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Risk factors for uterine adenomyosis diagnosed by MRI in women of reproductive age

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Background: Adenomyosis is a condition characterized by the presence of endometrial glands and stroma within the myometrium. It can manifest as either focal or diffuse. While histopathological examination of the uterus following hysterectomy remains the gold standard for definitive diagnosis, non-invasive imaging techniques, particularly magnetic resonance imaging (MRI), are crucial for diagnosis. This study aimed to investigate the risk factors and associated pathologies in women with MRI-confirmed adenomyosis.

Methods: In this case-control study, 50 women of reproductive age with MRI-confirmed adenomyosis were recruited as the case group, and fifty other women who underwent pelvic MRI due to various indications that were not diagnosed as adenomyosis were included as the control group. Pelvic MRI with and without intravenous contrast was done for all patients. Factors such as age, smoking, number of pregnancies, history of uterine surgery, endometriosis, ovarian cyst, and coexisting leiomyoma were searched and recorded in both groups, and their relationship with uterine adenomyosis was statistically analyzed. The software used was IBM-SPSS v.26. A Significance level of less than 5% was considered.

Results: No significant difference was found in terms of age ($P = 0.891$), smoking ($P = 0.999$), coexisting leiomyoma ($P = 0.687$), and ovarian cysts ($P = 1.00$) between case and control groups. The prevalence of endometriosis ($P < 0.0001$), history of uterine surgery ($P = 0.002$), and number of pregnancies ($P = 0.012$) were significantly higher in the case group.

Conclusion: The study findings suggest significant associations between endometriosis, number of pregnancies, and history of uterine surgery with adenomyosis. Therefore, managing these risk factors appropriately can substantially reduce the occurrence of adenomyosis.

Keywords: adenomyosis, magnetic resonance imaging, reproductive age, risk factors

Introduction

Common gynecological disorder adenomyosis involves endometrial glands and stroma within the myometrium, along with hypertrophy and hyperplasia of the surrounding myometrium[1,2]. The prevalence of this condition varies across studies, with research indicating that 2–8%[3-5] of hysterectomy patients have it. This variation in prevalence among different populations may be due to the lack of standardized diagnostic criteria[6]. While several diagnostic methods have been proposed, none provide a definitive diagnosis. Adenomyosis can significantly affect a woman's quality of life, leading to symptoms such as dysmenorrhea, menorrhagia, and infertility, and is often associated with complications such as miscarriage, preeclampsia, and adverse pregnancy outcomes[7]. The exact cause of adenomyosis remains unknown; however, factors such as age, parity, age at menarche, history of uterine procedures (e.g., dilation and curettage, cesarean section), weight, uterine size, spontaneous abortion, and endometrial hyperplasia have been associated with the development of the disease. The variable prevalence of adenomyosis across studies can be attributed to

HIGHLIGHTS

- This study identifies significant risk factors for uterine adenomyosis, including endometriosis, uterine surgery, and number of pregnancies.
- MRI is utilized as a non-invasive diagnostic tool for accurately detecting adenomyosis in women of reproductive age.
- The prevalence of endometriosis and history of uterine surgery was notably higher in women with adenomyosis.
- No significant correlation was found between age, smoking, coexisting leiomyoma, and ovarian cyst with the presence of adenomyosis.
- The findings emphasize the importance of managing identified risk factors to reduce the occurrence of uterine adenomyosis.

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This study has been registered in the ClinicalTrials.gov database with the Unique Identifying Number (UIN) NCT06697444.

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differences in study populations, diagnostic criteria, and potential misdiagnoses due to the lack of standardized diagnostic criteria. Uterine surgeries, which disrupt the myometrium-endometrium boundary by incising the uterine layers, are considered one of the main contributors to adenomyosis. This disruption allows endometrial glands and stroma to invade the myometrium[6,8,9]. Given its prevalence and the potential for complications, early and accurate diagnosis is critical for managing adenomyosis effectively, particularly in reproductive-aged women. Magnetic resonance imaging (MRI) is now considered the gold standard for diagnosing adenomyosis due to its excellent soft tissue differentiation and ability to detect changes in the junctional zone (JZ)[10].

Furthermore, recent studies, including one focused on the use of safe medications during pregnancy[11], underscore the importance of improving clinical understanding and expanding the contextual knowledge surrounding diagnosis and treatment approaches in conditions like adenomyosis.

Similar to normal endometrial tissue, myometrial invasion leads to cyclic bleeding under the influence of estrogen. Small fluid-filled collections may form in the uterine wall due to residual blood and tissue, which in turn stimulates ectopic endometrial glands. This can result in myometrial hypertrophy and hyperplasia. The JZ refers to the boundary between the endometrial and myometrial layers, where thickening occurs in adenomyosis. MRI's ability to detect these changes, especially in the JZ, makes it the most reliable non-invasive method to assess adenomyosis, offering advantages over other techniques such as ultrasound[1-5,12]. These studies suggest that adenomyosis may develop in women over the age of 35, leading to obstetric and surgical complications. These complications can include cesarean section, hysterectomy, uterine perforation, placenta accreta, placenta increta, uterine atony, postpartum hemorrhage, shock, mortality, and ectopic pregnancy[1]. Histopathological examination is essential for confirming the diagnosis. Hysterectomy remains an effective and permanent treatment for symptomatic adenomyosis. Recent studies have also shown that uterine excision may provide therapeutic benefits for managing the condition[3]. Preoperative imaging like transvaginal ultrasound determines involvement, and MRI plays a crucial role, as it is less operator-dependent and offers clearer insights into the extent of the disease[13]. Recurrence of adenomyosis may be reduced by surgical excision of the upper uterine cavity[14,15]. In addition to its high accuracy, MRI offers the advantage of visualizing other gynecological conditions that may co-exist with adenomyosis, such as fibroids or endometriosis, which can be crucial for comprehensive treatment planning[16]. Transabdominal and transvaginal ultrasonography and MRI are becoming typical non-invasive screening techniques in clinical settings due to fast imaging technology improvements. Non-invasive pelvic imaging using pelvic MRI is the current standard since ultrasonography is operator-dependent[17-19].

MRI scans distinguish the JZ myometrium from the endometrial and outer myometrium by its T2 features. Adenomyosis is cured by diffuse or localized thickening of this zone, where diffuse adenomyosis involves generalized thickening, while focal adenomyosis refers to isolated areas of adenomyotic foci. Adenomyosis is currently defined by diffuse or localized thickening of this zone[20,21]. Adenomyosis may be diagnosed by MRI, along with pelvic endometriosis, frozen pelvis, and other mimics[22]. MRI has good diagnostic accuracy in confirming the diagnosis and identifying the extent of disease and additional lesions[23-25]. Furthermore, given the limited studies on MRI-based diagnosis of adenomyosis and the significant clinical implications of this disease, along with the limited studies in this area in Iran, we aimed to investigate the risk factors for pathologies associated with MRI-confirmed uterine adenomyosis in reproductive-aged women and compare them to a control group. This study will contribute to future planning and developing preventive and control strategies for this impactful disease.

Materials and methods

Study design

A formal written introduction from university officials was obtained to approach research centers. The study objectives were fully explained to all research participants, and their written consent was obtained. The project implementers strictly maintained the confidentiality of all patient data. Ethical compliance was ensured by following the principles outlined in the Helsinki Declaration. The study was reviewed and approved by the Faculty of Medicine's Research Council ethics committee (IR.IAU.MSHD.REC.1399.061), and all participants provided informed consent prior to inclusion. This study has been reported in accordance with the Strengthening the Reporting of Cohort Studies in Surgery criteria[26], ensuring adherence to the journal's specific ethical and reporting requirements. This case-control study targeted women of reproductive age (15–50 years) who were referred to the imaging department of a university-affiliated hospital in Mashhad between 2021 and 2023. Participants were recruited consecutively as they presented for pelvic MRI based on clinical indication, ensuring that all individuals meeting the inclusion criteria were considered for participation. Pelvic MRI was requested for all patients at the discretion of a gynecologist or gyneco oncologist. Women who were diagnosed with uterine adenomyosis in MRI formed the case group. The control group consisted of women in the same age range who underwent pelvic MRI for various reasons and showed no evidence of adenomyosis on their MRI. Inclusion criteria for the case group were women aged 15–50 with MRI-confirmed uterine adenomyosis, while the control group consisted of women in the same age range without adenomyosis. Exclusion criteria included pregnant women and patients with pelvic malignancy. Matching for confounding factors such as age was done to ensure comparability between the case and control groups, and statistical analysis included appropriate adjustments for other confounders such as the number of pregnancies, smoking, and history of uterine surgery.

Study variables, including age, smoking, number of pregnancies, and history of uterine surgery, were collected through face-to-face interviews. Pelvic MRI was performed using a 1.5 Tesla Siemens MRI machine, with and without intravenous contrast. To reduce intestinal spasms and enhance soft tissue contrast, intramuscular hyoscine was administered. The imaging protocol focused on T1, T2, and T1 fat-saturated sequences, followed by intravenous gadolinium contrast (0.2 ml/kg). Post-contrast T1 images were captured in axial, coronal, and sagittal planes. Among the individuals imaged, those with MRI-confirmed adenomyosis were categorized as the case group, while others were included in the control group. A thickness of JZ exceeding 12 mm was considered diffuse adenomyosis; Focal adenomyosis

occurs when uterine adenomyotic foci are isolated from an intact JZ and have healthy muscle tissues between them.

During the interpretation of MR images, in addition to the presence or absence of adenomyosis, other accompanying pathologies such as endometriosis, ovarian cysts, and uterine fibroids were also searched and recorded. Inter-observer reliability for MRI interpretation was assessed by having two radiologists independently review the images and compare their findings. Finally, the findings were compared and analyzed between case and control groups. Data description involved tables and appropriate statistical measures, such as mean values. The t-test was applied to compare mean differences, while the chi-square test was used for nominal scale data. The SPSS v.26 software was utilized for analysis, and a significance level of less than 5% was considered for the tests.

Results

A total of 100 patients were studied. In the group without adenomyosis, the mean age distribution was 37.46 ± 9.74 years, whereas in the group with it, it was 35 ± 7.58 years. Since the *P* value was 0.891, the two groups had similar age distributions. For smoking status distribution, the chi-square test found no difference between groups ($P = 0.999$). The distribution of coexisting uterine fibroids did not change across groups ($P = 0.687$). Ovarian cysts were likewise similar across groups ($P = 1.00$).

The lack of significant differences in age, smoking, uterine fibroids, and ovarian cysts ($P = 0.891$, 0.999, 0.687, and 1.00, respectively) may be attributed to the relatively homogenous sample in terms of these factors. It is possible that these variables do not have a strong association with uterine adenomyosis, or the sample size was insufficient to detect small differences. Further studies with larger sample sizes or longitudinal designs may be needed to clarify these associations.

Differences in endometriosis distribution across groups were significant ($P = 0.0001$). Women with adenomyosis had a substantially different uterine surgical history ($P = 0.002$). Final parity distribution demonstrated a significant difference between groups ($P = 0.012$) (Table 1).

According to MRI findings, the distribution of adenomyosis type in women showed that three patients (6%) had focal adenomyosis, and 47 patients (94%) had diffuse adenomyosis.

A regression logistic model was used to investigate the relationship between variables and adenomyosis (Table 2). Among the variables, the presence of endometriosis ($P = 0.000$) and a history of uterine surgery ($P = 0.033$) showed significant association with adenomyosis.

Table 1

Distribution of study variables in women with confirmed adenomyosis

	No adenomyosis		Has adenomyosis.		Total		
	Number	%	Number	%	Number	%	*P* value
Endometriosis							0.0001*
No	37	74%	13	26%	50	50%	
Yes	13	26%	37	74%	50	50%	
History of uterine surgery							0.002*
No	43	86%	29	58%	72	72%	
Yes	7	14%	21	42%	28	28.5%	
Number of births							0.012*
Zero	34	68%	19	38%	53	53.3%	
One	5	10%	15	30%	20	20%	
Two	7	14%	10	20%	17	17%	
Three and more	4	8%	6	12%	10	10%	
Smoking							0.999
No	50	100%	49	98%	99	99%	
Yes	0	0%	1	2%	1	1%	
Uterine fibroids							0.687
No	27	54%	29	58%	56	56%	
Yes	23	46%	21	42%	44	44%	
Ovarian cyst							1.0
No	33	66%	33	66%	66	68.8%	
Yes	17	34%	17	34%	34	31.2%	

*$P<0.05$

Discussion

Females often have adenomyosis, which can cause dysmenorrhea, menorrhagia, dyspareunia, and persistent pelvic discomfort. Since adenomyosis is prevalent and its complications can lead to both physical and psychological issues in women, as well as affecting fertility and pregnancy, prevention is crucial. To effectively prevent adenomyosis, it is necessary to identify its risk factors and implement appropriate management strategies[27]. Various studies have shown that several factors, including age, age at menarche, number of pregnancies and childbirths, weight, uterine size, and previous uterine surgeries, can be involved in the development of adenomyosis. Although the findings from different studies may be consistent in some aspects and conflicting in others, the overall results can help identify the risk factors for adenomyosis[28].

Pathophysiologically, the most common explanation for adenomyosis is the aberrant invasion of the basal layer of the endometrium into the myometrium. The aberrant migration of the basal layer of the endometrium via intramuscular lymphatic channels or the existence of endometrial-like tissue in the uterine wall may start a new metaplastic process. Estrogen stimulation causes endometrial glands to behave like the basal layer and show particular patterns. Adenomyosis does not bleed or inflame like endometriosis[29].

Smooth muscle metaplasia and fibroblasts in the myometrium may potentially contribute to adenomyosis. Due to the variability in diagnostic criteria, adenomyosis prevalence ranges from 2% to 8% in earlier investigations[5]. Adenomyosis prevalence rises from mid-30s to 50. Adenomyosis affects 80% of women between 40 and 50, and 20% under 40, according to Shane *et al*[6].

In the current study, the mean age of individuals diagnosed with adenomyosis was recorded as 34.88 ± 8.69, indicating that the onset age of the disease in this population is lower than that in other studies, including the study mentioned above and also the research by Panganamamula *et al*[30] and the study by Balogun *et al*[31]. This difference may arise from variations in the populations studied or a higher prevalence of underlying factors for adenomyosis, particularly endometriosis, in the population under investigation.

The association between adenomyosis and endometriosis has been previously studied with highly variable results. In older reports and an extensive review, the prevalence of endometriosis in cases of adenomyosis varied between 10% and 80%, with the

Table 2

Analysis of variance table of the relationship between different variables and adenomyosis in women with adenomyosis

							95% CI for Exp (B)	
Variable	**B**	**S.E.**	**Wald**	**df**	**Sig.**	**Exp (B)**	**Upper**	**Lower**
Age	0.29	−0.369	0.656	11	0.418	0.971	1.043	0.904
Endometriosis	0.346	0.536	19.499	1	0.000*	0.096	0.272	0.034
History of uterine surgery	−1.114	−0.675	4.549	1	0.033*	0.237	0.89	0.063
Number of deliveries	−4.46	0.305	2.131	1	0.144	1.562	2842	0.858
Uterine fibroids	−0.489	−0.595	0.675	1	0.411	0.613	1.97	0.191
Ovarian cysts	0.0212	−0.533	0.157	1	0.0691	1.236	3.514	0.435
Constant	−3.003	−1.629	3.399	1	0.065	20.15	-	-

reported data likely based on incidental findings during surgery rather than data collected in a focused study on this issue[32]. Most patients in the current study were in the later stages of their reproductive years, and superficial endometriotic lesions may have disappeared by that time. In contrast, smaller invasive lesions may have remained undetected during surgery, such as deep endometriosis of the sacrouterine ligaments. Therefore, it is likely that only persistent and more significant lesions were considered[27].

Diagnosing small endometriotic lesions requires laparoscopy and a classification system considering a wide range of lesions, including minor ones. As expected, a comprehensive investigation on endometriosis and adenomyosis found a significant frequency of the latter in endometriosis patients[8]. In the current study, the association of endometriosis with adenomyosis was found to be 74% (P = 0.0001), which aligns closely with the findings of Leyendecker *et al*[33]. In both studies, a significant difference was observed between the case and control groups regarding the association with endometriosis. Regarding the history of uterine surgery, a significant correlation was also found between the case and control groups in the present study (P = 0.002), consistent with the study's results by Panganamamula *et al*[30].

In a recent study, no differences were observed in the type of surgical methods used for uterine procedures and the occurrence of adenomyosis[33]. This variable was not examined in the current study. Additionally, Vercellini *et al*[8] found in his study that a history of previous uterine surgery increases the risk of developing adenomyosis. The study's results by Bergholt *et al*[34]. are consistent with the present study; however, in Curtis's study[35], no significant correlation was found between a history of previous uterine surgery and the incidence of adenomyosis. This contrasts with findings from other research, which suggests that a history of previous uterine surgery is a factor contributing to the development of adenomyosis.

In the present study, the number of childbirths was significantly higher in the women of the case group (P = 0.012), which contrasts with the findings of another study[31]; this discrepancy may be due to differences in sample size and study type. However, the findings are consistent with those of Panganamamula *et al*[30] and Kitawaki *et al*[36]. According to the results, no significant association was found between adenomyosis and smoking, co-occurrence of uterine fibroids or ovarian cyst (P = 0.999, 0.687, and 1.00, respectively), which aligns with the findings of Curtis *et al*[35]. The lack of significant differences in age, smoking, uterine fibroids, and ovarian cysts (P = 0.891, 0.999, 0.687, and 1.00, respectively) may be attributed to the relatively homogenous sample in terms of these factors. It is possible that these variables do not have a strong association with uterine adenomyosis, or the sample size was insufficient to detect small differences. Further studies with larger sample sizes or longitudinal designs may be needed to clarify these associations. Adenomyosis may be classified into diffuse and focal types, where diffuse adenomyosis involves generalized thickening of the JZ, while focal adenomyosis refers to isolated adenomyotic foci within the myometrium.

One limitation of this study is the potential for selection bias, as the sample was derived from a single center, which may not fully represent the broader population. Additionally, the relatively small sample size could have reduced the statistical power of the study, making it more difficult to detect smaller differences in variables such as age, smoking, and the presence of uterine fibroids or ovarian cysts. Another limitation is the reliance on MRI for diagnosing adenomyosis without histopathological confirmation, which may affect the accuracy of the diagnosis. Furthermore, the exclusion of pregnant women from the study may limit the generalizability of the results to this specific population

Given that adenomyosis is a common condition among women of reproductive age, leading to menorrhagia and consequently iron-deficiency anemia, dysmenorrhea, reduced quality of life, and pregnancy complications such as placenta accreta, increta, uterine atony, and uterine rupture, prevention is necessary and beneficial[8]. Prevention efforts should begin by identifying the risk factors for adenomyosis, followed by actions to mitigate these risks. Identified risk factors for adenomyosis include age, previous uterine surgery, abortion, multiple pregnancies, early menarche, and high parity[37].

In the present study, some of these variables, including the presence of endometriosis, a history of uterine surgery, and the number of prior deliveries, were reported to be significantly higher among those with adenomyosis compared to the control group.

Conclusion

Based on the results of the present study, timely diagnosis and treatment of endometriosis, given its high prevalence among women with uterine adenomyosis, may play a significant role in controlling this disorder. Additionally, reducing unnecessary uterine surgeries can help prevent the development of adenomyosis. Practical implications suggest that healthcare providers should closely monitor women with known risk factors, such as a history of endometriosis or uterine surgery, and implement early interventions to manage these conditions. For women with

multiple pregnancies or a history of uterine surgery, personalized management plans should be considered to mitigate the risks of developing adenomyosis. Furthermore, future research should include larger and more diverse patient populations to validate the findings of this study. Longitudinal studies, incorporating women from various ethnic, age, and geographical backgrounds, could provide more robust data on the long-term effects of managing these risk factors. This would help refine strategies for early detection and prevention of uterine adenomyosis, especially in high-risk women.

Ethical approval

This study was conducted following ethical guidelines based on the Helsinki Declaration. Ethical approval was obtained from the Faculty of Medicine's Research Council at Mashhad Medical Sciences, Islamic Azad University. The study was approved with the ethics code IR.IAU.MSHD.REC.1399.061. All participants provided written informed consent before participation in the study, and the confidentiality of all patient data was strictly maintained throughout the research process.

Consent

Written informed consent was obtained from all participants involved in this study. For the publication of this research, no identifying details, including names, initials, or hospital numbers, are used to protect patient privacy.

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Author's contribution

N.A.: concept and design of the study, data collection, data analysis, interpretation of results, writing and revising the manuscript; L.H.: data collection, analysis and interpretation, reviewing and editing the manuscript; S.A.: data collection, statistical analysis, reviewing and editing the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest disclosure

The author declares no conflicts of interest in relation to this manuscript.

Research registration unique identifying number (UIN)

This study has been registered in the ClinicalTrials.gov database with the unique identifying number (UIN) NCT06697444 (https://clinicaltrials.gov/study/NCT06697444).

Guarantor

Narges Afzali.

Provenance and peer review

This manuscript was not commissioned and has been externally peer-reviewed.

Data availability statement

The datasets generated and/or analyzed during the current study are available upon reasonable request from the corresponding author. Due to privacy and ethical considerations, some data may not be publicly available.

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