Does prior uterine surgery increase the risks of uterine leiomyoma and adenomyosis? a retrospective study

Nihal Mavral[1], Pınar Kırıcı[2], Kadriye Yakut[3], Ayşe Filiz Yavuz[4]

[1]Hitit University Training and Research Hospital, Department of Obstetrics and Gynecology, Çorum, Turkey
[2]Adıyaman University, Faculty of Medicine, Department of Obstetrics and Gynecology, Adıyaman, Turkey
[3]Turkish Ministry of Health, Fethi Sekin City Hospital, Department of Perinatology Elazığ, Turkey
[4]Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara City Hospital, Department of Obstetrics and Gynecology, Ankara, Turkey

ABSTRACT

Aim: Women frequently undergo obstetric and gynecologic surgeries throughout their life, and the two common gynecologic conditions are uterine leiomyoma (UL) and adenomyosis. This study aims to investigate the relationship between the presence and the types of prior uterine surgery and the risks of developing UL and adenomyosis.

Material and Method: This study is a single-center eleven-year cross-sectional study, in which we studied the effects of previous uterine surgery on developing UL and adenomyosis in patients who underwent hysterectomy for any indication in our hospital between 01/01/2004 and 31/12/2014.

Results: During the time period, 1299 eligible patients were included in the study. The median age was 49.0 years and the study population was mostly consisted of multigravid women. The overall prevalence of UL was 61.9% and the overall prevalence of adenomyosis was 18.3%.In the univariate analysis of patient characteristics for UL, age, gravida and parity were found as statistically significant protective factors for UL (OR [95.0% CI]: 0.92 [0.91-0.93], 0.91 [0.88-0.95], 0.88 [0.83-0.93], respectively). On the other hand, women who underwent previous any uterine surgery had 1.28 folded (95.0% CI: 1.02-1.61) risk for UL. However, we found that only undergoing myomectomy statistically significantly increased the risk of UL (OR [95.0% CI]: 8.59 [2.62-27.91]) among the types of uterine surgery. In the multivariate model, the protective effect of age remained (adjusted OR [95.0% CI]: 0.92 [0.91-0.94]), and the risk-increasing effect of having previous myomectomy dropped slightly with retaining its statistical significance (adjusted OR [95.0% CI]: 5.87 [1.78-19.41]). We also conducted similar analysis for adenomyosis, and we found that gravida was a risk factor (OR [95.0% CI]: 1.06 [1.01-1.12]), conversely to its risk-decreasing effect for UL. Also, women who had a history of any uterine surgery had 1.42 folded (95.0% CI: 1.07-1.88), and women who had a history of D&C had 1.62 folded (95.0% CI: 1.02-1.61) risk adenomyosis. In the multivariate model for the risk of adenomyosis, the risk-increasing effects of the gravida and the history of D&C decreased very slightly with saving their statistical significances (adjusted OR [95.0% CI]: 1.06 [1.01-1.12], 1.44 [1.07-1.95], respectively).

Conclusion: According to our findings, the frequency of adenomyosis is higher but, the frequency of UL is compatible with the literature. Patients, who underwent uterine surgery previously, diagnosed with adenomyosis and UL more than the others who did not, but this seems to be a correlation rather than a causative association.

Keywords: Uterine surgery, hysterectomy, uterine leiomyoma, adenomyosis.

INTRODUCTION

Uterine leiomyoma (UL) is the most prevalent tumor in women, with estimates indicating they impact over 70% of women when they reach menopause (1, 2). It is predicted to be clinically evident in 25% of women of reproductive age and induce severe enough symptoms to warrant treatment in around 25% of women with ULs (3).Even though many studies on the epidemiology of ULs have been published, estimates of the incidence and prevalence of ULs vary greatly depending on the method of diagnosis, and the population studied; for example, estimates of the incidence of ULs range from 5.4 percent to 77 percent of women of reproductive age, depending on the method of diagnosis and the population studied(4).Furthermore, adenomyosis and UL frequently occur; simultaneous adenomyosis ranges from 15% to 57 percent in hysterectomy tissues of women with UL (5, 6). Age, multiparity, surgical disturbances of the endometrial-myometrial border, increased Follicle-

Kırıcı et al. Prior uterine surgery and Leiomyoma

J Health Sci Med 2022; 5(2): 445-450

stimulating hormone and prolactin levels, smoking habits, and a history of depression are all risk factors for adenomyosis (7,8).

UL prevalence is likely to be underestimated because many women are asymptomatic or acquire symptoms gradually, leaving the sickness undetected (9,10). Because of the uncertain extent and impact of undiscovered ULs, epidemiological statistics and evidence on related factors are skewed to represent severe disease (11). Furthermore, various risk variables, including biological, demographic, reproductive, and lifestyle factors, have been linked to the development of ULs (2). As a result, the true incidence and prevalence of ULs and their global impact on women's health and the role of potential risk factors are unknown at this time. ULs that have been pathologically diagnosed increase in frequency with age, peaking at 50 years old (12), and do not appear before puberty and become less common after menopause. ULs are shown to be 2-3 times more common in black women, but the incidence of ULs is similar in Hispanic, Asian, and White women (12). The lifetime risk for ULs was almost 70% in white women and 80% in black women, and if only clinically significant ULsare included, the incidence reaches 50% in Black women and 25% in White women (13).

In the United States, ULs are the most common reason for hysterectomy (14). The specific pathophysiology of UL formation is unknown(15). To the best of our knowledge, UL formation begins with a single uterine smooth muscle cell (myometrium), which is subsequently followed by deviations from normal cellular division signaling pathways(16). ULs are estrogen-dependent tumors, and, as compared to normal myometrium, they overexpress particular estrogen and progesterone receptors(17). The presence of ectopic endometrium with or without hyperplasia of myometrium characterizes adenomyosis, a myometrial lesion. Adenomyosis is a benign uterine condition characterized by heterotopic endometrial glands and stroma in the myometrium, as well as reactive fibrosis of the myometrium's surrounding smooth muscle cells. A variety of theories have been proposed during the last 80 years to explain how adenomyosis develops. The most widely accepted theory is that adenomyosis is caused by the invagination of the endometrium's basalis into the myometrium. This basalis invagination, according to a second idea, would occur along with the intramyometrial lymphatic system. A third idea proposes that ectopic intramyometrial endometrial tissue initiates a de novo metaplastic process (18). There is no data about that surgery might be a cause of UL and/or adenomyosis. We aimed to investigate the relationship between prior uterine surgery and UL, and adenomyosis, and to evaluate the effects of the type of uterine surgery on the risk of developing these diseases.

MATERIAL AND METHOD

Study Design and Setting

This study was planned retrospectively and was carried out with the decision of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date: 14.01.2015, Decision No: 02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-center eleven-year cross-sectional study was conducted in tertiary care training and research hospital in Ankara. The Obstetrics and Gynecologic Clinic of our hospital is consisted of 22 experienced obstetrician and gynecologists and residents, and we performed approximately 1200 gynecologic surgeries, 2500 C/S deliveries, and 3500 vaginal deliveries annuall.

Patients and Data

We did not calculate any prior minimum sample size because we had intended to include all eligible patients in the study according to the inclusion and exclusion criteria. The inclusion criteria of the studywere: (1) undergoing hysterectomy for any indication between 01/01/2004 and 31/12/2014, and (2) having the report of pathologic examination of uterine specimens; and the single exclusion criterion is the missing data of the variables of the study which were age, obstetrical and surgical history, and the pathologic examination findings.

We collected the data using Hospital Information Management System (HIMS) which is used almost in all public hospitals in Turkey, and patient files, and contacting with patients via telephone when it would be necessary particularly in some situations such as missing data in an essential patient information. Participants were determined by searching the terms "leiomyoma", "myoma uteri" and "adenomyosis" via HIMS.

Variables and Outcomes

Patients' demographics, obstetrical and clinical features, surgical history, and the pathologic examination findings, which are obtained from their pathology reports, were recorded. There are two primary outcomes of this study, which we used to evaluate the effects of patients' surgical features on them. These two primary outcomes are the risk of UL and the risk of adenomyosis in patients included in the study. As stated above, we investigated to how the presence and/or the type of prior uterine surgery affect the risk of developing these two health issues. The secondary outcomesof this study are the prevalence of UL and the prevalence of adenomyosis in hysterectomy patients.

Statistical Analysis

Statistical analyses were done using SPSS v 23 software (SPSS Inc., Chicago, IL, USA). The descriptive statistics were presented as median with interquartile rage (IQR)

J Health Sci Med 2022; 5(2): 445-450

Kırıcı et al. Prior uterine surgery and Leiomyoma

for numerical variables and frequency (n) with percentage (%) for categorical variables. The 95% confidence interval (95% CI) was calculated for overall prevalence of UL, and overall prevalence of adenomyosis. Binary logistic regression analyses of patient characteristics were performed to estimate the risks of the presence of dependent variables which were UL and adenomyosis. Then, the Odds ratios (ORs) with 95% CIs were calculated to present the risks of these two diseases. A value of p<0.05 was approved as the statistically significance level.

RESULTS

During the time period for data collection that we defined before beginning the study, we reviewed 1400 patients who met the inclusion criteria; thereafter 101 patients were excluded because of missing data, and finally 1299 patients were included in the study. **Table 1** presents demographics, obstetric and medical history, and pathologic findings of the patients. The median age was 49.0 years with an IQR of 45.0-55.0 years. Our study population, in which abortion was rare, was mostly consisted of multigravid women, and the median parity was 2.0 with an IQR of 1.0-4.0. According to the pathologic examination, there were UL in 657 (50.6%) patients, and adenomyosis in 96 patients (7.4%) purely; however, UL accompanied with adenomyosis in 147 patients (11.3%). The overall prevalence of UL was 61.9% and the overall prevalence of adenomyosis was 18.3% (**Table 1**).

In the univariate analysis of patient characteristics for UL, age, gravida and parity were found as statistically significant protective factors for developing UL (OR [95.0% CI]: 0.92 [0.91-0.93], 0.91 [0.88-0.95], 0.88 [0.83-0.93], respectively). On the other hand, women who underwent previous any uterine surgery had 1.28 folded (95.0% CI: 1.02-1.61) risk for UL when compared to the patients who did not undergo. However, we found that only undergoing myomectomy statistically significantly increased the risk of UL (OR [95.0% CI]: 8.59 [2.62-27.91]) among the types of uterine surgery. And this risk was also higher than having a prior any uterine surgery (**Table 2**).

Table 1. Demographics and clinical features of the patients	
Characteristics (n=1299)	
Age (years), median (IQR)	49.0 (45.0-55.0)
Gravida, median (IQR)	4.0 (2.0-5.0)
Parity, median (IQR)	2.0 (1.0-4.0)
Aborts, median (IQR)	0.0 (0.0-1.0)
Surgical history	
Previous C/S, n (%)	123 (9.5)
Previous myomectomy, n (%)	43 (3.3)
Previous D&C, n (%)	472 (36.3)
Previous hysteroscopy, n (%)	2 (0.2)
Pathological findings	
Pure UL, n (%)	657 (50.6)
Pure adenomyosis, n (%)	96 (7.4)
UL accompanied with adenomyosis, n (%)	147 (11.3)
Overall prevalence (95% CI)	
UL	61.9% (59.3%-64.5%)
Adenomyosis	18.3% (16.6%-20.8%)

We also performed a multivariate logistic regression analysis with the factors that were statistically significantly related the risk of developing UL. We did not include the parity because of its high correlation with the gravida, and, similarly, the presence of previous any uterine surgery because of its high-level correlation with previous myomectomy. In the multivariate model, the protective effect of age remained (adjusted OR [95.0% CI]: 0.92 [0.91-0.94]), and the risk-increasing effect of having previous myomectomy dropped slightly with retaining its statistical significance (adjusted OR [95.0% CI]: 5.87 [1.78-19.41]); however, the association between gravida and the risk of UL lost its statistical significance (**Table 2**).

We also repeated the univariate analysis of patient characteristics for adenomyosis, and we found that gravida was a risk factor for adenomyosis (OR [95.0% CI]: 1.06 [1.01-1.12]), conversely to its risk-decreasing effect for UL. Also, women who had a history of any uterine surgery had 1.42 folded (95.0% CI: 1.07-1.88), and women who had a history of D&C had 1.62 folded (95.0% CI: 1.02-1.61) risk for developing adenomyosis when compared to the females who did not undergo (**Table 3**).

Table 2. Univariate and multivariate logistic regression analyses of patient characteristics for UL						
Factors	**Univariate Analysis**			**Multivariate Analysis**		
	OR	95% CI	p	Adjusted OR	95% CI	p
Age (years)	0.92	0.91-0.93	<0.001	0.92	0.91-0.94	<0.001
Gravida (numbers)	0.91	0.88-0.95	<0.001	0.98	0.93-1.02	0.336
Parity (numbers)	0.88	0.83-0.93	<0.001			
Abortus (numbers)	0.93	0.82-1.07	0.311			
Previous (any) uterine surgery	1.28	1.02-1.61	0.032			
Previous C/S	0.99	0.68-1.46	0.980			
Previous myomectomy	8.59	2.62-27.91	<0.001	5.87	1.78-19.41	0.004
Previous D&C	1.10	0.87-1.39	0.415			

Kırıcı et al. Prior uterine surgery and Leiomyoma

J Health Sci Med 2022; 5(2): 445-450

Table 3. Univariate and multivariate logistic regression analyses of patient characteristics for adenomyosis						
Factors	**Univariate Analysis**			**Multivariate Analysis**		
	OR	95% CI	p	Adjusted OR	95% CI	p
Age (years)	1.00	0.98-1.01	0.669			
Gravida (numbers)	1.08	1.03-1.14	0.001	1.06	1.01-1.12	0.031
Parity (numbers)	1.06	0.99-1.12	0.103			
Abortus (numbers)	1.08	0.92-1.27	0.348			
Previous (any) uterine surgery	1.42	1.07-1.88	0.014			
Previous C/S	0.83	0.50-1.37	0.465			
Previous myomectomy	0.44	0.15-1.23	0.118			
Previous D&C	1.62	1.22-2.15	0.001	1.44	1.07-1.95	0.017

After evaluating the characteristics that showed a statistically significant impact on developing adenomyosis, we performed a multivariate logistic regression analysis. Similarly, in the multivariate model that we set to analyze the factors for the risk of UL, we preferred only one factor among the factors that showed high correlation. In the multivariate model for the risk of adenomyosis, the risk-increasing effects of the gravida and the history of D&C decreased very slightly with saving their statistical significances (adjusted OR [95.0% CI]: 1.06 [1.01-1.12], 1.44 [1.07-1.95], respectively) (**Table 3**).

DISCUSSION

The present study has shown that patients with UL are older, has higher gravida, parity, also previous any uterine surgery includes myomectomy. We have shown that patients with adenomyosis are most likely to have any uterine surgery also D&C and gravida also tend to end up with uterine surgery. In a study with 549 patients, researchers discovered that the incidence of adenomyosis ranged from 10% to 18% depending on the criteria used, and that there was no significant link between adenomyosis and uterine surgery, such as previous cesarean section, myomectomy, or dilation and curettage (D&C) (19). Another publication studied the pathologic species of 873 patients and found that 41.7 percent of them had adenomyosis. Adenomyosis and previous uterine surgery, such as cesarean section, myomectomy, D&C, and dilation and evacuation (D&E), were found to have no significant relationship in this study; however, uterine surgery (caesarian section, myomectomy, D&C, and D&E) is one of the most common factors associated with the incidence of adenomyosis (20). Our data has shown that 61.9% of patients have UL, and %18.3 of patients have adenomyosis. Literature has revealed that ULs occur in more than 70% of women based on ultrasonography screening studies and pathology data (21). According to the data of Yu et al. (22), they studied 1,185,855 women during the ten years, 3,425 women received the first diagnosis of adenomyosis and were considered potential incident cases. Our data controversially showed higher incidence.

Several authors define recurrence as the growth of UL left behind during surgery. One study found that the estimated rate of post-operative persistence of ULs was 29% when the myometrium was carefully examined by ultrasound scan six months after surgery (22). Recurrence, on the other hand, is a natural progression of the myometrial illness. Alterations cause the condition in the myometrium cells, such as spontaneous chromosomal rearrangement, responsible for the onset and proliferation of UL growth (23). Because most UL in a myomatous uterus are numerous and many of them measure less than 5 mm, it is difficult to distinguish between recurrence of ULs due to a surgeon's technical error and actual recurrence due to disease progression (24). The Fedele et al. (35), use of routine ultrasound at regular intervals to detect recurrence could have considered tiny ULs, which can be as small as 1 cm in diameter. The true incidence of these small myomatous nuclei in a population without myomatous pathology is unknown, and such small ULs may not be clinically significant. UL is found in more than half of women whose uteri were excised for reasons other than UL, according to Cramer and Patel (25). On the other hand, clinical signs and symptoms are not reliable because they are not unique to ULs (26). Furthermore, the recurrence may occur in a different location than the original, resulting in distinct symptoms. In addition to this, there are also methodological difficulties in the studies investigated fibroid recurrence such as loss to follow up and associated censored data (27). Also, there may be a possibility of sample bias in these studies. For example, most of the patients who lost to follow-up may be those who do not have recurrence and therefore do not come to the clinic. On the other hand, there may actually be uterine leiomyoma recurrence in these patients even if they do not have a symptom. For all these reasons, the true incidence of uterine leiomyoma recurrence is not known exactly and is probably higher than those found in studies.

In our study, we found that any previous uterine surgery increased the risk of uterine leiomyoma recurrence. We found that this risk was actually associated with

J Health Sci Med 2022; 5(2): 445-450

Kırıcı et al. Prior uterine surgery and Leiomyoma

previous myomectomy. It seems reasonable to find that the risk of being diagnosed with myoma uteri is high in patients who have undergone myomectomy because the disease tends to recur. However, residual myoma foci is probably the risk factor for new fibroid formation, not the myomectomy. Parity after myomectomy was associated with a decreased rate of UL recurrence, which is consistent with the findings of other studies. Parous women have a reduced risk of UL than nulliparous women, according to epidemiological studies. The discrepancy was attributed to either lower fertility due to UL or a protective impact of pregnancy on UL development by the researchers. In the Caucasian population, however, Stewart et al. discovered that parity after myomectomy increased the incidence of recurrence and the requirement for additional surgery for UL (14). Furthermore, our research revealed an exponential increase in recurrence rate with time, corroborated by previous studies. In literature, it was shown that half of the cases was re-operated and a hysterectomy was performed for one-third of patients in case of leiomyoma recurrence (27). For this reason, patients should be informed in detail about uterine leiomyoma recurrence and possible re-operation. Women should also be advised to complete their families as soon as possible following myomectomy.

Even though adenomyosis is a principal medical diagnosis, there is still much debate over its incidence, origin, concomitant pathology, and clinical manifestations. The 1940 Zaleski hypothesis that the displacement of viable endometrium causes adenomyosis during pregnancy and delivery, as well as recent reports of adenomyosis after endometrial ablation, prompted us to investigate whether prior uterine surgery, such as cesarean delivery, myomectomy, endometrial ablation, D&E, and D&C, is a risk factor for the development of adenomyosis (21, 28, 29). We identified a strong link between adenomyosis and prior uterine surgery in this retrospective analysis. We feel that our findings support the idea that any surgical intervention on the uterus disrupts the endometrial junction, resulting in adenomyosis. Patients with UL and adenomyosis, on the other hand, are more likely to undergo surgery, which could explain why there is such a strong link between surgical treatments and UL and adenomyosis. Thus, uterus surgery appears to raise the risk at first glance. If D&C increases the risk in subgroup analyses while having no effect on other types of surgery, D&C is a marker, not a cause. In other words, patients with adenomyosis tend to relapse and have adenomyosis again, more than patients without adenomyosis. This may cause increased D&C in patients with adenomyosis. This is also possible due to the hereditary predisposition and recurrence of adenomyosis.

Limitations

These investigations, including ours, were retrospective, and we believe that only a prospective study with a set sample size can provide a definitive response to this topic. Such a study may not be feasible due to the length of time that patients must be followed prospectively. We did not examine whether single or many cesarean deliveries in the past contributed to subsequent adenomyosis in our study, but it should be considered in future research. According to studies, the risk of adenomyosis increases following DC. There is no information about the cause of D&C in our study. If there were, we could compare the risks of D&Cs with and without adenomyosis. As a result, we could assess the myomectomy-UL recurrence strategy in this case. We, on the other hand, did not have that opportunity. In other words, myomectomy is only performed when ULs are present, but it can also be done for reasons other than D&C adenomyosis. Another drawback of this retrospective analysis is that data on adenomyosis was collected from post-operative pathology reports; pathologists did not re-examine the specimens for this condition. Adenomyosis is identified more commonly when a thorough histopathologic examination is performed. UL and adenomyosis were also classified, although these patients were not excluded from the UL accompanied with adenomyosis group. The increased occurrence of adenomyosis among women without ULs or with smaller ULs in our study could be due to more thorough examination by pathologists who could not make a histopathologic diagnosis of uterine material otherwise. Finally, important data such as patients' weight, height, age at first menstruation, and alcohol consumption, or size and location of the excised fibroids could not be reached by searching for terms on the system. The fact that these parameters were not included in the study was also determined as an important limitation.

CONCLUSION

According to the literature, there is no link between prior uterine surgery and adenomyosis. There is no information concerning the relationship between UL and past uterus surgery that we are aware of. According to our findings, the frequency of adenomyosis is higher compared to other studies reported. The frequency of UL is compatible with the literature. Patients, who underwent obstetric and gynecologic surgery previously, diagnosed with adenomyosis and UL more than the others who did not, but this seems to be a correlation rather than a causative association.

Kırıcı et al. Prior uterine surgery and Leiomyoma

J Health Sci Med 2022; 5(2): 445-450

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of Yıldırım Beyazıt University Faculty of Medicine Clinical Research Ethics Committee (Date: 14.01.2015, Decision No: 02).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Boosz AS, Reimer P, Matzko M, Römer T, Müller A. The conservative and interventional treatment of fibroids. Dtsch Arztebl Int 2014; 111: 877-83.

2. Flake GP, Andersen J, Dixon D. Etiology and pathogenesis of uterine leiomyomas: a review. Environ Health Perspect 2003; 111: 1037-54.

3. Islam MS, Protic O, Stortoni P, et al. Complex networks of multiple factors in the pathogenesis of uterine leiomyoma. Fertil Steril 2013; 100: 178-93.

4. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990; 94: 435-8.

5. Weiss G, Maseelall P, Schott LL, Brockwell SE, Schocken M, Johnston JM. Adenomyosis a variant, not a disease? Evidence from hysterectomized menopausal women in the Study of Women's Health Across the Nation (SWAN). Fertility and sterility 2009; 91: 201-6.

6. Shaikh H, Khan K. Adenomyosis in Pakistani women: four year experience at the Aga Khan University Medical Centre, Karachi. Journal of clinical pathology 1990; 43: 817-9.

7. García-Solares J, Donnez J, Donnez O, Dolmans M-M. Pathogenesis of uterine adenomyosis: invagination or metaplasia? Fertility and sterility 2018; 109: 371-9.

8. Chapron C, Vannuccini S, Santulli P, et al. Diagnosing adenomyosis: an integrated clinical and imaging approach. Human reproduction update 2020; 26: 392-411.

9. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010; 28: 204-17.

10. Evans P, Brunsell S. Uterine fibroid tumors: diagnosis and treatment. Am Fam Physician 2007; 75: 1503-8.

11. Payson M, Leppert P, Segars J. Epidemiology of myomas. Obstet Gynecol Clin North Am 2006; 33: 1-11.

12. Becker ER, Spalding J, DuChane J, Horowitz IR. Inpatient surgical treatment patterns for patients with uterine fibroids in the United States, 1998-2002. J Natl Med Assoc 2005; 97: 1336-42.

13. Becker ER. National trends and determinants of hospitalization costs and lengths-of-stay for uterine fibroids procedures. J Health Care Finance 2007; 33: 1-16.

14. Walker CL, Stewart EA. Uterine fibroids: the elephant in the room. Science 2005; 308: 1589-92.

15. Okolo S. Incidence, aetiology and epidemiology of uterine fibroids. Best Pract Res Clin Obstet Gynaecol 2008; 22: 571-88.

16. Townsend DE, Sparkes RS, Baluda MC, McClelland G. Unicellular histogenesis of uterine leiomyomas as determined by electrophoresis by glucose-6-phosphate dehydrogenase. Am J Obstet Gynecol 1970; 107: 1168-73.

17. Benassayag C, Leroy MJ, Rigourd V, et al. Estrogen receptors (ERalpha/ERbeta) in normal and pathological growth of the human myometrium: pregnancy and leiomyoma. Am J Physiol 1999; 276: E1112-8.

18. Vannuccini S, Petraglia F. Recent advances in understanding and managing adenomyosis. F1000Research 2019; 8: 283.

19. Bergholt T, Eriksen L, Berendt N, Jacobsen M, Hertz JB. Prevalence and risk factors of adenomyosis at hysterectomy. Hum Reprod 2001; 16: 2418-21.

20. Panganamamula UR, Harmanli OH, Isik-Akbay EF, Grotegut CA, Dandolu V, Gaughan JP. Is prior uterine surgery a risk factor for adenomyosis? Obstet Gynecol 2004; 104: 1034-8.

21. Levgur M, Abadi MA, Tucker A. Adenomyosis: symptoms, histology, and pregnancy terminations. Obstet Gynecol 2000; 95: 688-91.

22. Polena V, Mergui J-L, Perrot N, Poncelet C, Barranger E, Uzan S. Long-term results of hysteroscopic myomectomy in 235 patients. European J Obstet Gynecol Reprod Biol 2007; 130: 232-7.

23. Medikare V, Kandukuri LR, Ananthapur V, Deenadayal M, Nallari P. The genetic bases of uterine fibroids; a review. J Reprod Inferti 2011; 12: 181.

24. Parker WH. Etiology, symptomatology, and diagnosis of uterine myomas. Fertil Steril 2007; 87: 725-36.

25. Cramer SF, Patel A. The frequency of uterine leiomyomas. Am J Clin Pathol 1990; 94: 435-8.

26. Fields K, Neinstein L. Uterine myomas in adolescents: case reports and a review of the literature. J Pediatr Adolesc Gynecol 1996; 9: 195-8.

27. Fauconnier A, Chapron C, Babaki-Fard K, Dubuisson JB. Recurrence of leiomyomata after myomectomy. Human Reprod Update 2000; 6: 595-602.

28. Dreyfuss ML. Pathologic and clinical aspects of adenomyosis and endometriosis: A survey of 224 cases. Am J Obstet Gynecol 1940; 39: 95-9.

29. Curtis KM, Hillis SD, Marchbanks PA, Peterson HB. Disruption of the endometrial-myometrial border during pregnancy as a risk factor for adenomyosis. Am J Obstet Gynecol 2002; 187: 543-4.