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# Adenomyosis and accompanying gynecological pathologies

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**Abstract**
*Objective* The aim of the present study is to determine the potential risk factors for adenomyosis and to investigate its relationship with accompanying gynecological pathologies and clinical characteristics.
*Materials and method* This study is a retrospective analysis of 945 patients who underwent hysterectomy between May 2005 and January 2013 at the Sifa University Medical Faculty Hospital, Clinic of Obstetrics and Gynecology. The study included 327 patients with adenomyosis and 618 patients without adenomyosis by histopathological examination of the uterus.
*Results* There was a significant positive correlation between development of adenomyosis and presence of leiomyoma ($p < 0.0001$), history of previous abortion ($p < 0.0001$), history of previous pregnancy ($p = 0.0002$), and normal body mass index ($p < 0.0001$). However, no significant relationship existed between development of adenomyosis and smoking ($p > 0.4300$), normal delivery ($p = 0.9600$), cesarean delivery ($p = 0.5705$), endometrial hyperplasia ($p = 0.1721$), or ovarian endometriosis ($p = 0.8595$).
*Conclusion* Women who are multiparous have leiomyoma, a previous history of abortion, and a normal body mass index are at increased risk for development of adenomyosis. Adenomyosis might be one cause of unexplained recurrent spontaneous abortion during pregnancy.

**Keywords** Abortion · Adenomyosis · Epidemiology · Risk factors · Uterine leiomyomas

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## Introduction

Adenomyosis is a benign lesion of myometrial tissue characterized by the presence of endometrial glands and stroma within the myometrium. Its diagnosis primarily depends on the histological examination of hysterectomy specimens [1]. However, recent advances in imaging methods, such as transvaginal ultrasonography (TVUSG) and magnetic resonance imaging (MRI), have allowed for the preoperative diagnosis of adenomyosis [2].

The prevalence of adenomyosis ranges between 5 and 70 % in hysterectomy samples obtained for gynecological purposes [3]. The risk factors for adenomyosis include advanced age, multiparity, history of cesarean delivery, smoking, and increased serum estrogen levels [4–6]. Adenomyosis commonly causes various symptoms, including dysmenorrhea, menorrhagia, and chronic pelvic pain [7].

Of all studies performed on adenomyosis, ours has one of the largest sample sizes to date. In this study, we aimed to determine the risk factors for adenomyosis and investigate other histopathological conditions of the ovaries and uterus that accompany adenomyosis in patients who

**Table 1** The indications of the operation with or without adenomyosis

| The indications for the operation | With adenomyosis *n* (%) | Without adenomyosis *n* (%) | Total |
|---|---|---|---|
| Treatment-resistant menometrorrhagia and endometrial hyperplasia | 71 (21.7) | 103 (16.7) | 174 (%18.4) |
| Leiomyoma | 159 (%48.6) | 323 (%52.3) | 482 (%51.2) |
| Ovarian cyst | 39 (%11.9) | 76 (%12.3) | 115 (%12.2) |
| Uterine prolapse | 26 (%7.9) | 60 (%9.7) | 86 (%9.1) |
| Menopausal bleeding | 29 (%8.9) | 42 (%6.8) | 71 (%7.1) |
| Endometrial carcinoma | 3 (%0.9) | 14 (%2.3) | 17 (%1.9) |
| Total | 327 | 618 | 945 |

underwent hysterectomy for various gynecological indications and were diagnosed with uterine adenomyosis by pathological examination.

## Materials and method

This study was performed by retrospective assessment of all patients (a total of 945 patients) who underwent hysterectomy for various indications, including leiomyoma, benign endometrial hyperplasia, treatment-resistant menometrorrhagia, ovarian cysts, postmenopausal bleeding, descensus uteri, and endometrial carcinoma between May 2005 and January 2013 at Sifa University Medical Faculty Hospital, Clinic of Obstetrics and Gynecology. Data relating to complaints of dysmenorrhea, dyspareunia, and chronic pelvic pain were examined. Medical records and imaging data of all patients were accessed through the hospital automation system (Hospital Information System: HIS, Picture archiving computed system: PACS).

All specimens were reviewed by the same two pathologists, and adenomyosis was diagnosed based on histological characteristics [8]. Patients were divided into two groups based on the histopathological examination of the uterus: the adenomyosis group (327 patients) and the control group (618 patients). Age, body mass index, number of pregnancies, number of deliveries, number of spontaneous abortions, mode of previous deliveries, menopausal state, and other uterine and ovarian pathologies accompanying adenomyosis were recorded. Patients with more than 1 year since the last menstrual period were considered to be menopausal. All patients underwent TVUSG prior to hysterectomy. For patients with suspected malignancy for whom a clear diagnosis could not be made, MRI results were accessed and examined. The preoperative complaints of the patients were classified as dyspareunia, dysmenorrhea, and chronic pelvic pain. Continual pelvic pain for more than 6 months was classified as chronic pelvic pain. The patients were classified as non-smokers and smokers by their smoking status. Surgical indications included treatment-resistant menometrorrhagia and endometrial hyperplasia, leiomyoma, ovarian mass, uterine prolapse, menopausal bleeding, and endometrial carcinoma (Table 1).

The pathological conditions accompanying adenomyosis in the postoperative histopathological examination of the uterus included leiomyoma, endometrial hyperplasia, and ovarian endometriosis (Table 2).

The ovarian pathological conditions accompanying adenomyosis included endometriosis, malignant ovarian tumors, and benign ovarian tumors (teratoma, fibrothecoma). A history of any malignancy was assessed as part of each patient's past history.

Statistical analyses were conducted using R-3.0.2 for Windows via R-Studio and MedCalc.org with the odds ratio tool. The odds ratios of adenomyosis and their corresponding 95 % confidence intervals (CI) according to various considered factors were estimated by the Mantel–Haenszel method (Mantel and Haenszel 1959).

## Results

A total of 945 patients were enrolled in the study. Of these, 327 had adenomyosis diagnosed by histopathological examination, while 618 patients did not have adenomyosis and were included as the control group.

Among the entire study group, 29 of 203 patients with dysmenorrhea prior to hysterectomy, 31 of 199 with chronic pelvic pain prior to hysterectomy, and 8 of 85 with dyspareunia prior to hysterectomy had no pathology apart from adenomyosis in the uterus and ovaries (Table 3).

The indications for hysterectomy were examined (Table 1). One hundred seventy-four (18.4 %) patients required surgery for treatment-resistant menometrorrhagia and endometrial hyperplasia, 484 (51.2 %) for leiomyoma, 115 (12.1 %) for ovarian mass, 86 (9.1 %) for uterine prolapse, 71 (7.5 %) for menopausal bleeding, and 17 (1.8 %) for endometrial carcinoma.

**Table 2** The Histopathological findings, accompanying adenomyosis in the postoperative examination of uterus and over

| Histopathology | With adenomyosis (*n*) | Without adenomyosis (*n*) | Odds ratio (95 % CI) | *p* value |
|---|---|---|---|---|
| Leiomyoma | 184 | 427 | 0.5236 (0.3991–0.6868) | $p < 0.0001$ |
| Endometrial hyperplasia | 31 | 77 | 0.7358 (0.4737–1.1429) | $p = 0.1721$ |
| Endometriosis | 14 | 28 | 0.9425 (0.4891–1.8163) | $p = 0.8595$ |

**Table 3** Preoperative symptoms in patient with or without adenomyosis

| Symptoms | With adenomyosis *n* (%) | Without adenomyosis *n* (%) | Total |
|---|---|---|---|
| Dysmenorrhea | 29 (%14.3) | 174 (%85.7) | 203 |
| Chronic pelvic pain | 31 (%15.6) | 168 (%84.4) | 199 |
| Dyspareunia | 8 (%9.4) | 77 (%90.6) | 85 |

The demographic characteristics of the study population, which included age, number of deliveries, mode of delivery, number of spontaneous abortions, menopausal state, and body mass index are summarized on Table 4. The mean age of patients with adenomyosis who underwent hysterectomy and the control group was 50.7 years (range 32–82) and 48.1 years (range 25–90), respectively. There was no significant difference in age between the two groups. The prevalence of adenomyosis was significantly different between those younger than 40 years and those between 50 and 59 years of age ($p < 0.0001$). No significant correlation was found between smoking and the prevalence of adenomyosis ($p > 0.4300$).

Compared to nulliparous women, multiparous women had a significantly higher prevalence of adenomyosis ($p = 0.0002$). No significant correlation was found between adenomyosis and normal delivery ($p = 0.9600$) or cesarean delivery ($p = 0.5705$), while a history of spontaneous abortion was significantly correlated to adenomyosis ($p < 0.0001$). The prevalence of adenomyosis was significantly higher in patients with a normal body mass index (BMI = 18.5–24.99; normal weight) ($p < 0.0001$).

We also investigated the concurrence of adenomyosis with the uterine pathologies leiomyoma and endometrial hyperplasia, which were detected by postoperative histopathological examination (Table 2). While there was no significant correlation between adenomyosis and the presence of endometrial hyperplasia ($p > 0.1721$), there was a significant tendency of leiomyoma and adenomyosis to occur simultaneously ($p < 0.0001$). Regarding ovarian pathologies, no significant correlation was observed between endometriosis and adenomyosis ($p < 0.8595$) (Table 2).

The history of malignancy was also examined. Among patients with adenomyosis, 1 had a history of thyroid cancer, 1 had a history of breast cancer, 1 had a history of simultaneous endometrioid tumor in the ovary and uterus, 1 had a history of borderline ovarian tumor, 2 had a history of serous epithelial ovarian cancer, 1 had a history of a poorly differentiated endometrioid tumor, 1 had a history of ovarian carcinoid tumor, and 3 had a history of adult granulosa cell ovarian tumor.

Transvaginal ultrasonography performed for patients with adenomyosis prior to hysterectomy diagnosed adenomyosis in 54 of 327 (16.4 %) patients ($p > 0.05$), while a preoperative MRI diagnosed adenomyosis in 8 of 79 (10.1 %) patients ($p > 0.05$).

## Discussion

Adenomyosis is a benign lesion of myometrial tissue characterized by the presence of endometrial glands and stroma within the myometrium. Many theories have been proposed regarding the pathogenesis of adenomyosis. Among these theories, the invagination of the endometrium into the myometrium is the theory that has drawn the greatest attention [9]. The observation of the continuity of the islets of ectopic endometrial tissue characteristic of adenomyosis and surface endometrium on microscopic examination supports this theory. Because the stratum basalis of the endometrium is non-functional in adenomyosis, hemosiderin pigmentation is rarely observed on microscopic examination [10]. The prevalence of adenomyosis ranges 5–70 % in hysterectomy specimens obtained for gynecological indications [3, 11, 12]. The reason for this great variability in prevalence in histopathological examinations may be due to the varied indications for hysterectomy or to the diagnostic criteria used by the pathologists examining the specimens. In our study population, 367 (34.7 %) of 945 patients who underwent hysterectomy for gynecological indications were diagnosed with adenomyosis. Yeniel et al. reported prevalence of adenomyosis similar to that of our study [11].

It has been reported that adenomyosis may be asymptomatic or may produce symptoms such as dysmenorrhea, dyspareunia, and chronic pelvic pain [4, 7]. Similarly, we found that 11.0 % of patients with adenomyosis had dysmenorrhea, 41.9 % had chronic pelvic pain, and 43 % had dyspareunia. However, the non-specific character of these symptoms hampers the diagnosis.

**Table 4** The demographic, reproductive properties, and the smoking status of the patients

| | With adenomyosis ($n = 327$) | Without adenomyosis ($n = 618$) | Odds ratio (95 % CI) | $p$ value |
|---|---|---|---|---|
| Age | | | | |
| Below 40 years | 10 | 115 | 0.1380 (0.0712–0.2673) | $p < 0.0001$ |
| 40–49 years | 151 | 274 | 1.0771 (0.8229–1.4099) | $p = 0.5885$ |
| 50–59 years | 130 | 150 | 2.0589 (1.5439–2.7457) | $p < 0.0001$ |
| Over 60 years | 36 | 79 | 0.8441 (0.5551–1.2835) | $p = 0.4279$ |
| Pregnancy | | | | |
| Yes | 319 | 559 | 4.2086 (1.9857–8.9199) | $p = 0.0002$ |
| No | 8 | 59 | | |
| Normal delivery | | | | |
| Yes | 285 | 497 | 1.6521 (1.1297–2.4159) | $p = 0.0096$ |
| No | 42 | 121 | | |
| Cesarean section | | | | |
| Yes | 56 | 97 | 1.1099 (0.7742–1.5912) | $p = 0.5705$ |
| No | 217 | 521 | | |
| Abortion | | | | |
| Yes | 179 | 244 | 1.8489 (1.4099–2.4245) | $p < 0.0001$ |
| No | 148 | 373 | | |
| Smoking | | | | |
| Yes | 21 | 32 | 1.2567 (0.7125–2.2168) | $p = 0.4300$ |
| No | 306 | 586 | | |
| Body mass index | | | | |
| 18.5 or less (underweight) | 3 | 5 | 1.1315 (0.2687–4.7647) | $p = 0.8663$ |
| 18.5–24.99 (Normal weight) | 50 | 164 | 0.4975 (0.3505–0.7061) | $p = 0.0001$ |
| 25–29.99 (Overweight) | 131 | 226 | 1.1534 (0.8758–1.5189) | $p = 0.3096$ |
| 30–34.99 (Obesity–class 1) | 94 | 140 | 1.3717 (1.0114–1.8604) | $p = 0.0421$ |
| 35–39.99 (Obesity–class 2) | 37 | 63 | 1.1199 (0.7284–1.7218) | $p = 0.6058$ |
| 40 or greater | 12 | 18 | 1.2656 (0.6020–2.6608) | $p = 0.5344$ |

In our study, the prevalence of adenomyosis was higher in multiparous women, and this finding has been suggested by other studies [3, 4, 13, 14]. However, the mode of delivery did not affect the prevalence of adenomyosis.

Our results found a significant correlation between the history of abortion and adenomyosis ($p < 0.0001$). This close correlation may be due to a problem in the uterus created by adenomyosis. It has been reported that adenomyosis was closely related to the occurrence of abortion but did not affect implantation rates in a group of infertile patients following oocyte donation [15]. Factors related to the uterus may play a role in recurrent fetal loss [16]. These factors include uterine fibroids, endometrial polyps, uterine adhesions, and uterine septa. There are a limited number of studies on the relationship between adenomyosis and fetal loss. The close association between adenomyosis and recurrent fetal loss in our study suggests that adenomyosis may be a factor of unexplained recurrent fetal loss. One study performed in patients undergoing in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) reported that the presence of adenomyosis adversely affects the outcome of IVF/ICSI [17].

Bergholt et al. [4] reported no relationship between adenomyosis and the number of previous deliveries or history of abortion or uterine surgery. Similar to our report, Shrestha reported that multiparity and a history of abortion increased the risk of adenomyosis, while the mode of delivery did not affect the rate of adenomyosis [18]. The higher prevalence of adenomyosis in multiparous women may be related to facilitated trophoblastic invasion of the myometrium by foci of adenomyosis or to hormonal changes of pregnancy [19].

Adenomyosis, endometrial hyperplasia, and endometriosis are estrogen-dependent pathologies [4, 20]. Bergholt et al. [4] found a positive relationship between endometrial hyperplasia and adenomyosis. This positive relationship was attributed by the authors to the fact that both pathologies share similar etiologic factors. Among the factors, the most important was suggested to be an increased estrogen level. In our study, however, we did not find a relationship

between endometrial hyperplasia and adenomyosis ($p = 0.1721$). Similarly, there was also no association between adenomyosis and ovarian endometriosis ($p = 0.8595$). However, we did find a close correlation between adenomyosis and leiomyoma ($p < 0.0001$). Parazzini et al. [[3] found no association between smoking and adenomyosis, while Yenial et al. [11] reported that smokers had a higher prevalence of adenomyosis compared to non-smokers. We found no relationship between adenomyosis and smoking.

TVUSG and MRI are helpful for establishing a preoperative clinical diagnosis of adenomyosis [21, 22]. Adenomyosis should always be considered when investigating patients with non-specific complaints such as chronic pelvic pain, dysmenorrhea, and dyspareunia. It has been reported that preoperative MRI is the most reliable diagnostic method for establishing the diagnosis of adenomyosis, as evidenced by comparison of postoperative histopathological results with preoperative TVUSG and MRI examinations [21]. However, MRI is not readily available due to its higher cost. In our study, a preoperative MRI was not effective for making a preoperative diagnosis of adenomyosis. This may have stemmed from diversity of interpretations made by different radiologists.

Our study has some limitations. The first limitation was that this study was a retrospective study. Second, it only included women who underwent hysterectomy. Therefore, the study population cannot represent the population as a whole. However, the statistical power of our study was due to its large sample population. The third limitation was that only a limited number of patients underwent MRI examination. Thus, our study was unable to determine whether MRI is an effective diagnostic modality.

In conclusion, this study showed that adenomyosis is more frequent in women who are multiparous, have leiomyoma, and are normal body index. We also found that adenomyosis is more common in women with spontaneous fetal losses. Patients with unexplained recurrent fetal loss should be evaluated for the presence of adenomyosis. Future studies are needed on this subject.

**Conflict of interest** This notice is to document that there is no conflict of interest.

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