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Original Article

Association of health and lifestyle factors with uterine fibroids among Saudi women: A case–control study

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الملخص

أهداف: الهدف من هذه الدراسة هو قياس العلاقة بين تليف الرحم وعوامل الخطر المختلفة (تعدد الولادات، الإجهاض، السكري، ارتفاع ضغط الدم، النشاط البدني، التدخين، التاريخالعائلي لالتهاب الرحم، واستخدام حبوب منع الحمل) بين النساء السعوديات.

طرق: أجريت دراسة الحالات والشواهد في مركزين طبيين في الرياض، بين امرأة. تم تأكيد الحالات عن طريق الموجات فوق الصوتية. تم جمع المعلومات الديموغرافية وعوامل الخطر من خلال المقابلة والسجلات الطبية. تم حساب انتشار عوامل الخطر المختلفة مع فاصلة ثقة ٩٥٪. تم استخدام تحليل الانحدار اللوجستي غير المشروط لقياس الارتباط بين تليف الرحم وعوامل الخطر المختلفة.

نتائج: كان أكثر من نصف المشاركين يعانون من السمنة المفرطة. كان متوسط مؤشر كتلة الجسم للحالات ٣١.٢ (±٦.٨١)، بينما كان٢٩.٤ (±٧.٠٢) للشواهد. كان لدى النساء اللواتي يبلغن من العمر ٤٠ عامًا فما فوق أربع أضعاف احتمالات الإصابة بتليف الرحم مقارنة بالنساء الأصغر من ٤٠ عامًا (نسبه الأرجحية المصحح ٤.٢٤ بفاصلة ثقة ٩٥٪ بين ٢.٦٣ و٦.٨٥)(ارتبط وجود تاريخ عائلي لتليف الرحم مع احتمالات متزايدة بالإصابة بتليف الرحم بنسبة ٦٩٪ (نسبه الأرجحية المصحح ١.٦٩ بفاصلة ثقة ٩٥٪ بين ١.٠٢ و٢.٨١) . ارتبطت السمنة بزيادة احتمالات الإصابة بتليف الرحم بنسبة ٧٤٪ (نسبه الأرجحية المصحح ١.٧٤ بفاصلة ثقة ٩٥٪ بين ١.٠٠ و٢.٥٩)، بينما قللت الولادات السابقة من احتمالات الإصابة بتليف الرحم بنسبة ٦٢٪ (نسبه الأرجحية المصحح ٠.٣٨، بفاصلة ثقة ٩٥٪ بين ٠.١٩ و٠.٧٥).

الاستنتاجات: ساعدت هذه الدراسة في تحديد بعض عوامل الخطر المرتبطة بتليف الرحم في النساء السعوديات. العمر فوق ٤٠ عامًا، والسمنة والتاريخ العائلي من تليف الرحم هي عوامل خطر مهمة للتليف الرحم، بينما يبدو أن تعدد الولادات يحمي من الإصابة بتليف الرحم في النساء السعوديات. التعرف المبكر على عوامل الخطر مهم لمنع مضاعفات تليف الرحم.

الكلمات الدالة: الأورام الليفية؛ الورم العضلي الليفي؛ الورم العضلي الأملس؛ الورم الليفي الرحمي؛ تليف الرحم

Abstract

Objectives: The objective of this study was to measure the association between uterine fibroids (UFs) and several risk factors (parity, miscarriage, diabetes, hypertension, physical activity, smoking, family history of UF and contraceptive pill use) among Saudi women.

Methods: A case–control study was conducted in 478 women at two medical centers in Riyadh. Cases were confirmed by ultrasound. Demographic and risk factor information was collected from interviews and medical records. The prevalence of risk factors was calculated with 95% confidence interval (CI). Unconditional logistic regression analysis was used to measure the associations between UFs and the risk factors.

Results: More than half the participants were obese. The average body mass index (BMI) was 31.2 (±6.81) for cases and 29.4 (±7.02) for controls. Women 40 years or older had four times the odds of UFs than women younger than 40 years (adjusted odds ratio [AOR] = 4.24, 95% CI = 2.63, 6.85). Having a family history of UFs was associated with 69% greater odds of UFs (AOR = 1.69, 95% CI = 1.02, 2.81). Being obese was associated with 74% greater odds of UFs (AOR = 1.74,

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95% CI = 1.00, 2.59), whereas previous live births decreased the odds of UFs by 62% (AOR = 0.38, 95% CI = 0.19, 0.75).

Conclusions: This study identified risk factors associated with UFs in the Saudi population. Age over 40 years, obesity and a family history of UFs are important risk factors for UF, whereas parity appears to be protective against UF development in Saudi women. Early recognition of these risk factors is important to prevent UF complications.

Keywords: Fibroids; Fibromyoma; Leiomyomas; Uterine fibroid; Uterine fibroma

Introduction

Uterine fibroids (UFs), benign monoclonal tumors in smooth muscle, are the most common pelvic tumor and benign tumor in women. Approximately 70% of women have one or more UFs by the age of 50.[1] Moreover, approximately 30% of women with UFs seek treatment because of symptoms such as abnormal uterine bleeding, pelvic pain, dyspareunia, and bladder or rectum obstruction.[1] The diagnosis depends primarily on patients' symptoms. Occasionally, UFs are found incidentally in asymptomatic women during routine pelvic examinations.[2,3]

Two major risk factors for UFs are race and age. Western studies have suggested that African American women are at higher risk of UFs than White women.[3,4] Additionally, women 41–60 years of age are ten times more likely to develop UFs than women 21–30 years of age.[5] Other studies have suggested that women over the age of 40 are four times more likely than women under the age of 40 to have UF.[3,6]

Other factors that may increase the risk of developing UFs include nulliparity, genetic factors, early menarche, obesity and hypertension, whereas contraceptive pill use is considered to have a protective effect on the development of UFs, for unclear reasons.[2–7] Deletions in chromosome 7 are thought to be associated with the development of UFs.[8] In addition, several studies have indicated that each fibroid develops from a single cell with an inactive allele that arose independently in the uterus.[9,10] One Saudi study has linked somatic MED12 mutations to UFs.[4]

Pregnancy has been shown to be protective against the development of fibroids in several studies: having three or more deliveries are thought to be associated with a five-fold decrease in the risk of UFs.[11] Other factors, such as tobacco use, have been explored as a determinant of UFs. However, studies have indicated conflicting evidence regarding the relationship between cigarette use and UFs.[12]

In KSA, the incidence of UFs at reproductive age is 21.2%.[13] UFs pose a major burden on fertile Saudi women, according to a cross-sectional study in Saudi women over 18 years of age. The most commonly associated UF disorders are anxiety and depression, in 55.2% and 23.8% of cases, respectively.[13] Symptoms of UFs include bleeding, stomach discomfort, infertility and irregular menstruation.[14] However, most local published studies have relied on women's self-reports and their subjective responses. Additionally, most UFs are undiagnosed.[3] Little is known regarding the risk factors associated with UFs in the Saudi population. Many worldwide epidemiological studies have observed a higher prevalence of UFs among women with diabetes mellitus and hypertension than in the general female population. According to the World Health Organization, 14% of Saudi women have diabetes, and 17% have hypertension.[15] Because of the high prevalence of these important risk factors among the Saudi population, their association with UF is worthy of study.

Few studies have investigated the effect of physical activity on the development of UFs.[7] The level of physical activity, another possible risk factor for UF, is very low in Saudi population.[16] Additionally, global studies have reported that a high body mass index (BMI) increases the risk of UFs.[17] In KSA, 33.7% of the population is obese, and 58.8% is physically inactive.[18] Thus, assessing the relationships of these two features with UFs in this population is warranted.

The primary objective of this study was to measure the associations between several reported risk factors for UFs (obesity, age, family history of UF, contraceptive use, previous live births, history of miscarriage, physical activity, smoking, diabetes and hypertension) and the development of UFs among a sample of Saudi women. According to the literature, we hypothesized that obesity, age, family history of UFs, history of miscarriage, physical inactivity, diabetes and hypertension would be associated with higher odds of UF, whereas having a previous live birth and contraceptive pill use would be associated with lower odds of UFs.

Understanding the relationships between UFs and these risk factors may aid in planning and developing community-based disease prevention measures for those who are most at risk, thus ultimately decreasing the burden of UFs.

Materials and Methods

We conducted a case–control study from April to December 2019 at both Dr. Talal Merdad Medical Centre and King Saud University Medical City in Riyadh, KSA. We included women 18 years of age and older, who were referred to the ultrasound department from obstetrics and gynecology clinics at these two centers.

The sample size was calculated with OpenEpi (Open Source Epidemiologic Statistics for Public Health Version 2.3.1) by using the methods of Kelsey et al. and Fleiss, with a continuity correction (see Supplementary file).[19,20] Assuming a 95% confidence level (Z_α), power (1-β) of 80% (Z_β), ratio of controls to cases: 1:1 (r), proportion of controls exposed to diabetes of 13.8% (P_1),[21] hypothetical proportion of cases exposed to diabetes of 24.25% (P_2) and odds ratio of 2.0,[22] we calculated necessary sample sizes of 239 cases and 239 controls.

Cases were defined as women with a confirmed UF diagnosis identified by a radiologist through lower abdominal ultrasound examination or pelvic ultrasound. Cases were

classified according to the International Classification of Disease and Health Problems tenth edition, codes D25.0 through D25.9.[23] That is, women with uterine masses characterized as well-defined, solid, concentric and hypo-echoic, and causing a variable amount of acoustic shadowing were categorized as cases. Self-reports of "no fibroids" were not considered, because undiagnosed fibroids are common.

Controls were selected from obstetrics and gynecology clinics at the same two centers, and were identified as women visiting these clinics for a routine checkup and physical examination for reasons other than UFs, who were confirmed to be free of UFs and other gynecological abnormalities, and who had no previous history of UFs. Confirmation of the absence of UFs was made via ultrasound examination and medical records. Women with a suspected history of UFs were excluded (Figure 1).

Exposure variables included age (continuous), marital status (never married vs. ever married), BMI (continuous), parity (less than or equal to two vs. more than two live births), smoking status (smokers vs. non-smoker), family history of UFs (yes, no), history of miscarriages (yes, no) and use of oral contraceptive pills (yes, no). BMI was further categorized as underweight (BMI less than 19 kg/m^2), normal weight (BMI between 19 and 25 kg/m^2), overweight (BMI between 25 and 30 kg/m^2) and obese (BMI more than 30 kg/m^2). However, because approximately half the sample was obese, BMI was analyzed as a dichotomous variable (obese, not obese). Data were also collected on physical activity (none, less than 3 h/week, 3–5 h/week and more than 5 h/week), presence of type 2 diabetes (yes, no) and presence of hypertension (yes, no). After exploratory analysis indicated that approximately half the sample was not physically active, physical activity was transformed into a binary variable (no physical activity vs. physical activity at least once per week).

The study outcome variable was the presence of UFs, which, for descriptive purposes, was classified according to

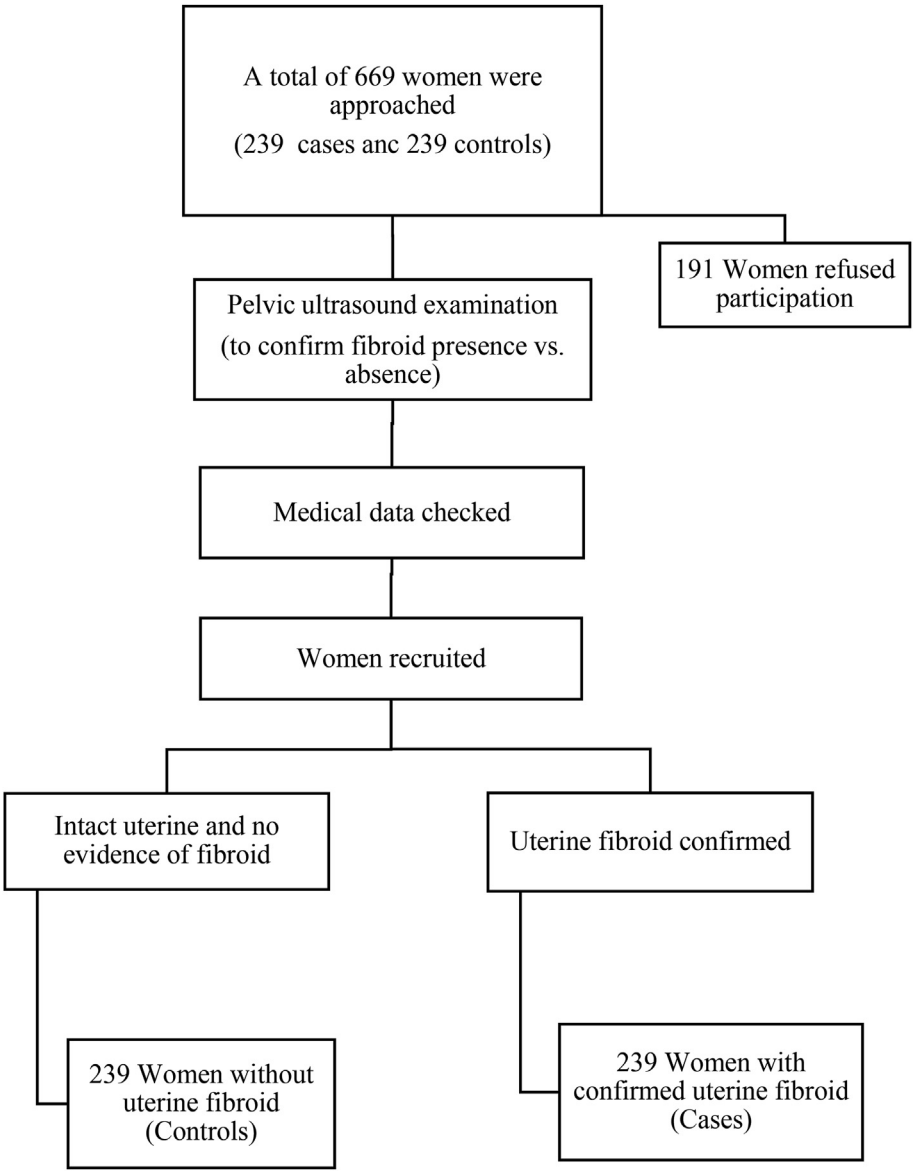

Figure 1: Flow-chart for ascertainment of cases and controls.

UF location into five categories: (1) intramural fibroid, (2) subserosal fibroid, (3) submucosal fibroid, (4) intramural subserosal fibroid, and (5) intramural submucosal fibroid.

Data were recorded on a data collection form, which was used to inquire about the study measures through brief interviews. All women participating in the study provided written consent before the interview. Participation in the study was voluntary. Approval from the King Saud University College of Medicine Research Center Institutional Review Board was obtained before this study was conducted (KSU-IRB No. E19-3999).

We calculated the means and standard deviations for continuous measures, whereas counts and percentages were calculated for categorical measures. We compared the frequencies of descriptive characteristics between cases and controls with the χ^2 test. To assess the association between UFs and the selected risk factors, we used unconditional logistic regression analysis with fibroid status as the dependent variable and (continuous) age, binary BMI, family history of UFs, history of miscarriage, parity, physical activity, diabetes, hypertension and smoking status as independent variables. These risk factors were selected in the model on the basis of previous evidence of their importance as determinants of UFs and their confounding effects.[2–10] For logistic regression analysis, the crude odds ratio (OR), adjusted odds ratio (AOR) and 95% confidence interval (CI) are reported. The alpha level for this study was set to 0.05. All statistical analyses were performed in the SPSS statistical program version 23 (IBM, Armonk, NY, USA).

Results

A total of 239 cases and 239 controls participated in this study (response rate = 71.3%). During the sample collection, 191 people declined to participate in the study; however, data were collected until the required sample size was reached. The most common type of UF was intramural (64.4%), followed by intramural subserosal (15.9%), subserosal (15.5%), submucosal (2.9%) and intramural submucosal (1.3%). The mean age was 44.6 years (±8.83) among cases and 38.4 years (±10.96) among controls. The average BMI was 31.2 (±6.81) for cases and 29.4 (±7.02) for controls.

The two groups were fairly similar in terms of marital status, history of miscarriage, use of contraceptive pills, physical activity and diabetes (Table 1). The frequency of

Table 1: Distribution of characteristics among cases and controls ($N = 478$).

Characteristic	Cases		Controls		*p*-value*
	Count	(%)	Count	(%)	
Age					
40 years or older	177	(74.1%)	104	(43.5%)	
Younger than 40 years	62	(25.9%)	135	(56.5%)	<0.001
Obesity					
Yes	205	(85.8%)	172	(72.0%)	
No	34	(14.2%)	67	(28.0%)	<0.001
Marital status					
Ever married	194	(81.2%)	199	(83.3%)	
Never married	45	(18.8%)	40	(16.7%)	0.632
Family history of UF					
Yes	57	(23.8%)	37	(15.5%)	
No	182	(76.2%)	202	(84.5%)	<0.001
Contraceptive pill use					
Yes	83	(34.7%)	98	(41.0%)	
No	156	(65.3%)	141	(59.0%)	0.187
Previous live birth					
No	81	(33.9%)	62	(25.9%)	
Yes	158	(66.1%)	177	(74.1%)	0.072
History of miscarriage					
Yes	92	(38.5%)	102	(42.7%)	
No	147	(61.5%)	137	(57.3%)	0.402
Smoking status					
Smoker	7	(2.9%)	31	(13.0%)	
Non-smokers	232	(97.1%)	208	(87.0%)	<0.001
Physical activity					
Yes	100	(41.8%)	110	(46.0%)	
No	139	(58.2%)	129	(54.0%)	0.407
Diabetes					
Yes	37	(15.5%)	29	(12.1%)	
No	202	(84.5%)	210	(87.9%)	0.353
Hypertension					
Yes	53	(22.2%)	34	(14.2%)	
No	186	(77.8%)	205	(85.8%)	<0.001

*p-value for the χ^2 test comparing characteristics between cases and controls.

older women was higher among cases (74.1%) than controls (43.5%). Women with UFs had a significantly higher prevalence of obesity, family history of UF and hypertension ($p < 0.001$), whereas a significantly greater proportion of controls were smokers ($p < 0.001$) (Table 1).

After controlling for other covariates, we determined that the odds of UFs among women 40 years of age or older were approximately four times those of women who younger 40 years (AOR = 4.24, 95% CI = 2.63, 6.85), thus suggesting that UF affected primarily older women in our study sample. Additionally, a family history of UFs was associated with 69% greater odds of having UFs (AOR = 1.69, 95% CI = 1.02, 2.81). Similarly, being obese was associated with 74% greater odds of having UFs (AOR = 1.74, 95% CI = 1.00, 2.59). Additionally, having a previous live birth was associated with lower odds of UFs (AOR = 0.38, 95% CI = 0.19, 0.75).

Table 2: Association between participant characteristics and uterine fibroids (N = 478).

Characteristic	Crude OR	95% CI	AOR	95% CI
Age				
40 years or older	3.71	(2.52, 5.45)	4.24	(2.63, 6.85)
Younger than 40 years	Ref		Ref	
Obesity				
Yes	2.34	(1.48, 3.72)	1.70	(1.00, 2.89)
No	Ref		Ref	
Marital status				
Ever married	1.15	(0.72, 1.84)	0.81	(0.37, 1.73)
Never married	Ref		Ref	
Family history of UF				
Yes	1.71	(1.08, 2.71)	1.69	(1.02, 2.81)
No	Ref		Ref	
Contraceptive pill use				
Yes	0.77	(0.53, 1.11)	0.83	(0.53, 1.30)
No	Ref		Ref	
Previous live birth				
Yes	1.03	(0.72, 1.48)	0.38	(0.19, 0.75)
No	Ref		Ref	
History of miscarriage				
Yes	0.84	(0.58, 1.21)	0.77	(0.49, 1.21)
No	Ref		Ref	
Smoking status				
Smoker	0.202	(0.08, 0.47)	0.31	(0.12, 0.76)
Non-smokers	Ref		Ref	
Physical activity				
Yes	0.84	(0.58, 1.21)	1.04	(0.69, 1.55)
No	Ref		Ref	
Diabetes				
Yes	1.33	(0.78, 2.24)	0.89	(0.49, 1.60)
No	Ref		Ref	
Hypertension				
Yes	1.72	(1.06, 2.76)	1.25	(0.73, 2.15)
No	Ref		Ref	

Notes: AOR = adjusted odds ratio. CI = confidence interval. Logistic regression analysis was controlled for only the variables in this table. The model used fibroid status as the dependent variable and age, BMI, family history of UF, history of miscarriage, parity, physical activity, diabetes, hypertension, and smoking status as independent variables.

Unexpectedly, smoking was associated with 69% lower odds of having UFs in this study (AOR = 0.31, 95% CI = 0.12, 0.76).

Although not statistically significant, having hypertension was associated with 25% greater odds of having UFs (AOR = 1.25, 95% CI = 0.73, 2.15). Similarly, contrary to our hypothesis, diabetes was associated with lower odds of UFs in this study (AOR = 0.89, 95% CI = 0.49, 1.60). Furthermore, we did not observe an association between physical activity and the odds of having UFs (AOR of approximately 1; Table 2).

Discussion

This study assessed the association between UFs and multiple risk factors by using a case–control study design. The most important results of this study can be summarized as follows. First, the odds of UFs among women ages 40 years and older were four times that of women younger than 40 years. Second, having a family history of UFs was associated with 69% greater odds of UFs. Third, obesity was associated with 74% greater odds of UFs. Finally, having a previous live birth was associated with 62% lower odds of UFs.

The positive association between UFs and age was in agreement with findings from other studies conducted in the United States and Belgium, which have estimated that 60%–70% of women have one or more UFs by age 50,[2,24] owing to the accumulation of hormonal changes during the reproductive lifespan in women. A remarkable feature of UFs is their dependency on the ovarian steroids estrogen and progesterone.[25] Experimental and clinical studies have proposed that estrogen and progesterone stimulate the growth of UFs during the reproductive years.[25,26]

Family history was another important risk factor observed in this study, thus confirming findings from a previous study conducted in Thailand.[27] This association may be attributed to genetic factors.[3] Exome sequencing has indicated that most UFs display highly specific exon 2 mutations in mediator complex subunit 12 (MED12).[1,28] Several studies representing various population groups have validated and replicated this finding, reporting MED12 mutations in between 52% and 80% of women with UFs.[28] By contrast, a different study has detected no single candidate gene associated with the development of UFs.[11]

Obesity is a major burden on the Saudi community. In this study, more than half the women were obese. The positive association between UFs and obesity observed in our study was expected, because it has been repeatedly reported in the literature.[25,29] One study has clarified this relationship by suggesting that fat distribution influences the development of UFs, on the basis of an observed association between ultrasound measurement of preperitoneal fat thickness and visceral fat distribution and the presence of UFs.[30] Furthermore, high BMI is correlated with lower circulating levels of sex hormone-binding globulin (SHBG), which increase the bioavailability of circulating estrogens in obese women, thus ultimately enhancing the growth of UFs.[7]

Our results have indicated an inverse association between having a previous live birth and UFs, in agreement with previous observations suggesting a protective effect of parity

on UFs.[31] The previous literature has suggested a 20%–50% lower UF risk in women with previous live births than nulliparous women.[3,25] Baird and Dunson have proposed that parity is protective because of remodeling during uterine involution after delivery.[31] However, the hormonal changes that occur during uterine involution are not well understood.

We did not have sufficient evidence to demonstrate a statistically significant association between contraceptive pill use and UFs. However, previously reported evidence of the effects of contraceptive pill use suggests that they are protective against UF development.[3,7] By contrast, one study has found an inconsistent relationship between using contraceptives and UFs.[28] The conflicting reports regarding the effects of contraceptive pills on UFs may be due to the variability in concentrations of estrogen and progesterone in these pills.

Contrary to our expectations, diabetes was associated with 11% lower odds of UFs, albeit not statistically significantly. Diabetes has been inversely associated with UF risk in some studies[32]; however, this association is inconsistent across the literature.[7] Some research has suggested that the biological reason for such an inverse relationship may be explained by the high circulating levels of insulin-like growth factor-1 (IGF-1), which lead to elevation of SHBG, thereby decreasing circulating estradiol levels.[33,34] By contrast, IGF-1, an important growth factor for UF cells, is usually found in low concentrations among women without diabetes.[33] Consequently, being free of diabetes might be expected to protect against UF, whereas having diabetes might increase the risk of UFs. Diabetes medication may also play a role in ameliorating the effect of IGF-1 on the development of UFs by decreasing the proliferative effects of UF cells in comparison to normal cells.[35] Thus, the inverse relationship between diabetes and UFs observed in our study may be associated with diabetes treatment.

In our study, smoking decreased the odds of UFs by 69% (AOR = 0.31, 95% CI = 0.12, 0.76). Although this finding was counterintuitive, it is in agreement with results from many previous studies.[3,11] One study has reported that smoking increases the risk of UF, whereas other studies have not documented any well-defined relationship.[12,25,33,36] Smoking is thought to have an antiestrogenic effect through the production of enzymes promoting estrogen metabolism and enhancing the formation of inactive estrogen.[11,33] Nevertheless, this finding should not encourage smoking to prevent UFs, because smoking is notoriously associated with many deleterious health consequences.

This study has several strengths. First, we used ultrasound examination to identify confirmed cases and controls. Most previous studies have relied on women's self-reports, and their subjective responses might have caused misclassification of UFs. Second, we used a case–control study design to assess the association between UFs and important risk factors. To our knowledge, this study design is the first of its kind exploring this specific topic in the region. Third, we sampled a substantial number of participants to help clarify the associations.

However, our study has several limitations that should be noted. One limitation was the potential recall bias associated with self-reporting of risk factors. For example, family history would not be accurately measured if women were unaware of the health conditions of their relatives. Moreover, we were unable to determine the date of onset of UFs. Consequently, the temporal relationship between the measured risk factors and the onset of UFs is difficult to deduce. Furthermore, the possible reason for the unexpected protective association observed between smoking and UFs may be associated with the dichotomous measure of smoking in our study, which did not capture the duration or intensity of tobacco use and its relationship with UFs. Finally, the design of the study prevents conclusions from being drawn regarding the causative effects of these risk factors on UFs. Thus, further prospective studies are needed to confirm such relationships.

Conclusion

In conclusion, this study sheds light on several risk factors associated with UFs among the Saudi population. The results suggest that being older than 40 years, being obese and having a family history of UFs are important factors that may increase the risk of UF, whereas parity may protect against UF development. Although not statistically significant, decreased odds of UFs in relation to diabetes were observed. To enable early diagnosis and avoid complications, women would need to be educated about the identified important UF risk factors, as well as the symptoms and signs associated with UFs. The literature regarding this topic in Middle Eastern countries remains limited, and more research is required to better understand the interactions of such risk factors among the diverse populations of these countries.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

Approval from the King Saud University College of Medicine Research Center Institutional Review Board was obtained before this study was conducted (KSU-IRB No. E19-3999), 15 May 2019.

Consent

All women involved provided written consent before the interview. Participation in the study was voluntary, and data were kept strictly confidential.

Authors contributions

RM was the principal investigator of this study, and prepared the study protocol, collected the data, analyzed the data and prepared the manuscript. RD supervised the study;

reviewed the data analysis plan; wrote the abstract, author contributions, acknowledgments and conflicts of interest sections; and revised and edited all manuscript submission materials. YS supervised the case and control enrollment. YS also revised and edited the final manuscript submission materials. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtumed.2022.06.005.

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