To the best of our knowledge, this is the first case–control study to identify a positive association between UL and MetS in a large community population.

Table 2

Comparison of the prevalence of metabolic components.

	Without UL, N = 615	With UL, N = 615	*P*
Central obesity, %	84 (13.6)	108 (17.5)	0.072
High BP, %	110 (17.9)	126 (20.5)	0.258
Hyperglycemia, %	28 (4.5)	62 (10.1)	<0.001
Hypertriglyceridemia, %	65 (10.6)	77 (12.5)	0.303
Low HDL-C, %	135 (21.9)	168 (27.3)	0.033
MetS, %	35 (5.7)	51 (8.3)	0.097

P values were obtained by McNemar test. Central obesity, WC ≥ 85 cm. High BP, systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or treatment of hypertension. Hyperglycemia, FPG ≥ 100 mg/dL or treatment of diabetes. Hypertriglyceridemia, triglyceride level ≥ 150 mg/dL or treatment of a lipid abnormality. Low HDL-C: HDL-C < 50 mg/dL. HDL-C = high-density lipoprotein cholesterol, WC = waist circumference, BP = blood pressure, UL = uterine leiomyoma, MetS = metabolic syndrome.

The main pathophysiology underlying the relationship between UL and MetS has been proposed to be IR.[19] During recent years, IR has attracted attention in the gynecologic and obstetric fields in the context of tumorigenesis in, for example, breast and endometrial cancer.[20,21] Hyperinsulinemia induced by IR, may be a natural candidate for a key role which would provide a biologically possible link between hormone-associated artherogenic determinants by theoretical evidence as followings. First, IR has been proposed to underlie pathophysiologic pathways connecting obesity, diabetes, HTN, dyslipidemia, and atherosclerosis.[22] Second, insulin has been observed to promote mitosis, vascular smooth muscle proliferation (in rats), and the growth of UL cells in tissue culture.[23] Tyrosine kinases signaling pathways are signal transduction process of cell proliferation, differentiation, migration, metabolism, and programed cell apoptosis, contributing to normal cellular communication and maintenance of homeostasis.[24] Insulin changes the expressions of tumor cell receptors, by changing the receptor tyrosine kinase signal pathway, and stimulates tumorigenesis.[25] Third, it has been suggested that insulin plays a role, a specific gonadotropic function, by stimulating ovarian secretion through

Table 3

The correlation between UL size quartiles and metabolic variables.

	R	*P*	γ	*P*
Age, y	0.146	<0.001		
WC, cm	0.058	0.151	0.042	0.302
BMI, kg/m^2	0.143	<0.001	0.121	0.003
Body fat, %	0.052	0.199	0.029	0.480
Muscle mass, kg	0.079	0.051	0.078	0.054
Systolic BP, mm Hg	0.067	0.096	0.043	0.282
Diastolic BP, mm Hg	0.063	0.121	0.038	0.343
Fasting plasma glucose, mg/dL	0.085	0.035	0.078	0.055
TGs, mg/dL	0.024	0.558	0.010	0.814
HDL-cholesterol, mg/dL	−0.061	0.133	−0.051	0.205
Total cholesterol, mg/dL	0.063	0.122	0.033	0.410
LDL-cholesterol, mg/dL	0.066	0.102	0.035	0.382
Fasting insulin, μIU mL	0.010	0.811	0.006	0.883
HOMA-IR	0.026	0.523	0.021	0.607

Quartile range: first Q < 1.5 cm, 1.5 cm ≤ second Q < 2.3 cm, 2.3 cm ≤ third Q < 3.3 cm, fourth Q ≥ 3.3 cm. *P* value obtained by Pearson correlation analysis after log transformation except body fat and muscle mass. *R*, correlation coefficient; γ, partial correlation coefficient for age. BP = blood pressure, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein, TG = triglyceride, WC = waist circumference, BMI = body mass index.

insulin receptors or IGF receptors.[26] Some studies have showed insulin stimulates hormone production and reduces the association between sexual hormones and globulins, and that this increases the levels of estrogen hormones and other tumor-promoting factors.[8,19] Accordingly, hyperinsulinemia may directly or indirectly influence the development of UL by promoting myometrial smooth muscle cell proliferation or increasing circulating levels of ovarian hormones. Although we failed to show a significant positive correlation between insulin or HOMA-IR and UL, we did find that higher levels of FPG, which are associated with elevated IR, were related to a higher prevalence of UL and an increased number of ULs. Therefore, our results provide circumstantial evidence that UL is associated with IR. There are many evidences for a direct and independent impact of hyperinsulinemia on tumor development through proliferative and antiapoptotic programs in both premalignant and malignant tissues. Likewise, growing preclinical, clinical, and epidemiologic

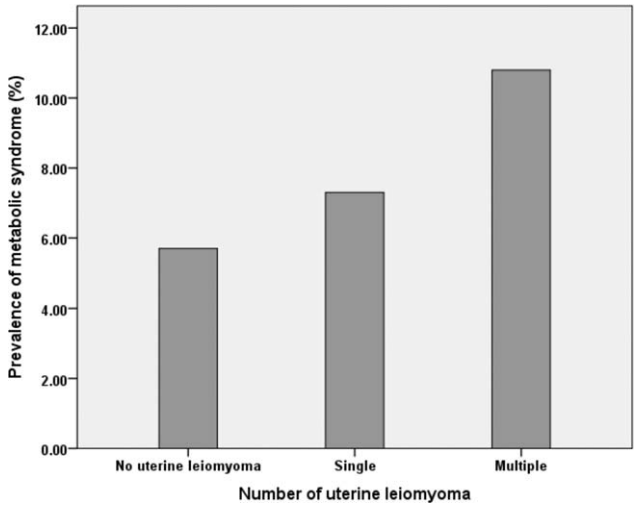

Figure 1. Prevalence of metabolic syndrome according to number of uterine leiomyoma present in individual patients.

evidence suggests that metformin, which is the most commonly used drug for treatment of DM and elevated IR, may prove to be a valuable drug for cancer therapy.[27] Therefore, our study results provide a possibility that the management of hyperinsulinemia may be a therapeutic strategy for management of UL.

However, experimental reports on the presence of a direct association between UL and IR disagree. A recent animal study supported the allosteric effect of IR, as HOMA-IR was observed to promote the production of rat uterine smooth muscles.[11] In contrast, Sadlonova et al[28] demonstrated no significant differences between IR parameters, including FPG, insulin, C peptide, and SHBG, in 56 cases and 20 healthy controls.

In the present study, both WC and body fat were significantly higher in the UL group than in controls matched for age and reproductive characteristics. Furthermore, although nonsignificant, the prevalence of central obesity (WC ≥ 85 cm) was greater in the UL group. These findings are in line with previous reports that suggested a positive association between obesity and the incidence of UL. Marshall et al[29] in a large prospective study of registered nurses in the United States found that the risk of UL increased with BMI and that UL was associated with weight gain. In contrast, several studies reported found no association between the incidence of UL and obesity.[12,30] A combination of several counteracting effects could explain this lack of an association. Although there is evidence that women with central obesity have low SHBG levels, an altered estrogen metabolism, and hyperinsulinemia, which would be expected to stimulate UL development,[6,7] there is also evidence that obesity is related to anovulation, which might decrease the risk of UL.[31] Furthermore, disparate findings regarding the prevalence of obesity might have been due to the use of different definitional criteria, measurement protocol, and control inclusion and exclusion criteria. Nonetheless, the apparent relationship between obesity and UL might be related to obesity-associated hormonal effects. For example, an increase in obesity is followed by an increase in the conversion of circulating adrenal androgens to estrone due an accumulation of adipose tissue.[29] Furthermore, the hepatic production of SHBR is reduced, resulting in more unbound physiologically active estrogen.[4] In obese premenopausal women, reduced estradiol metabolism via the hydroxylation route decreases the conversion of estradiol to inactive metabolites, which could cause a relatively hyperestrogenic state.[7] Previous studies have suggested increased estrogen and adipokine levels produced by excessive fat accumulation and elevated levels of systemic inflammatory cytokines might increase the risk of tumorigenesis.[21,32]

Regarding nonhormonal factors, the coexistence of UL and HTN has been mentioned in earlier studies.[6,13,33] Our study shows BP was higher in the UL group than in the control group and higher in those with several UL lesions than in those with 1 lesion. This relationship between BP and UL might be due to a common pathophysiology. Several vasoactive peptides and growth factors, such as angiotensin II, endothelin-1, IGF-1, platelet-derived growth factor, transforming growth factor-β, and creatine kinase, enhance smooth muscle proliferation and vascular remodeling or contractility, which might result in uterine fibroids and HTN.[34] Moreover, other authors have hypothesized that smooth muscle proliferation in uterine myometrium is analogous to atherosclerotic alterations in smooth muscle and a consequence of transforming growth factor-β stimulation caused by HTN-induced smooth muscle damage.[6,33,35] Others have proposed that UL promotes HTN by inducing the uterine production of angiotensinogenase, which hydrolyzes

Table 4

Metabolic profiles adjusted for age according to numbers of ULs.

Variables	Numbers of ULs			*P* for trend
	One, N = 439	Two, N = 119	Three or more, N = 57	
Age, y	42.7 ± 5.2	44.5 ± 4.8	45.5 ± 3.4	<0.001
WC, cm	77.5 ± 7.6	77.6 ± 7.8	78.9 ± 7.7	0.402
BMI, kg/m^2	23.0 ± 2.9	23.2 ± 3.0	24.2 ± 2.6	0.024
Body fat, %	28.3 ± 4.6	28.7 ± 4.9	30.2 ± 4.5	0.020
Muscle mass, kg	38.8 ± 3.7	38.5 ± 4.0	38.8 ± 4.1	0.938
Systolic BP, mm Hg	116.2 ± 14.6	117.5 ± 16.9	122.5 ± 15.0	0.019
Diastolic BP, mm Hg	71.8 ± 9.5	72.4 ± 10.3	75.3 ± 8.8	0.051
Fasting plasma glucose, mg/dL	86.1 ± 9.5	88.5 ± 17.5	89.2 ± 20.4	0.049
TGs, mg/dL	88.3 ± 45.4	92.7 ± 49.1	105.1 ± 42.9	0.028
HDL-cholesterol, mg/dL	58.9 ± 13.7	60.1 ± 14.9	54.3 ± 12.6	0.028
Total cholesterol, mg/dL	185.9 ± 31.6	192.5 ± 29.7	195.4 ± 30.8	0.164
LDL-cholesterol, mg/dL	112.9 ± 27.9	118.6 ± 25.2	121.8 ± 28.7	0.142
Fasting insulin, μIU mL	4.76 ± 2.6	4.65 ± 2.6	5.22 ± 2.9	0.267
HOMA-IR	1.03 ± 0.6	1.08 ± 0.9	1.20 ± 0.9	0.186

P values were obtained using the general linear model after adjusting for age. BP = blood pressure, HDL = high-density lipoprotein, HOMA-IR = homeostasis model assessment of insulin resistance, LDL = low-density lipoprotein, TG = triglyceride, WC = waist circumference, UL = uterine leiomyoma, BMI = body mass index.

angiotensinogen.[36] Although this reverse-causality interpretation has been questioned, it has been suggested that urinary tract obstruction by UL causes HTN.[8]

It is well known that estrogen and its receptors are regulators of several aspects of lipid metabolism, and that impaired estrogen signaling is associated with the developments of metabolic diseases.[37] Estrogens influence TG accumulation, increase HDL-C levels, and modulate the expression of lipoprotein lipase, which catalyzes the conversion of TG into free fatty acid in the liver. As UL is an estrogen-related tumor, a relationship is believed to exist between dyslipidemia and the risk of UL, and consistent with this hypothesis, in the present study, the prevalences of low HDL-C and of LDL-C levels were significantly higher in UL group. However, findings on this issue conflict; He et al[38] reported an inverse association between HDL-C and UL (OR = 0.46; 95% CI, 0.25–0.84) in a hysterectomy-confirmed group, whereas Parazzini et al[39] did not observe an association between hyperlipidemia and UL.

4.1. Strengths and limitations

This study had several noteworthy features. Its primary strength is the ultrasonogram-based screening performed for UL among matched premenopausal women irrespective of clinical symptoms, as this allowed women with asymptomatic or symptomatic UL to be precisely classified according to UL status. Furthermore, the study had a relatively large sample cohort, and information on medical histories, demographics, lifestyles, and laboratory results was collated, which allowed adjustments for important potential confounders during the analysis. In addition, MetS was diagnosed based on medical examinations and UL was diagnosed by gynecology professionals, whereas self-reported MetS or UL has been used in previous papers. These 2 diagnostic features minimized recall bias and disease misclassifications.

However, this analysis has several limitations. Despite careful control to minimize the confounding effects, we cannot rule out the possibility that misclassification of outcome affected our results, and the cross-sectional nature of the study prevented our confirming the causal effect of MetS in the pathogenesis of UL. Finally, because only Korean women were recruited, our findings cannot be generalized to other ethnicities or geographic regions.

In conclusion, the present study shows that women with UL are at greater risk of prevalence of MetS regardless of confounding factors. We suggest the biological mechanism responsible for UL may involve IR aggravation, which is atherosclerotic pathway as nonhormonal factor. In our view, the clinical relevance of a relation between UL and IR is that the early detection and management of metabolic abnormality be considered in women

Table 5

OR for UL by metabolic component.

	Crude OR (95% CI)	Model 1 OR (95% CI)*	Model 2 OR (95% CI)†
Central obesity	1.15 (0.94–1.42)	1.15 (0.93–1.42)	1.14 (0.93–1.41)
High BP	1.09 (0.89–1.32)	1.10 (0.90–1.34)	1.09 (0.89–1.34)
Hyperglycemia	1.42 (1.09–1.85)	1.43 (1.10–1.86)	1.45 (1.10–1.89)
Hypertriglyceridemia	1.10 (0.86–1.39)	1.10 (0.87–1.40)	1.10 (0.86–1.40)
Low HDL-C	1.15 (0.96–1.37)	1.15 (0.97–1.38)	1.17 (0.97–1.40)
MetS	1.20 (0.90–1.60)	1.22 (0.91–1.62)	1.21 (0.90–1.63)

High BP, systolic BP ≥ 130 mm Hg or diastolic BP ≥ 85 mm Hg, or treatment of hypertension. Hyperglycemia, fasting plasma glucose ≥100 mg/dL or treatment of diabetes. Hypertriglyceridemia, triglyceride level ≥150 mg/dL or treatment of lipid abnormality. Low HDL-C < 50 mg/dL. CI = confidence interval, HDL-C = high-density lipoprotein cholesterol, WC = waist circumference, BP = blood pressure, MetS = metabolic syndrome, OR = odd ratio.

* Adjusted for age.

† Adjusted for age, age at first birth, menarche age, parity, use of oral contraceptives or intrauterine devices, and health-related habits.

presenting with UL. Further prospective research is required to prove causality and to determine the role played by metabolic abnormalities in the natural history of UL.

5. Conclusion

Our study found that MetS and each of their components was associated with an increased prevalence of UL when age and reproductive variables were adjusted among the parous premenopausal women without symptom. Our results provide the clue that MetS may increase a risk of UL. These findings have clinically important implications for designing UL prevention or management strategies.

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