Risk factors and disorders associated with uterine adenomyosis diagnosed on magnetic resonance imaging in women of reproductive age

Non-ACT (Not interventional)

01/01/2023

Abstract

Background: In adenomyosis, endometrial glands and stroma are present. It might be focused or diffuse. While definitive diagnosis relies on histopathology of the uterus after hysterectomy, non-invasive imaging techniques, especially magnetic resonance imaging (MRI), play essential roles in its diagnosis. This study aimed to investigate 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, smoking, coexisting leiomyoma, and ovarian cyst between case and control groups. The prevalence of endometriosis, history of uterine surgery, and number of pregnancies were significantly higher in the case group.

Conclusion: The study findings suggest that there is a meaningful association between endometriosis, the number of pregnancies, and uterine surgery with adenomyosis; therefore, proper control and management of these risk factors can significantly affect the occurrence of adenomyosis.

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

Introduction

Common gynecological disorder adenomyosis involves endometrial glands and stroma in the myometrium and hypertrophy and hyperplasia of the surrounding myometrium [1, 2]. The prevalence of this illness varies per study. Research shows 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]. Although various diagnostic methods have been described, none are definitive. Adenomyosis' cause is unknown, however age, parity, menarche age, history of uterine procedures such dilation and curettage, cesarean section, weight, uterine size, spontaneous abortion, and endometrial hyperplasia have been linked. The variable prevalence of adenomyosis across studies can be attributed to differences in study populations, diagnostic criteria for adenomyosis, and misdiagnoses due to the lack of standardized diagnostic criteria. One of the main causes of adenomyosis is uterine surgeries, which incision uterine layers and destroy the endometrium-myometrium boundary, allowing endometrial glands and stroma to be replaced [6-8].

Like normal endometrial tissue, myometrial invasion causes cyclic bleeding under estrogen. Small fluid-filled uterine wall collections may arise from the residual blood and tissue stimulating the ectopic endometrial glands. Myometrium hypertrophy and hyperplasia may also result. Endometrial tissue invading the myometrium enlarges the uterus, making it spherical [1-5]. These studies suggest that adenomyosis may arise in certain women over 35 and cause obstetric and surgical difficulties. Cesarean section, hysterectomy, uterine perforation, placenta accreta, placenta increta, uterine atony, postpartum hemorrhage, shock, mortality, and ectopic pregnancy are complications [1].

Histopathology may confirm a diagnosis [3]. Hysterectomy is an effective and permanent therapy for symptomatic adenomyosis. Recent investigations have revealed that uterine excision may also treat the condition. Preoperative imaging like transvaginal ultrasound determines involvement. Recurrence of adenomyosis may be reduced by surgical excision of the upper uterine cavity [9]. 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 [10].

MRI scans distinguish the junctional zone myometrium from the endometrial and outer myometrium by its T2 features. Adenomyosis is currently defined by diffuse or localized thickening of this zone [11, 12]. Adenomyosis may be diagnosed by MRI, along with pelvic endometriosis, frozen pelvis, and other mimics [13]. MRI has good diagnostic accuracy in confirming the diagnosis and identifying the extent of disease and additional lesions [14]. 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 principles based on the Helsinki Declaration and the university's research ethics committees were observed throughout all stages of the study. The study was conducted following approval from the Faculty of Medicine's Research Council and after obtaining an ethics code (IR.IAU.MSHD.REC.1399.061) and a formal introduction letter.

This case-control study targeted women of reproductive age (15-50 years) who were referred to the imaging department of the Hospitals of Islamic Azad University of Mashhad in 2021-2023. 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. Exclusion criteria included pregnant women and patients with pelvic malignancy.

Study variables, including age, smoking, number of pregnancies, and history of uterine surgery, were searched through face-to-face interviews with all patients. Pelvic MRI was performed using a 1.5 Tesla Siemens MRI machine, with and without intravenous contrast. To minimize intestinal spasms, intramuscular hyoscine was administered before imaging, and the vaginal and rectal gel was locally applied to improve soft tissue contrast. The imaging protocol included T1 and T2 weighted sequences along with T1 fat-saturated sequences (T1 with fat suppression). Following this, intravenous contrast (gadolinium) was administered at 0.2 ml per kg, and T1 post-contrast 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 junctional zone (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. 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.

Result

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 co-existing uterine fibroids did not change across groups (P=0.687). Ovarian cysts were likewise similar across groups (P=1.00).

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

Table 1: Distribution of study variables in women with confirmed adenomyosis

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

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 and a history of uterine surgery showed significant association with adenomyosis (P<0.05).

Table 2: Analysis of variance table of the relationship between different variables and adenomyosis in women with adenomyosis

Variable	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for 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	-	-

Discussion

Females often have adenomyosis, which may 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 essential. To prevent adenomyosis, it is necessary to identify its risk factors and take appropriate measures to address them [15]. 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 [16].

Pathophysiologically, aberrant invasion of the basal layer of the endometrium into the myometrium is the most common explanation. 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 [17].

Smooth muscle metaplasia and fibroblasts in the myometrium may potentially contribute to adenomyosis. Due to varied diagnostic criteria, adenomyosis prevalence ranges from 2% to 8% in prior 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. [18] and the study by Balogun et al. [19]. 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 reported data likely based on incidental findings during surgery rather than data collected in a focused study on this issue [20]. Most patients in the current study were in the advanced 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 [15].

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 [7].

In the current study, the association of endometriosis with adenomyosis was found to be 74% (P-Value=0.0001), which aligns closely with the findings of Leyendecker et al. [21]. 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-Value=0.002), consistent with the study's results by Panganamamula et al. [18].

In a recent study, no differences were observed in the type of surgical methods used for uterine procedures and the occurrence of adenomyosis [21]. This variable was not examined in the current study. Additionally, Vercellini et al. [7] 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. [22]. are consistent with the present study; however, in Curtis's study [23], 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-Value=0.012), which contrasts with the findings of another study [19]; this discrepancy may be due to differences in sample size and study type. However, the findings are consistent with those of Panganamamula et al. [18] and Kitawaki et al. [24]. According to the results, no significant association was found between adenomyosis and smoking, co-occurrence of uterine fibroids or ovarian cyst (P-Value= 0.999, P-Value=0.687, and P-Value=1.00, respectively), which aligns with the findings of Curtis et al. [23].

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 [7]. 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 [25].

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.

References

[1] M.S. Khandeparkar, S. Jalkote, M. Panpalia, S. Nellore, T. Mehta, K. Ganesan, F.R. Parikh, High-resolution magnetic resonance imaging in the detection of subtle nuances of uterine adenomyosis in infertility, Global Reproductive Health 3(3) (2018) e14.

[2] C. Chapron, C. Tosti, L. Marcellin, M. Bourdon, M.-C. Lafay-Pillet, A.-E. Millischer, I. Streuli, B. Borghese, F. Petraglia, P. Santulli, Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes, Human reproduction 32(7) (2017) 1393-1401.

[3] B. Trabert, N.S. Weiss, C.B. Rudra, D. Scholes, V.L. Holt, A case-control investigation of adenomyosis: impact of control group selection on risk factor strength, Women's health issues 21(2) (2011) 160-164.

[4] C.A. Stratopoulou, J. Donnez, M.-M. Dolmans, Origin and pathogenic mechanisms of uterine adenomyosis: what is known so far, Reproductive Sciences 28(8) (2021) 2087-2097.

[5] Y. Sonan, S. Aoki, K. Enomoto, K. Seki, E. Miyagi, Placenta accreta following hysteroscopic lysis of adhesions caused by Asherman's syndrome: a case report and literature review, Case Reports in Obstetrics and Gynecology 2018(1) (2018) 6968382.

[6] B. Shane, M. Burns, K. Dahlquist, Preventing post-partum Hemorrhage: managing the third stage of labor (2001).

[7] P. Vercellini, D. Consonni, D. Dridi, B. Bracco, M.P. Frattaruolo, E. Somigliana, Uterine adenomyosis and in vitro fertilization outcome: a systematic review and meta-analysis, Human reproduction 29(5) (2014) 964-977.

[8] M. Harmsen, T. Van den Bosch, R. De Leeuw, M. Dueholm, C. Exacoustos, L. Valentin, W. Hehenkamp, F. Groenman, C. De Bruyn, C. Rasmussen, Consensus on revised definitions of Morphological Uterus Sonographic Assessment (MUSA) features of adenomyosis: results of modified Delphi procedure, Ultrasound in Obstetrics & Gynecology 60(1) (2022) 118-131.

[9] T. Tellum, S. Nygaard, M. Lieng, Noninvasive diagnosis of adenomyosis: a structured review and meta-analysis of diagnostic accuracy in imaging, Journal of minimally invasive gynecology 27(2) (2020) 408-418. e3.

[10] Z. Liu, Y. Guo, X. Pan, X. Yang, Histopathological characteristics of adenomyosis: structure and microstructure.(٢٠٢٣) ,

[11] C.K. Rasmussen, T. Van den Bosch, C. Exacoustos, G. Manegold-Brauer, B.R. Benacerraf, W. Froyman, C. Landolfo, M. Condorelli, A.G. Egekvist, H. Josefsson, Intra-and inter-rater agreement describing myometrial lesions using morphologic uterus sonographic assessment: a pilot study, Journal of Ultrasound in Medicine 38(10) (2019) 2.٦٧٣-٢٦٨٣

[12] L. Zannoni, M. Ambrosio, D. Raimondo, A. Arena, S. Del Forno, G. Borghese, R. Paradisi, R. Seracchioli, Question mark sign and transvaginal ultrasound uterine tenderness for the diagnosis of adenomyosis: a prospective validation, Journal of ultrasound in medicine 39(7) (2020) 1405-1412.

[13] D. Raimondo, A. Raffone, A.C. Aru, M. Giorgi, I. Giaquinto, E. Spagnolo, A. Travaglino, F.A. Galatolo, M.G.C.A. Cimino, J. Lenzi, Application of deep learning model in the sonographic diagnosis of uterine adenomyosis, International Journal of Environmental Research and Public Health 20(3) (2023) 1724.

[14] N. Di Donato, V. Bertoldo, G. Montanari, L. Zannoni, G. Caprara, R. Seracchioli, N. Di Donato, A simple sonographic sign associated to the presence of adenomyosis, Ultrasound Obstet Gynecol 46(1) (2015) 126-7.

[15] F. Taran, E. Stewart, S. Brucker, Adenomyosis: epidemiology, risk factors, clinical phenotype and surgical and interventional alternatives to hysterectomy, Geburtshilfe und Frauenheilkunde.924-931(2013)(09)73.

[16] T. Van den Bosch, M. Dueholm, F. Leone, L. Valentin, C.K. Rasmussen, A. Votino, D. Van Schoubroeck, C. Landolfo, A. Installé, S. Guerriero, Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group, Ultrasound in Obstetrics & Gynecology 46(3) (2015) 284-298.

[17] J. Donnez, O. Donnez, M.-M. Dolmans, Introduction: uterine adenomyosis, another enigmatic disease of our time, Fertility and sterility 109(3) (2018) 369-370.

[18] U.R. Panganamamula, O.H. Harmanli, E.F. Isik-Akbay, C.A. Grotegut, V. Dandolu, J.P. Gaughan, Is prior uterine surgery a risk factor for adenomyosis?, Obstetrics & Gynecology 104(5 Part 1) (2004) 1034-1038.

[19] M. Balogun, Imaging diagnosis of adenomyosis, Reviews in Gynaecological and Perinatal Practice 6(1-2) (2006) 63-69.

[20] J. Rawson, Prevalence of endometriosis in asymptomatic women, The Journal of reproductive medicine 36. 513-515(1991)(7).

[21] G. Leyendecker, A. Bilgicyildirim, M. Inacker, T. Stalf, P. Huppert, G. Mall, B. Böttcher, L. Wildt, Adenomyosis and endometriosis. Re-visiting their association and further insights into the mechanisms of auto-traumatisation. An MRI study, Archives of Gynecology and Obstetrics 291 (2015) 917-932.

[22] T. Bergholt, L. Eriksen, N. Berendt, M. Jacobsen, J. Hertz, Prevalence and risk factors of adenomyosis at hysterectomy, Human reproduction 16(11) (2001) 2418-2421.

[23] K.M. Curtis ,S.D. Hillis, P.A. Marchbanks, H.B. Peterson, Disruption of the endometrial-myometrial border during pregnancy as a risk factor for adenomyosis, American journal of obstetrics and gynecology 187(3) (2002) 543-544.

[24] J. Kitawaki, Adenomyosis: the pathophysiology of an oestrogen-dependent disease, Best practice & research Clinical obstetrics & gynaecology 20(4) (2006) 493-502.

[25] P. Humaidan, J.A.G. Velasco, M. Cozzolino, Local intraendometrial estrogen biosynthesis leading to progesterone resistance impacts implantation in adenomyosis and endometriosis, Fertility and Sterility 120(4) (2023) 927.