Focal adenomyosis is associated with primary infertility

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Objective: To study the association between adenomyosis and infertility, according to the adenomyosis phenotype as diagnosed by magnetic resonance imaging (MRI).

Design: A single-center, cross-sectional study.

Setting: University hospital-based research center.

Patient(s): Patients between 18 and 42 years of age who were surgically explored for benign gynecological conditions at our institution between May 2005 and May 2018. Only women with uterine MRIs performed by a senior radiologist were retained for this study.

Intervention(s): Primary and secondary infertile women were compared with women without infertility. In addition, the women were diagnosed according to the MRI findings as having adenomyosis (focal adenomyosis of the outer myometrium [FAOM] and/or diffuse adenomyosis phenotypes) or no adenomyosis.

Main Outcome Measure(s): Primary and secondary infertility-associated factors.

Result(s): A total of 496 women were included in the study population. Three groups were compared: a no infertility group (n = 361), a primary infertility group (n = 84), and a secondary infertility group (n = 51). Among them, 248 women did not present adenomyosis lesions and 248 women had a radiological diagnosis of adenomyosis. The presence of FAOM was significantly associated with primary infertility. Diffuse adenomyosis was not found to be associated with infertility. The distribution of endometriosis or leiomyomas was not significantly different between the groups. After a multinomial regression model including the women’s age and associated endome-triosis or leiomyoma, the presence of FAOM was identified as an independent associated factor of primary infertility (adjusted odds ratio 1.9; 95% confidence interval 1.1–3.3).

Conclusion(s): The presence of FAOM was associated with primary infertility. This study opens the door to future clinical and basic studies aimed at better characterization of FAOM and its infertility-related physiopathology. (Fertil Steril® 2020;:–. © 2020 by American Society for Reproductive Medicine.)

Key Words: Adenomyosis, infertility, MRI, focal adenomyosis, diffuse adenomyosis

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Uterine adenomyosis is a benign gynecological disease characterized by the presence of endometrial glands and stroma within the myometrium (1). Adenomyosis was previously only diagnosed retrospectively, based on histological analysis of uteri after hysterectomy. At present, the diagnosis of adenomyosis is based on magnetic resonance imaging (MRI) and transvaginal ultrasonography criteria (2–5), which has resulted in an increase in the prevalence of adenomyosis in the last few years, as demonstrated by the diagnosis in younger women of reproductive age (6–8).

Adenomyosis is a heterogeneous disease that is present in different configurations in the myometrium, notably with diffuse and/or focal lesions of internal or external layers of the myometrium. Several classifications have been proposed, none of which currently has a reference value (3, 8–10). One of them refers to a diffuse phenotype where numerous foci of endometrial glands and stroma are dispersed.
diffusely within the internal myometrium, and to a focal phenotype when circumscribed nodular aggregates are observed in the outer shell of the uterus, separated from the junctional zone (focal adenomyosis of the outer myometrium [FAOM]) (8). Several lines of evidence suggest that these two phenotypes could be considered to be distinct entities with different pathogeneses (8, 11–13). The clinical presentations of adenomyosis-affected women are also heterogeneous (3, 8, 14), specifically in terms of infertility, defined as at least 12 months of unprotected intercourse without achieving a pregnancy (15–17). Indeed, the prevalence of infertility, as well as the mechanisms implicated in the occurrence of infertility, in women with adenomyosis are far from being elucidated, based on the current literature (18, 19). Several pathophysiological hypotheses have been proposed, but no definitive conclusions have been reached (19–21). Controversial results have been found in studies assessing the impact of adenomyosis on assisted reproductive technologies outcomes, with some highlighting a negative impact of the disease and others showing no detrimental effect (22, 23). This heterogeneity of data in the actual literature may be partly explained by the fact that two distinct adenomyosis phenotypes (i.e., FAOM and diffuse) are not always considered separately, and they could be responsible for distinct fertility consequences. At present, the role of one or the other form in the physiopathology of adenomyosis-related infertility is still unknown.

Therefore, the aim of our study was to determine whether there is an association between the adenomyosis phenotypes (FAOM and/or diffuse forms), as diagnosed by MRI, and infertility.

**MATERIALS AND METHODS**

**Study Design and Population**

We performed a observational cross-sectional cohort study between May 2005 to May 2018 using data from a database, the structure of which has already been detailed and published elsewhere (8). Signed informed written consent was obtained from all of the included patients. The study protocol was approved by the ethics committee of our institution (Comité Consultatif de Protection des Personnes dans la Recherche Biomedicale de Paris-Cochin reference no. 05-2006). All of the data were fully anonymized before use.

The database consists of data from nonpregnant women between 18 and 42 years of age who underwent surgery for benign gynecological pathologies. The indications for surgery were benign gynecologic disease associated with infertility, defined as at least 12 months of unprotected intercourse not resulting in pregnancy (15, 17); pelvic pain, defined as the presence for at least 6 months of dysmenorrhea and/or intermenstrual pelvic pain and/or dyspareunia of moderate to severe intensity (24); a pelvic mass (e.g., a uterine myoma, benign ovarian cyst, etc.); and miscellaneous conditions, for example, uterine bleeding, a request for tubal ligation, and so on. Excluded from this population were women with cancer or infectious disease and/or those who refused to provide their consent for participation in the study.

For the purpose of this study, only women who had an MRI uterine evaluation during the preoperative workup and who were referred to experienced radiologists (A.-E.M. or C.B.) for image-based diagnosis of adenomyosis were retained. In this study, three groups were compared: two study groups of women who presented with infertility (primary or secondary infertility [25]) and a control group of women without a history of infertility.

**MRI Examination**

Magnetic resonance imaging is part of the preoperative assessment for patients included in the database. To diagnose adenomyosis based on MRI findings, three criteria were assessed on T2-weighted acquisitions (2, 26): the maximal junctional zone (JZmax) thickness corresponding to a low signal intensity band of myometrium lining the endometrium (27); the ratio JZmax and the myometrial thickness (ratio max) using the maximal thickness of the JZ and the corresponding thickness of the myometrium obtained at the same level of measurement; and the presence of high-intensity spots within the myometrium. Diffuse adenomyosis was defined by the association of the following two criteria (8): a JZmax of at least 12 mm; and a ratio max > 40%, as previously described. Focal adenomyosis was defined on T2-weighted images as a localized, ill-defined, low signal intensity mass, inhomogeneous circumscribed area located in the outer shell of the uterus, with indistinct margins separated from the JZ (8, 28), which remained intact and with preserved healthy muscular structures between the adenomyosis and the JZ (3). Lesion measurements (length * width) were provided systematically. The radiologists were informed that adenomyosis and/or endometriosis were suspected, but they were blinded to the results of the clinical findings and to the previous imaging examinations.

**Data Collection and Statistics**

For each patient, the data were recorded during face-to-face interviews conducted by the surgeon in the month before the surgery, using a structured previously published questionnaire (29). For the purpose of this study, the following data were collected: age, body mass index, smoking habits, obstetrical history, characteristics of the menstrual cycle and menstruation, existence of dysmenorrhea, existence and duration of infertility, and MRI examination.

All of the data were compiled into a digital database and analyzed using IBM SPSS Statistics software (version 23). \( P < .05 \) was considered statistically significant. For univariate statistical analysis, we used the following tests: Pearson’s \( \chi^2 \) test or Fisher’s exact test for the qualitative variables and a Mann–Whitney test or Kruskal–Wallis test for the quantitative variables, as appropriate.

A second analysis was then performed to identify associated factors of primary or secondary infertility with a multinomial logistic regression. Potential confounding factors found to be statistically significant at the threshold of \( P < .15 \) after univariable analysis were included in the logistic regression model. When two variables were highly correlated,
we introduced only one of them in the model and we sup-pressed the other, as was done for the presence of FAOM and the location of focal lesions (anterior or posterior), the latter having been suppressed. In case of significant differences, odds ratios and their 95% confidence intervals were calculated.

RESULTS

During the study period, 496 women were enrolled. The women were assigned to three groups according to their fertility status: 361 (72.8%) of the women did not have any infertility issue (the no infertility group), 84 (16.9%) had a primary infertility (the primary infertility group), and 51 (10.3%) had secondary infertility (the secondary infertility group).

The baseline characteristics of all included women are presented in Table 1. The mean age and standard deviation for the overall population was 31.5 ± 5.5 years. In the primary infertility group, significantly more women had at least an FAOM lesion compared with the no infertility or secondary infertility groups (42/84 [50%] vs. 111/361 [30.7%] and 17/51 [33.3%], respectively; P ≤ .01). The presence of diffuse adenomyosis was not significantly associated with the presence of primary or secondary infertility (101 women with diffuse adenomyosis/361 [28.0%] in the no infertility group, 21/84 [25.0%] in the primary infertility group, and 17/51 [33.3%] in the secondary infertility group; P = .58). In all of the women affected by adenomyosis (i.e., the women with focal, diffuse, or the association of both types of adenomyosis lesions; n = 248), the prevalence of infertility was 30.2% (75/248 patients), with 19.8% (49/248) for primary infertility and 10.5% for secondary infertility (26/248). The MRI characteristics are detailed in Table 2. No differences were found between the different study groups in terms of the presence of endometriosis or leiomyoma(s) (Table 2).

A multinomial logistic regression analysis was performed to adjust for confounding factors (Table 3). The women’s age, the presence of FAOM or diffuse adenomyosis, the presence of endometriosis, and the presence of leiomyoma(s) were included in the analysis. As shown in Table 3, after multivariable analysis, the presence of FAOM remained an independent associated factor of primary infertility (adjusted odds ratio 1.9; 95% confidence interval 1.1–3.3).

DISCUSSION

Main Findings

This cross-sectional study highlighted that, in a population of women younger than 42 years of age who underwent surgery for a benign gynecological disease, the focal adenomyosis of the outer myometrium phenotype was significantly associated with primary infertility. Conversely, diffuse adenomyosis did not appear to be associated with fertility status.

Strengths and Limitations

The strengths of this study are as follows: The selection of the study population was based on strict imaging criteria. All of the included women had undergone a pelvic MRI performed by two senior radiologists with a high level of expertise in gynecological imaging. The diagnosis of adenomyosis was based on strict and previously published MRI criteria, which

**TABLE 1**

Baseline characteristics of the patients (n = 496).

<table>
<thead>
<tr>
<th>Variable</th>
<th>No infertility (n = 361)</th>
<th>Primary infertility (n = 84)</th>
<th>Secondary infertility (n = 51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>31.2 ± 5.9</td>
<td>31.9 ± 4.2</td>
<td>32.5 ± 4.0</td>
<td>.179a</td>
</tr>
<tr>
<td>Age, y &lt; 30</td>
<td>31 (27/36)</td>
<td>32 (29/35)</td>
<td>33 (30/35)</td>
<td></td>
</tr>
<tr>
<td>Age, y 30–35</td>
<td>94 (26.0)</td>
<td>33 (39.3)</td>
<td>24 (47.1)</td>
<td>.003b</td>
</tr>
<tr>
<td>Age, y &gt; 35</td>
<td>119 (33.0)</td>
<td>26 (31.0)</td>
<td>17 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m² &lt; 20</td>
<td>106 (29.4)</td>
<td>27 (32.1)</td>
<td>6 (11.8)</td>
<td>.192b</td>
</tr>
<tr>
<td>Body mass index, kg/m² 20–24</td>
<td>191 (52.9)</td>
<td>41 (48.8)</td>
<td>31 (60.8)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m² ≥ 25</td>
<td>46 (12.7)</td>
<td>11 (13.1)</td>
<td>10 (19.6)</td>
<td></td>
</tr>
<tr>
<td>Body mass index, kg/m² ≥ 30</td>
<td>18 (5.0)</td>
<td>5 (6.0)</td>
<td>4 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Smoking habits</td>
<td></td>
<td></td>
<td></td>
<td>.620b</td>
</tr>
<tr>
<td>Never</td>
<td>221 (61.2)</td>
<td>48 (57.1)</td>
<td>32 (62.7)</td>
<td></td>
</tr>
<tr>
<td>Previous smoker</td>
<td>104 (28.8)</td>
<td>24 (28.6)</td>
<td>16 (31.4)</td>
<td></td>
</tr>
<tr>
<td>Actual smoker</td>
<td>36 (10.0)</td>
<td>12 (14.3)</td>
<td>3 (5.9)</td>
<td></td>
</tr>
<tr>
<td>Presence of dysmenorrhea</td>
<td></td>
<td></td>
<td></td>
<td>.610b</td>
</tr>
<tr>
<td>Primary</td>
<td>184 (51.0)</td>
<td>49 (58.3)</td>
<td>23 (45.1)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>135 (37.4)</td>
<td>28 (33.3)</td>
<td>22 (43.1)</td>
<td></td>
</tr>
<tr>
<td>Presence of menorrhagia</td>
<td>221 (61.2)</td>
<td>49 (58.3)</td>
<td>29 (56.9)</td>
<td>.773b</td>
</tr>
<tr>
<td>Irregular menstruation</td>
<td>65 (18.0)</td>
<td>15 (17.9)</td>
<td>8 (15.7)</td>
<td>.921b</td>
</tr>
<tr>
<td>Length of infertility, mo</td>
<td>37.0 ± 26.8</td>
<td>43.7 ± 40.0</td>
<td>26 (22.5–55.5)</td>
<td>.537c</td>
</tr>
</tbody>
</table>

Note: For continuous variables, data are reported as means ± standard deviation and medians (range 25/75); and for qualitative variables, the data are reported as n (%).

a Kruskal-Wallis test.

b χ² test.

c Mann-Whitney test.
is a widely accepted technique for diagnosing adenomyosis (2, 3, 8). Magnetic resonance imaging is a useful technique for diagnosing adenomyosis as it allows clinicians to diagnose the disease in women who are relatively young, compared with diagnoses based on histology of the uterus, which require a hysterectomy (30). During the preoperative workup, the radiologists were informed that a gynecological disease was suspected, but they were blinded to the results of the clinical findings and the previous imaging examinations. Many patients were enrolled (496 women). The clinical data were recorded using a structured questionnaire during face-to-face interviews.

Our study also has several limitations. The present study is limited to a certain degree by the cross-sectional nature of its design. This study retrospectively analyzed data that were collected at a single point in time, for each woman. This type of study is, however, a good way to determine the prevalence of and to identify associations between factors (31). The recruitment was performed at a single center. All of the included women required surgical intervention for a benign gynecological condition. They, therefore, do not represent an “ideal population,” and this may have decreased the external validity of the study, possibly resulting in the selection of a higher proportion of endometriosis-affected women. However, although this selection could have introduced a degree of bias, the proportion of endometriosis-affected women was not significantly different between the analyzed groups, and we performed a multinomial logistic regression to adjust on the endometriosis status. This demonstrated that FAOM remains an independent factor of primary infertility in our population. Finally, it cannot be excluded that other unexplored causes of infertility were present in the primary and secondary infertility groups, notably the presence of a male factor.

### Interpretation

Our study highlights that adenomyosis is an associated factor for infertility, in a population of reproductive-age women. We found that almost one-third of the adenomyosis population...
had reported infertility, and most of these patients exhibited FAOM. Using specific imaging tools, therefore, appears to be crucial to properly characterize the adenomyosis phenotype and to offer optimal management to infertile women. In our study, MRI was used to diagnose adenomyosis. Magnetic resonance imaging has the advantage of being more reproducible and reliable than pelvic ultrasound in cases of coexisting uterine pathologies (10). Nevertheless, pelvic ultrasound can also be considered to be a relevant tool for diagnosing adenomyosis, with the advantage of lower cost and easier access compared with MRI (6, 32).

Although associated endometriosis could be present in both focal and diffuse adenomyosis forms, the presence of the focal phenotype is more frequently associated with severe forms of endometriosis, especially deep infiltrating endometriosis lesions (3, 8). Indeed, in our population, there was associated endometriosis in 96.3% of the women with only focal adenomyosis lesions of the outer myometrium and in 61.5% of the women with only diffuse adenomyosis lesions. As endometriosis is a known risk factor of infertility (33), the role of each disease on patient infertility may be hard to disentangle. However, we showed that the FAOM form remained independently associated with primary infertility in a multivariable analysis that took the presence of endometriosis into account.

The prevalence of infertility in a population of adenomyosis-affected women (irrespective of the phenotype) is still insufficiently described in humans. In nonhuman primates, a clear association has already been suggested between adenomyosis and primary infertility (18). Indeed, in 37 baboons with histologically confirmed adenomyosis, the prevalence of primary infertility was significantly increased. This strong association was still significant after the exclusion of baboons exhibiting an association of adenomyosis and endometriosis (18). Our results, in addition to previous data, have confirmed the potential role of adenomyosis in primary infertility (14, 18).

In humans, Puente et al. determined that there was an approximately 25% incidence of adenomyosis in a population of infertile women screened by pelvic ultrasound (34). The number of adenomyosis features detected by ultrasound appears to correlate with the chances of pregnancy, thus confirming the negative influence of adenomyosis on reproduction (35). Although the tool for diagnosis was different, in keeping with previous findings, our results also highlight that adenomyosis is associated with infertility in a population of reproductive-age women. Moreover, we also demonstrated in our population that the presence of focal adenomyosis of the outer myometrium was associated with primary infertility. Our results raise the question of whether the diffuse and the focal form are two distinct forms of adenomyosis with specific pathogeneses. Their respective impact on the uterine environment for pregnancy remains an open question. This environment has been reported to potentially be nonconducive to embryo development in adenomyosis, thereby leading to impaired implantation (19, 36) and increased risk of early pregnancy loss (37, 38). Various mechanisms have been described, such as altered uterine contractility (19, 20), modified endometrial vascularization (39), abnormal levels of free radicals (40), an abnormal inflammation response (19, 41), or a dysregulated gene expression profile in eutopic endometrium (37, 42). The mechanisms involved could be dissimilar depending on whether the focal or the diffuse form of adenomyosis is involved. The exact process by which infertility occurs in case of FAOM remains to be elucidated.

CONCLUSION

Based on a population of reproductive-age women operated for a benign gynecological disease, our study demonstrated that focal adenomyosis of the outer myometrium, but not diffuse adenomyosis, was significantly associated with primary infertility. Further studies are needed to better characterize the pathophysiological mechanisms of adenomyosis-related infertility and the therapeutic options available for such patients.

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REFERENCES


