Association of uterine leiomyoma with type 2 diabetes mellitus in young women: a population-based cohort study

Cheol-Young Park[1], Ji-Hee Sung[2], Kyung-Soo Kim[3], and Kyungdo Han[4]

[1]Kangbuk Samsung Hospital Department of Internal Medicine Division of Endocrinology and Metabolism
[2]Samsung Medical Center
[3]CHA Bundang Medical Center
[4]Soongsil University Department of Statistics and Actuarial Science

May 10, 2023

Abstract

Objective: To evaluate the association between uterine leiomyoma (UL) and development of type 2 diabetes mellitus in young women using a nationwide database. **Design:** Nationwide population-based cohort study **Setting:** South Korea. **Population or Sample:** Women aged between 20 and 40 years at baseline who underwent at least one health checkup between 2009 and 2012 and followed until December 31, 2018 **Methods**: We excluded those who were previously diagnosed with type 2 diabetes mellitus (n = 28,136), those diagnosed with type 2 diabetes mellitus within the first year of entry (n = 1,607), those who had hysterectomy during the study period (n = 18,485), and those with missing data (n = 166,012). Cox proportional hazards models were used to analyze the risk of developing type 2 diabetes according to the presence of UL. **Main outcome Measures:** Incidence of the development of type 2 diabetes mellitus according to the presence of UL **Results:** 2,755,790 women were selected and he mean age of the enrolled population was 29.70 y, and mean body mass index was 21.31 kg/m ^{2}. Among 2,541,550 participants, 18,375 (0.72%) women had UL. Over a median 7.45 years of follow-up, 23,829 women (0.94%) were diagnosed with type 2 diabetes. The incidence of type 2 diabetes in women with UL (1.805/1,000 person-years) was higher than in those without UL (1.289/1000 person-years). In the multivariable-adjusted model, the hazard ratio for type 2 diabetes in women with UL was 1.216 (95% confidence interval [CI] 1.071-1.382), as compared to those without UL. Compared to women without UL, women with UL who did not undergo myomectomy had a risk 1.328 times (95% CI 1.143-1.542) higher for developing type 2 diabetes. Interestingly, women with UL who underwent myomectomy had no increased risk for developing type 2 diabetes. **Conclusions:** This study found that young women with UL are more likely to develop type 2 diabetes than those without UL. In addition, myomectomy seemed to attenuate the risk for developing type 2 diabetes in young women with UL.

Association of uterine leiomyoma with type 2 diabetes mellitus in young women: a population-based cohort study

Ji-Hee Sung[1,*] | Kyung-Soo Kim[2,*] | Kyungdo Han[3]| Cheol-Young Park[4]

[1]Department of Obstetrics and Gynecology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. obgysung@gmail.com

[2]Department of Internal Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea. kks982@hanmail.net

[3]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Republic of Korea. hkd917@naver.com

[4]Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea, cydoctor@chol.com

Article Word Count: 2,930 words

Table/Figure Number: 4

* Ji-Hee Sung and Kyung-Soo Kim contributed equally to the work.

Corresponding author: Cheol-Young Park, MD, PhD

Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea

Tel: +82-2-2001-1869, Fax: +82-2-2001-1588, E-mail: cydoctor@chol.com

Short title: Uterine leiomyoma and type 2 diabetes mellitus

Abstract

Objective: **T** o evaluate the association between uterine leiomyoma (UL) and development of type 2 diabetes mellitus in young women using a nationwide database.

Design: Nationwide population-based cohort study

Setting: South Korea.

Population or Sample: Women aged between 20 and 40 years at baseline who underwent at least one health checkup between 2009 and 2012 and followed until December 31, 2018

Methods : We excluded those who were previously diagnosed with type 2 diabetes mellitus (n = 28,136), those diagnosed with type 2 diabetes mellitus within the first year of entry (n = 1,607), those who had hysterectomy during the study period (n = 18,485), and those with missing data (n = 166,012). Cox proportional hazards models were used to analyze the risk of developing type 2 diabetes according to the presence of UL.

Main outcome Measures: Incidence of the development of type 2 diabetes mellitus according to the presence of UL

Results: 2,755,790 women were selected and he mean age of the enrolled population was 29.70 y, and mean body mass index was 21.31 kg/m^2. Among 2,541,550 participants, 18,375 (0.72%) women had UL. Over a median 7.45 years of follow-up, 23,829 women (0.94%) were diagnosed with type 2 diabetes. The incidence of type 2 diabetes in women with UL (1.805/1,000 person-years) was higher than in those without UL (1.289/1000 person-years). In the multivariable-adjusted model, the hazard ratio for type 2 diabetes in women with UL was 1.216 (95% confidence interval [CI] 1.071-1.382), as compared to those without UL. Compared to women without UL, women with UL who did not undergo myomectomy had a risk 1.328 times (95% CI 1.143-1.542) higher for developing type 2 diabetes. Interestingly, women with UL who underwent myomectomy had no increased risk for developing type 2 diabetes.

Conclusions: This study found that young women with UL are more likely to develop type 2 diabetes than those without UL. In addition, myomectomy seemed to attenuate the risk for developing type 2 diabetes in young women with UL.

Keywords: Type 2 diabetes mellitus, uterine fibroids, surgery, young women, incidence

1 | Introduction

Uterine leiomyoma (UL) is one of the most common benign tumors of the uterus; by menopause, the incidence of UL in the general female population is 70%.[1,2] UL is often asymptomatic and rarely becomes malignant; however, it may cause pelvic pain, dysmenorrhea, excessive uterine bleeding, and infertility in women of

reproductive age. Old age, younger age at menarche, and premenopausal state are risk factors for developing UL, as it is linked to longer duration of exposure to ovarian hormones.[3,4]

Insulin resistance was suggested as one of the possible pathophysiological explanations for UL development.[5,6]Furthermore, hyperinsulinemia induced by insulin resistance can upregulate serum insulin-like growth factor-1 and epidermal growth factor levels.[7-9] This can affect the development of UL by enhancing either ovarian hormone secretion or myometrial smooth muscle cell proliferation, or both. A report that supports this rationale stated that metabolic syndrome was associated with UL.[10] Another study reported that the risk of development of UL was decreased with the use of metformin in women with type 2 diabetes mellitus.[11] Based on these reports, we can assume that there is a possible association between type 2 diabetes and UL. However, there is no large scale, population-based study that has investigated the association between presence of UL and development of type 2 diabetes. The aim of this study was to evaluate the association between UL and development of type 2 diabetes in a large population of young women using a nationwide database.

2 | methods

2.1 | Data source

We conducted a nationwide population-based cohort study using claims and health checkup data from the National Health Insurance Service-National Sample Cohort (NHIS-NSC). The NHIS is a single-payer health care system for all Korean residents managed by the Korean government, covering more than 98% of the Korean population. The claims data encompasses sociodemographic variables; diagnosis statements defined by the International Classification of Diseases, 10th revision (ICD-10); prescriptions; and hospital visits dates. Our study protocol was approved by the NHIS review committee and Institutional Review Board of Kangbuk Samsung hospital (IRB No. KBSMC-07-034). Informed consent was waived by IRB as the data set provided from NHIS is deidentified to protect privacy.

2.2 | Study design and participants

We selected 2,755,790 women aged between 20 and 40 years at baseline who underwent at least one health checkup between 2009 and 2012. The time point at the first health checkup for each patient between 2009 and 2012 was considered the index date. We excluded those who were previously diagnosed with type 2 diabetes mellitus (n = 28,136), those diagnosed with type 2 diabetes mellitus within the first year of entry (n = 1,607), those who had uterine myomectomy during the study period (n = 18,485), and those with missing data for least 1 variable (n = 166,012). Finally, a total of 2,541,550 patients were eligible for inclusion and were followed until December 31, 2018.

2.3 | Study outcomes and follow-up

he end point of this study was the incidence of type 2 diabetes mellitus. The study population was followed from the index date to the date of incident type 2 diabetes mellitus, or until December 31, 2018. The median follow-up duration was 7.45 years.

2.4 | Measurements

Blood pressure (both systolic and diastolic values) was measured by a trained clinician while the participants were seated. Blood samples were obtained after at least 8 hours of fasting. The levels of glucose, total cholesterol, triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and creatinine were measured. Estimated glomerular filtration rate (eGFR) was calculated using the equation from the Modification of Diet in Renal Disease study: eGFR=186.3×serum creatinine$^{-1.154}$xage$^{-0.203}$x0.742 (for women).

Information about lifestyle factors, including smoking status, alcohol intake status, exercise frequency, and past medical history (history of hypertension, dyslipidemia, impaired fasting glucose [IFG], and chronic kidney disease [CKD]) was obtained using a standardized self-assessment questionnaire. Drinking status was divided into three categories: nondrinker, mild drinker, and heavy drinker; heavy alcohol consumption was

defined as drinking more than 30 g of alcohol per day. Regular physical activity was defined as more than 30 minutes of moderate physical activity performed at least five times per week, or more than 20 minutes of strenuous physical activity performed at least three times per week. Low income was defined as being within the lowest 20% of the total population based on monthly income.

2.5 | Definitions

Uterine leiomyoma was identified in case of female patient admittance with ICD-10 code D25 at least once or diagnosis with ICD-10 codes D25 upon outpatient clinic visit at least twice within one year from the index date. Myomectomy was defined as an ICD-10 code for myomectomy (QZ961, R4120-4126, R4130, R4141, R4145, R4146, RZ564-566, HA636, HA621, M6644) logged within one year of the index date. Type 2 diabetes mellitus was defined as having fasting plasma glucose (FPG) concentrations [?]126 mg/dL or having been prescribed anti-diabetic drugs under ICD-10 codes E11–E14.

Hypertension was defined as blood pressure [?]140/90 mm Hg or having been prescribed anti-hypertensive drugs under ICD-10 codes I10-13, I15. Dyslipidemia was defined using ICD-10 codes E78 and at least one record per year for a prescription for a lipid-lowering agent or by a total cholesterol level [?]240 mg/dL. Impaired fasting glucose was defined as FPG 100-125 mg/dL, and CKD was defined as eGFR <60 mL/min/1.73 m^2.

2.6 | Statistical analyses

Continuous variables are presented as mean +- standard deviation or median (interquartile range), while categorical variables are presented as numbers (%). Baseline clinical characteristics were compared between groups using Student's t-test for continuous variables and χ^2 test for categorical variables. Incidence rates are presented as the number of events occurring per 1000 person-years. The Cox proportional hazards model was used to estimate adjusted hazard ratio with a 95% confidence interval (CI) for type 2 diabetes mellitus. The covariates were as follows: age, smoking status, alcohol consumption, and regular exercise in model 1; and age, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index (BMI) in model 2. The cumulative incidence of type 2 diabetes mellitus according to the presence of UL and myomectomy was estimated using the Kaplan-Meier method. Subgroup analyses were performed according to age, BMI, smoking status, alcohol consumption, regular exercise, and having hypertension, dyslipidemia, and CKD. All data analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). A P-value < 0.05 was considered significant.

2.7 | Data and resource availability statements

Restrictions apply to the availability of these data. Data were obtained from Korea NHIS and are available at https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do (accessed on 1st April 2022) with the permission of Korea NHIS.

3 | Results

Baseline characteristics of patients are presented in Table 1. A total of 2,541,550 women were eligible, of whom 18,375 (0.72%) were diagnosed with UL. The mean age was 29.70 y, and mean BMI was 21.31 kg/m^2. Women with UL were older; had higher BMI, blood pressure, FPG, total cholesterol, TG, and LDL cholesterol; and had higher prevalence of hypertension, dyslipidemia, and IFG, as well as lower HDL cholesterol, than those without UL. However, women with UL were revealed to have a lower rate of current smoking and heavy drinking status as compared to those without UL. There was no significant difference in CKD prevalence or regular exercise frequency between women with UL and those without UL.

Over a median 7.45 years of follow-up, 23,829 women (0.94%) were diagnosed with type 2 diabetes mellitus (Table 2). The incidence rate of type 2 diabetes mellitus in women with UL (1.805/1,000 person-years) was higher than that in those without UL (1.289/1000 person-years) ($P< 0.0001$). The cumulative incidence of type 2 diabetes mellitus in women with UL was higher than that in those without UL ($P = 0.0026$) (Fig. 1A). The unadjusted HR for type 2 diabetes mellitus in women with UL was 1.403 (95%CI 1.236-

1.593) compared to that in those without UL. Although the HR for type 2 diabetes mellitus was slightly decreased after adjustment for age, smoking status, alcohol consumption, and regular exercise (model 1), women with UL still showed an elevated HR for type 2 diabetes mellitus(HR 1.195, 95%CI 1.053-1.358). In multivariable-adjusted model (model 2), the HR for type 2 diabetes mellitus in women with UL was 1.216 (95%CI 1.071-1.382).

Subgroup analyses stratified by age, BMI, smoking status, alcohol consumption, regular exercise, and having hypertension, dyslipidemia, and CKD were performed (Table 3). Women with UL showed a higher risk for type 2 diabetes mellitus than women without UL in various subgroups, except in those with BMI [?]25 kg/m^2 and a history of CKD.

Women with UL who underwent myomectomy were older and had higher BMI than those with UL who did not undergo myomectomy (Supplementary Table 1). There was no significant difference in other baseline characteristics between the two groups. Compared with women without UL, women with UL who did not undergo myomectomy had a 1.505 times (95%CI 1.297-1.748) higher risk for type 2 diabetes mellitus, as opposed to no increased risk for type 2 diabetes mellitus in those with UL who underwent myomectomy (Table 2). Women with UL who did not undergo myomectomy still had an elevated HR for type 2 diabetes (HR 1.287, 95%CI 1.108-1.495) after adjustment for age, smoking status, alcohol consumption and regular exercise (model 1). In the multivariable-adjusted model (model 2), the HR for type 2 diabetes in women with UL who did not undergo myomectomy was 1.328 (95% CI 1.143-1.542). However, risk for type 2 diabetes mellitus was not increased in women with UL who underwent myomectomy in models 1 and 2. The cumulative incidence of type 2 diabetes mellitus in women with UL who did not undergo myomectomy was higher than that in those with UL who underwent myomectomy ($P = 0.0357$) (Fig. 1B).

4 | Discussion

4.1 | Principal findings

This population-based cohort study demonstrated that young women with UL appear to be at a higher risk for type 2 diabetes mellitus than those without UL. Incidence rate of type 2 diabetes mellitus in women with UL was higher than that in women without UL. However, women with UL who underwent myomectomy did not have an increased risk for developing type 2 diabetes mellitus as compared to those without UL. The risk for type 2 diabetes mellitus was higher in women with UL who did not undergo myomectomy as compared to that in those without UL.

4.2 | Results in the context of what is known

To our knowledge, there is no large-scale, population-based, longitudinal study evaluating the association between presence of UL and development of type 2 diabetes mellitus in young women. This study revealed that UL was associated with an elevated risk for type 2 diabetes mellitus and that myomectomy seemed to attenuate the risk for type 2 diabetes mellitus in young women with UL.

Several studies indicate an association between obesity and UL.[2,12,13] Ciavattni et al. performed an observational case-control study including 71 women of childbearing age diagnosed with UL and 145 women as control group.[12] Women with UL had higher BMI ($P = 0.0034$), preperitoneal fat thickness ($P< 0.0001$), and subcutaneous fat thickness ($P = 0.0003$); however, only preperitoneal fat thickness showed an independent significant association with the presence of UL in multivariate analysis ($P < 0.0001$). Another study, including 89 patients with UL and 81 healthy women without UL, showed that increased body fat (especially abdominal visceral fat) is associated with an increased risk of UL.[13] Recently, a meta-analysis examining 24 studies found a positive association between obesity and the risk/prevalence of UL (odds ratio [OR] 1.19, 95% CI 1.09-1.29).[2] Consistent with the result of previous studies, women with UL had a BMI higher than that of women without UL in our study, although both groups had relatively low BMI. However, in subgroup analysis stratified by BMI, women with BMI [?]25 kg/m^2 revealed no significant difference in the incidence rate of type 2 diabetes mellitus between women with UL and without UL. This might be due to well-known close association between obesity and the development of type 2 diabetes mellitus. Relative high incidence

rate of women with or without UL with BMI [?]25 kg/m^2 compared to women with BMI less than 25 kg/m^2 support this hypothesis (Table 3). Similarly, there was no difference in the incidence rate of type 2 diabetes mellitus between women with UL and without UL in whom with CKD history. These findings also might be due to the inseparable association between CKD and development of type 2 diabetes mellitus.[14]

Beyond obesity, several studies reported that various metabolic components were associated with UL.[10,15] Takeda et al investigated whether UL is associated with any specific criteria of metabolic syndrome.[15] In their case-control study, BMI, blood pressure, TG, and FPG were significantly higher in 213 women with UL compared to those in 159 women without UL. Moreover, the risk of UL was correlated with increased metabolic component levels; the OR of three metabolic components for UL was 3.64 (95%CI 2.28-5.82). Another study that enrolled 1,230 parous premenopausal women reported that women with UL had higher waist circumferences, body fat, blood pressure, and LDL cholesterol than women without UL.[10] Increasing evidence suggests that UL seems to share pathogenic features with the development of metabolic syndrome. In our study, women with UL had poor metabolic profiles, such as higher blood pressure, FPG, total cholesterol, TG, LDL cholesterol, and lower HDL cholesterol, when compared with women without UL.

Although the two disease states are likely to be related, few studies have evaluated the association between UL and type 2 diabetes mellitus. A nested case-control study enrolling 3,789 participants reported a protective association between UL and type 2 diabetes with a relatively greater protective effect observed among European Americans than African Americans.[16] However, this study was limited by design and population as it was a cross-sectional study that included relatively old women (mean age: 47 y in UL group; 44 y in control group). On the other hand, the previously mentioned study by Tak et al revealed that hyperglycemia is significantly associated with an increased risk of UL (OR: 1.45, 95%CI 1.10-1.89).[10]Furthermore, in a Taiwanese population-based cohort study, metformin use was associated with a lower risk of UL (HR: 0.467, 95%CI 0.387-0.564) in 21,996 women with new-onset type 2 diabetes mellitus.[11] However, there was no longitudinal study to evaluate the risk for type 2 diabetes mellitus solely in connection with the presence of UL, especially in young women.

4.3 | Clinical implications

Over a median 7.45 years of follow-up, women with UL had 21.4% higher risk for type 2 diabetes mellitus compared to women without UL in our study. Since the mean age of participants was 29.70 years, young women with UL are advised to pay attention to the prevention and monitoring of type 2 diabetes mellitus.

The pathophysiology of how UL affects the development of type 2 diabetes mellitus is unclear. The development of UL is known to be dependent on ovarian steroid hormones.[4] Considering the hormonal changes in obese women or women with metabolic syndrome, it is likely that rather than UL itself, the uterus, endometrium, and ovaries might affect the development of type 2 diabetes mellitus.[17-20] A retrospective population-based cohort study found that the risk of diabetes was higher in women with hysterectomy compared to that in those without hysterectomy (HR 1.37, 95%CI 1.23-1.52) and that diabetes risk was not increased in women with hysterectomy and oophorectomy (HR: 1.28, 95%CI 0.93-1.76).[21] Interestingly, myomectomy seemed to attenuate the risk for type 2 diabetes mellitus in women with UL in our study. Compared to women without UL, women with UL who did not undergo myomectomy had a higher risk for type 2 diabetes (HR 1.328, 95%CI 1.143-1.542), but women with UL who underwent myomectomy did not. These findings suggest a possible effect of UL on the development of diabetes. UL has increased responsiveness and hypersensitivity to gonadal steroids through increased expression of steroid hormone receptors.[21-24] Along with estrogen, which is considered a primary mitogenic factor for the uterus, progesterone and progesterone receptors are reported to play a key role in the development and growth of UL.[23] In response to estrogen and progesterone, uterine fibroids can increase in size by cell proliferation, hypertrophy, and accumulation of extracellular matrix.[24] Increased progesterone level is associated with reduced insulin sensitivity, which can lead to development of type 2 diabetes.[25,26] An animal study showing improved glucose homeostasis in progesterone receptor knockout mice supports the adverse effect of progesterone on glucose tolerance and insulin release.[27] A reasonable explanation for the reduction of type 2 diabetes risk associated with myomectomy may be the reduction of progesterone receptor expression through the mechanical removal of the UL.

4.4 | Research implications

Further prospective study to determine the direct association between UL and the development of type 2 diabetes mellitus is warranted. In addition, investigating the effect of the size and numbers of the UL on the development of type 2 diabetes mellitus is needed.

4.5 | Strength and limtations

Several limitations should be considered when interpreting the results of this study. First, the definition of UL was not based on imaging, but instead, on ICD-10 codes and outpatient clinic visits. Since UL is mostly asymptomatic in early stages, women who have asymptomatic UL may have been undiagnosed, which may cause the prevalence of UL to be underestimated. Second, information about the size and number of ULs was not available due to the database characteristics. Third, gynecologic information, including parity, presence of polycystic ovarian syndrome, or hormonal status, were also inaccessible; these factors can affect the development of type 2 diabetes mellitus, and their absence lowers the generalizability of our results. Finally, because this study was conducted using the Korean nationwide database, the results might not be generalizable to other ethnicities. However, this study is valuable because, to our knowledge, it is the first large-scale, longitudinal study to evaluate the association between presence of UL and development of type 2 diabetes mellitus in young women.

5 | Conclusions

The study results suggest that UL was associated with a higher risk for developing type 2 diabetes mellitus in young women. Furthermore, myomectomy seemed to attenuate the risk for type 2 diabetes mellitus in women with UL, suggesting the importance of type 2 diabetes mellitus screening and prevention in young women with UL.

Author contributions

C.Y.P, K.H, J.H.S and K.S.K were involved in the conception, design, and conduct of the study and the analysis and interpretation of the results. J.H.S and K.S.K wrote the first draft of the manuscript, and all authors edited, reviewed, and approved the final version of the manuscript.

C.Y.P is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article.

ETHICAL STATEMENT

Our study protocol was approved by the NHIS review committee and Institutional Review Board of Kangbuk Samsung hospital on July 2022 (IRB No. KBSMC-07-034).

References

1. American College of Obstetricians, Gynecologists' Committee on Practice Bulletins-Gynecology. Management of Symptomatic Uterine Leiomyomas: ACOG Practice Bulletin, Number 228. Obstet Gynecol. 2021;137(6):e100-e15.

2. Qin H, Lin Z, Vasquez E, Luan X, Guo F, Xu L. Association between obesity and the risk of uterine fibroids: a systematic review and meta-analysis. J Epidemiol Community Health. 2021;75(2):197-204.

3. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet. 2020;149(1):3-9.

4. Kim JJ, Kurita T, Bulun SE. Progesterone action in endometrial cancer, endometriosis, uterine fibroids, and breast cancer. Endocr Rev. 2013;34(1):130-62.

5. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. Lancet. 2005;365(9468):1415-28.

6. Hebbar S, Chaya V, Rai L, Ramachandran A. Factors influencing endometrial thickness in postmenopausal women. Ann Med Health Sci Res. 2014;4(4):608-14.

7. Januzzi JL, Jr., Butler J, Sattar N, Xu J, Shaw W, Rosenthal N, et al. Insulin-Like Growth Factor Binding Protein 7 Predicts Renal and Cardiovascular Outcomes in the Canagliflozin Cardiovascular Assessment Study. Diabetes Care. 2021;44(1):210-6.

8. Yang Y, Yao S, Ding JM, Chen W, Guo Y. Enhancer-Gene Interaction Analyses Identified the Epidermal Growth Factor Receptor as a Susceptibility Gene for Type 2 Diabetes Mellitus. Diabetes Metab J. 2021;45(2):241-50.

9. Jeong IK, Byun JK, Noh J, Kim SW, Chung YS, Park TS, et al. Reference Ranges of Serum Insulin-Like Growth Factor-I and Insulin-Like Growth Factor Binding Protein-3: Results from a Multicenter Study in Healthy Korean Adults. Endocrinol Metab (Seoul). 2020;35(4):954-9.

10. Tak YJ, Lee SY, Park SK, Kim YJ, Lee JG, Jeong DW, et al. Association between uterine leiomyoma and metabolic syndrome in parous premenopausal women: A case-control study. Medicine (Baltimore). 2016;95(46):e5325.

11. Tseng CH. Metformin use is associated with a lower risk of uterine leiomyoma in female type 2 diabetes patients. Ther Adv Endocrinol Metab. 2019;10:2042018819895159.

12. Ciavattini A, Delli Carpini G, Moriconi L, Clemente N, Orici F, Boschi AC, et al. The association between ultrasound-estimated visceral fat deposition and uterine fibroids: an observational study. Gynecol Endocrinol. 2017;33(8):634-7.

13. Sun K, Xie Y, Zhao N, Li Z. A case-control study of the relationship between visceral fat and development of uterine fibroids. Exp Ther Med. 2019;18(1):404-10.

14. Levey AS, Bilous R, Shlipak MG. CKD and Diabetes: What Can We Learn From Their Similarities and Differences? Am J Kidney Dis. 2016;67(3):360-3.

15. Takeda T, Sakata M, Isobe A, Miyake A, Nishimoto F, Ota Y, et al. Relationship between metabolic syndrome and uterine leiomyomas: a case-control study. Gynecol Obstet Invest. 2008;66(1):14-7.

16. Chiang CH, Chen W, Tsai IJ, Hsu CY, Wang JH, Lin SZ, et al. Diabetes mellitus risk after hysterectomy: A population-based retrospective cohort study. Medicine (Baltimore). 2021;100(4):e24468.

17. Kang S, Park YM, Kwon DJ, Chung YJ, Namkung J, Han K, et al. Reproductive Life Span and Severe Hypoglycemia Risk in Postmenopausal Women with Type 2 Diabetes Mellitus. Diabetes Metab J. 2022;46(4):578-91.

18. Oguz SH, Yildiz BO. An Update on Contraception in Polycystic Ovary Syndrome. Endocrinol Metab (Seoul). 2021;36(2):296-311.

19. Luo J, Manson JE, Urrutia RP, Hendryx M, LeBlanc ES, Margolis KL. Risk of Diabetes After Hysterectomy With or Without Oophorectomy in Postmenopausal Women. Am J Epidemiol. 2017;185(9):777-85.

20. Appiah D, Winters SJ, Hornung CA. Bilateral oophorectomy and the risk of incident diabetes in postmenopausal women. Diabetes Care. 2014;37(3):725-33.

21. Cermik D, Arici A, Taylor HS. Coordinated regulation of HOX gene expression in myometrium and uterine leiomyoma. Fertil Steril. 2002;78(5):979-84.

22. Harrison-Woolrych ML, Charnock-Jones DS, Smith SK. Quantification of messenger ribonucleic acid for epidermal growth factor in human myometrium and leiomyomata using reverse transcriptase polymerase chain reaction. J Clin Endocrinol Metab. 1994;78(5):1179-84.

23. Brandon DD, Bethea CL, Strawn EY, Novy MJ, Burry KA, Harrington MS, et al. Progesterone receptor messenger ribonucleic acid and protein are overexpressed in human uterine leiomyomas. Am J Obstet Gynecol. 1993;169(1):78-85.

24. Williams AR, Critchley HO, Osei J, Ingamells S, Cameron IT, Han C, et al. The effects of the selective progesterone receptor modulator asoprisnil on the morphology of uterine tissues after 3 months treatment in patients with symptomatic uterine leiomyomata. Hum Reprod. 2007;22(6):1696-704.

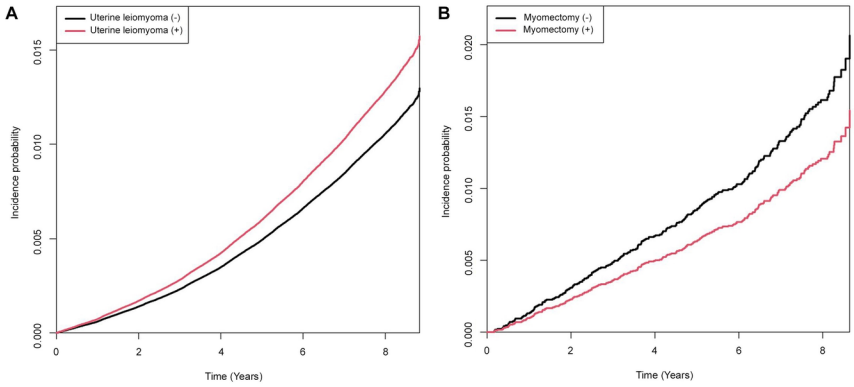
25. Padmanabhan S, Lee VW, McLean M, Athayde N, Lanzarone V, Khoshnow Q, et al. The Association of Falling Insulin Requirements With Maternal Biomarkers and Placental Dysfunction: A Prospective Study of Women With Preexisting Diabetes in Pregnancy. Diabetes Care. 2017;40(10):1323-30.

26. Ryan AS, Nicklas BJ, Berman DM. Hormone replacement therapy, insulin sensitivity, and abdominal obesity in postmenopausal women. Diabetes Care. 2002;25(1):127-33.

27. Picard F, Wanatabe M, Schoonjans K, Lydon J, O'Malley BW, Auwerx J. Progesterone receptor knockout mice have an improved glucose homeostasis secondary to beta -cell proliferation. Proc Natl Acad Sci U S A. 2002;99(24):15644-8.

Figure Legend

Figure 1 The cumulative incidence of type 2 diabetes mellitus. A:stratified according to presence of uterine leiomyoma adjusted for age, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index ($P = 0.0026$). B:stratified according to myomectomy adjusted for age, smoking status, alcohol consumption, regular exercise, hypertension, dyslipidemia, and body mass index ($P = 0.0357$).



Hosted file

tables.docx available at https://authorea.com/users/616749/articles/642576-association-of-uterine-leiomyoma-with-type-2-diabetes-mellitus-in-young-women-a-population-based-cohort-study

Hosted file

BJOG_Uterine_myoma_DM_Supple Table.docx available at https://authorea.com/users/616749/articles/642576-association-of-uterine-leiomyoma-with-type-2-diabetes-mellitus-in-young-women-a-population-based-cohort-study