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Focal adenomyosis of the outer myometrium and deep infiltrating endometriosis severity

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47 Authors have nothing to disclose

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50

51 **CAPSULE**

52 The fact that focal adenomyosis is a marker for greater severity of deep infiltrating endometriosis is
53 of prime importance because it impacts the management strategy.

54 **ABSTRACT**

55 **Objective:** To determine whether the presence of focal adenomyosis of the outer myometrium
56 (FAOM) at preoperative magnetic resonance imaging is associated with the severity of deep
57 infiltrating endometriosis.

58 **Design:** An observational cross-sectional study involving 255 symptomatic deep infiltrating
59 endometriosis patients. Comparisons were performed according to the presence of FAOM.

60 **Setting:** A French university hospital

61 **Patients:** Women with a preoperative magnetic resonance imaging and complete surgical exeresis
62 of endometriotic lesions with histologically documented deep infiltrating endometriosis.

63 **Intervention(s):** Surgical management for deep infiltrating endometriosis.

64 **Main outcomes and measures:** The presence of multiple deep infiltrating endometriosis lesions,
65 the mean number and location of deep infiltrating endometriosis lesions, and the mean total revised
66 American Society for Reproductive Medicine scores.

67 **Results:** The prevalence of FAOM at the preoperative magnetic resonance imaging in the 255 deep
68 infiltrating endometriosis patients was 56.5%. The mean number of deep infiltrating endometriosis
69 lesions was significantly higher in the FAOM (+) group compared to the FAOM (-) group ($3.5 \pm$
70 2.1 vs. 2.2 ± 1.5 , $p < 0.01$). The mean total revised American Society for Reproductive Medicine
71 score was higher in case of FOAM coexisting with deep infiltrating endometriosis. After adjusting
72 for confounding factors, the presence of FAOM was significantly associated with multiple deep
73 lesions (aOR = 2.5, 95% CI [1.3 to 5.0]).

74 **CONCLUSION:** FAOM was significantly associated with greater deep infiltrating endometriosis
75 severity. This needs to be integrated into the management strategy. Furthermore, a pathogenic link
76 between deep infiltrating endometriosis and FAOM cannot be excluded.

77

78 **KEYWORDS:** Diffuse adenomyosis, focal adenomyosis, deep infiltrating endometriosis, magnetic
79 resonance imaging, complete surgery

80

81

82 **INTRODUCTION**

83 Adenomyosis and endometriosis are benign gynecological conditions that typically cause pain
84 and/or infertility (1, 2), thereby exerting a negative impact on the patients' quality of life (3).
85 Adenomyosis is a heterogeneous disease that manifests as different forms: diffuse adenomyosis,
86 focal adenomyosis of the outer myometrium (FAOM), and cystic adenomyoma (4, 5). However, the
87 focal form is not necessarily and exclusively of the outer myometrium. Indeed, the pathogenesis of
88 focal adenomyosis not associated with endometriosis and the pathogenesis of FAOM associated
89 with endometriosis may differ. (5) Endometriosis is also a heterogeneous disease, with three
90 phenotypes: superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA), and deep
91 infiltrating endometriosis (DIE) (6). Various endometriosis classifications are available such as the
92 revised American Society for Reproductive Medicine (rASRM) score and the Enzian classification
93 (7, 8).

94 Endometriosis and adenomyosis are defined by the presence of endometrial tissue outside the
95 uterine cavity (9) and within de myometrium (10), respectively. Although the pathogenesis of
96 endometriosis and adenomyosis are controversial, both are the consequence of ectopic location of
97 endometrial cells (11). Common molecular deregulated processes observed in these two pathologies
98 could explain their association. The abundance of publications on either adenomyosis or DIE
99 contrasts with the lack of studies of the association of these two pathologies (12). It has recently
100 become clear that adenomyosis can either arise on its own or coexist with endometriosis, and it is
101 now widely recognized that there is a strong clinical relationship between endometriosis and
102 adenomyosis according to their respective phenotypes (13-15). Additionally, a close histological
103 and biological relationship between extrinsic adenomyosis and DIE in 10 women with extrinsic
104 adenomyosis with coexisting DIE lesions has been reported (16).

105 Major advances in imaging now allow radiological diagnosis, according to strict well-defined
106 criteria, of adenomyosis (13, 17) and endometriosis (17). The aim of our work was to study the
107 relationship between FAOM diagnosed at preoperative magnetic resonance imaging (MRI) and the

108 characteristics of the associated DIE in a selected population of symptomatic operated patients with
109 histologically proven DIE.

110 **MATERIALS AND METHODS**

111

112 **Study design**

113 From January 2011 to December 2017, 255 consecutive women with FAOM and DIE were
114 assessed for surgical treatment at our tertiary referral centre (the Cochin Hospital, Paris, France).
115 Each woman was included only once in the data set. We performed an observational, cross-
116 sectional study using a prospective database. Data were collected from a previously published
117 structured questionnaire (18). The institutional review board of our institution (the Comité
118 Consultatif de Protection des Personnes dans la Recherche Biomédicale, n°2006/04) approved the
119 study protocol, and all of the included patients provided informed written signed consent.

120

121 **Patients**

122 The study population comprised a continuous series of nonpregnant women of less than 42 years of
123 age who had undergone complete surgical exeresis of symptomatic endometriosis for pain
124 refractory to medical treatment and/or infertility. The indications for surgery were (possibly more
125 than one per patient): (i) gynaecological symptoms including severe chronic pelvic pain, defined as
126 the presence of severe dysmenorrhoea and/or severe intermenstrual pelvic pain and/or severe
127 dyspareunia for at least 6 months (19); (ii) gastrointestinal symptoms including painful constipation,
128 rectal bleeding, and dyschezia, with or without menstrual exacerbation; (iii) perineal neuropathic
129 pain or sciatica; (iv) ureteral obstruction with ureterohydronephrosis, and (v) infertility defined as at
130 least 12 months of unprotected intercourse that failed to result in pregnancy (20). Women with
131 infectious diseases, chronic viral infections (e.g., hepatitis or HIV) or cancer, and/or those who
132 refused to provide their consent for participation in the study were not included in the cohort.

133

134 **Preoperative work-up**

135 All of the women had a preoperative pelvic MRI examination that allowed adenomyosis to be
136 diagnosed according to the diffuse or focalized phenotype. All of the pelvic MRI examinations were
137 performed preoperatively according to a standardized protocol, as previously described (13). Three
138 criteria were assessed on T2-weighted acquisitions for diagnoses of diffuse adenomyosis: (i) the
139 Maximal Junctional Zone (JZ_{\max}) thickness corresponding to a low signal intensity band of
140 myometrium lining the endometrium; (ii) the JZ_{\max} to myometrial thickness ratio (ratio_{\max}) using
141 the maximal thickness of the JZ and the corresponding thickness of the myometrium obtained at the
142 same level of measurement; (iii) the presence of high-intensity spots within the myometrium (21).
143 Diffuse adenomyosis was defined by the association of the two following criteria: (i) a JZ_{\max} of at
144 least 12 mm and (ii) a $\text{ratio}_{\max} > 40$ (13). By definition, focal adenomyosis was defined on T2-
145 weighted images as a localized, ill-defined, low signal intensity mass and dishomogeneous
146 circumscribed area in the outer shell of the myometrium, with indistinct margins, separated from
147 the junctional zone (22) associated with preserved healthy muscular structures between the
148 adenomyosis and the JZ, that refer exclusively to subtype II of the originally described Kishi's
149 classification (5). This type of lesion should be considered to be FAOM (13). The radiologist was
150 asked to thoroughly define the focal adenomyosis location within the myometrium on axial and
151 sagittal T2 planes (anterior or posterior wall of the uterus). The experienced radiologists (AEM and
152 CB), who are referring practitioners for image-based diagnosis of endometriosis, were informed
153 that endometriosis and/or adenomyosis were suspected but they were blinded to the results of the
154 clinical findings and previous imaging examinations (23).

155

156 **Operative technique**

157 Multidisciplinary meetings selected the women for whom complete surgery would be performed.
158 The surgical procedure, performed mainly by laparoscopy, started with a complete exploration of
159 the pelvis and abdominal cavity to assess the extent of endometriotic disease (i.e., stages and mean
160 scores: total, implants, and adhesions) according to the American Society for Reproductive

161 Medicine (ASRM) classification (24). The surgery consisted of complete surgical excision of the
162 endometriotic lesions. Perioperative care was assessed as previously described (25). All of the
163 women underwent complete surgical excision of their endometriosis lesions during the study period
164 at our institution.

165

166 **Pathological examination of the surgical specimens**

167 All of the women had histological confirmation of DIE. The endometriosis was considered to be
168 DIE when the muscularis (regardless of the location: bladder, intestine, or intrinsic ureter) was
169 infiltrated by endometriotic tissue after radical surgery (e.g., bowel resection, partial cystectomy, or
170 ureteral resection) (26). For other locations (i.e., uterosacral ligament(s) (USL), the extrinsic ureter,
171 or the vagina), DIE was arbitrarily defined as endometriotic tissue infiltrating beneath the
172 peritoneum surface by more than 5 mm (27). The DIE sites were classified as five different
173 locations: USL, the vagina, bladder, intestine, and ureter (26).

174

175 **Data and statistical analysis**

176 For each patient, the general data were recorded using a previously published structured
177 questionnaire (28) during the face-to-face interviews conducted by the surgeon in the month
178 preceding the surgery. The following data were collected: age (years), body mass index (BMI,
179 calculated as the body weight (kg) divided by the square of the height (m²)), geographical origin,
180 any tobacco use, a history of endometriosis among first-degree relatives, the mean age at menarche
181 (years), menorrhagia, menstrual cycle (always, often, or never regular), lifestyle habits (previous
182 use of an intrauterine device and/or oral contraceptive pills (OCP), obstetrical history (nulligravida,
183 nulliparity, or history of miscarriage), and history of surgery for endometriosis.

184 The clinical symptoms that were recorded included: the presence and the duration of infertility
185 (primary or secondary), the occurrence and the duration of pelvic pain, various symptoms during
186 adolescence (history of fainting spells, school absenteeism during menstruation). The intensity of

187 gynecological pelvic painful symptoms (dysmenorrhea, deep dyspareunia, non-cyclic chronic pelvic
188 pain), gastrointestinal symptoms (29), and urinary tract symptoms (30) were assessed using a 10-cm
189 visual analogue scale (VAS) (31). The intensity of each type of preoperative pain symptom was
190 rated as moderate (VAS < 7) or severe (VAS ≥ 7) (32).

191 The severity of the DIE was assessed based on the following parameters: (i) the mean number of
192 DIE lesions (2); (ii) the DIE surgical classification. In cases with multiple DIE lesions, the patients
193 were classified according to the worst finding, from least to most severe: USL, the vagina, bladder,
194 intestine, or ureter (33); (iii) the presence of an associated OMA: (34, 35) size (cm), unilateral or
195 bilateral nature, and side (right or left) in case of a unilateral cyst; (iv) during surgery, the extent of
196 endometriosis (pouch of Douglas involvement), stages, and mean scores (total, implants, adhesions)
197 were assessed according to the revised American Society for Reproductive Medicine (ASRM)
198 classification (24).

199 For analysis purposes, the DIE patients were allocated into two groups according to the MRI
200 findings: the FAOM (+) group (the study group) included patients with associated FAOM at the
201 preoperative MRI, and the FAOM (-) group (the control group) comprised those without associated
202 FAOM at the preoperative MRI. The continuous variables were reported as means and the standard
203 deviation. The qualitative and quantitative variables were compared using the Student's t-test.
204 Correlations between qualitative variables were studied using Pearson's chi-square test. A P-value
205 < 0.05 was considered statistically significant. The analysis started by comparison of the FAOM (+)
206 and the FAOM (-) groups in terms of their general demographic characteristics and the clinical
207 symptoms. We then tried to define whether a preoperative radiological diagnosis of FAOM could
208 help to preoperatively predict the characteristics of DIE. To determine whether the presence of
209 FAOM was associated with multiple DIE lesions, we performed a univariate analysis comparing the
210 general demographic characteristics and the clinical symptoms according to the presence of unique
211 or multiple DIE lesions, and we then created multivariate models. We conducted a multiple logistic
212 regression analysis to predict the severity of the DIE (using a presence of DIE lesions multiple

213 (n>1) or not (=1) as the variable of interest) according to the presence of radiological FAOM
214 adjusted on variables significantly associated to the severity of the DIE in the univariate analysis at
215 a threshold of 0.10. The adjusted odds ratios (aOR) and their 95% confidence intervals (95% CI9)
216 reflecting the association between our variable of interest, the presence of FAOM, and the presence
217 of multiple DIE lesions, were assessed through a multivariate logistic regression model.
218 Correlations between variables were tested, and if 2 variables were highly correlated, only one of
219 them was introduced in the model. Backward stepwise selection was used to retain variables with a
220 p-value of < 0.05 in each final model. The analysis was performed using Stata 11.0 software
221 (StataCorp, College Station, TX, USA).

222

223

224 RESULTS

225 The 255 patients of the study presented a total of 729 histologically proven DIE lesions. These
226 lesions were distributed as follows: 229 USL (31.4%) (105 unilateral - 48 right-side and 57 left-
227 side, 62 bilateral), 116 vaginal (15.9%), 45 bladder (6.2%), 319 intestinal (43.7%), and 20 ureteral
228 (2.7%) (16 unilateral - 4 right-side and 12 left-side, 2 bilateral). The mean number of DIE lesions
229 per patient was 2.9 ± 1.9 (range 1 to 11). The mean number of intestinal DIE lesions per patient was
230 1.3 ± 1.7 (range 0 to 10). Of these 255 DIE patients, 71 had a single DIE lesion (27.8%) whereas
231 multiple DIE lesions were observed in 184 patients (72.2%). Of the patients with intestinal lesions
232 ($n = 148$), 69 had a single intestinal lesion (46.6%), whereas multiple intestinal lesions were
233 observed in 79 patients (53.4%). The patient distribution according to the worst DIE classification
234 was as follows: USL(s) 19.2% ($n = 49$ patients), vagina 11.8% ($n = 30$ patients), bladder 8.2% ($n =$
235 21 patients), intestine 53.7% ($n = 137$ patients), and ureter 7.1% ($n = 18$ patients). Ninety-six DIE
236 patients ($n = 96$; 37.6%) had an associated OMA. The mean OMA size was 3.8 ± 2.3 cm (range 1 to
237 12). The OMA anatomical distribution was as follows: unilateral 69.8% ($n = 67/96$ patients; right-
238 side $n = 23$, left-side $n = 44$), and bilateral 30.2% ($n = 29/96$ patients).

239 For the entire study population ($n = 255$), the preoperative MRI findings were as follows: (i) the
240 mean junctional zone thickness was 8.4 ± 5.4 mm (range 1 to 36); (ii) the mean myometrium
241 thickness was 16.2 ± 4.7 mm (range 5 to 47); and (iii) the mean junctional zone/myometrium ratio
242 was 0.51 ± 0.33 (range 0.06 to 3.6). Diffuse adenomyosis was observed in 29.0% ($n = 74$ patients).
243 FAOM was observed in 56.5% of the patients ($n = 144$ patients: isolated anterior ($n = 19$), associated
244 posterior and anterior ($n = 6$), isolated posterior ($n = 119$)). The mean size of the posterior FAOM
245 was 15.6 ± 5.6 mm (range 2 to 34) and the mean size of the anterior FAOM was 18.8 ± 4.9 mm
246 (range 7 to 30).

247 The results of the comparison of the patient baseline characteristics between the FAOM (+) and the
248 FAOM (-) groups are detailed in Table 1. The patients were comparable except in terms of previous

249 surgeries for endometriosis ($p < 0.01$), and previous surgery for OMA ($p < 0.01$), which were
250 observed more frequently in the FAOM (+) group (Table 1). The results of the comparison of
251 infertility and pelvic pain are detailed in Table 2. The MRI diffuse adenomyosis characteristics
252 according to the presence or not of FAOM are presented in supplemental table 1. Associated diffuse
253 adenomyosis was observed significantly more frequently in the FAOM (+) group compared to the
254 FAOM (-) group ($n = 50/144$ (34.7%) vs. $n = 24/111$ (21.6%), respectively; $p = 0.02$) (Supplemental
255 table 1).

256 For the DIE lesions, the rate of multiple DIE lesions was significantly higher in the FAOM (+)
257 group compared to the FAOM (-) group ($n = 119/144$ (82.6%) vs. $n = 65/111$ (58.6%, respectively),
258 $p < 0.01$) and the mean total number of DIE lesions was significantly higher in the FAOM (+) group
259 compared to the FAOM (-) group (3.5 ± 2.1 vs. 2.2 ± 1.5 , respectively; $p < 0.01$). The FAOM (+)
260 patients exhibited significantly more associated OMAs than the FAOM (-) patients. The anatomical
261 distribution of the DIE lesions was more severe in the FAOM group with: (i) more frequent
262 intestinal involvement; (ii) a higher mean number of intestinal lesions; and (iii) more severe ASRM
263 classification parameters. Looking specifically at the patient surgical classification, bladder,
264 digestive, and ureter, DIE were observed significantly more frequently in the FAOM (+) group
265 compared to the FAOM (-) group (Table 34).

266 As we showed that the characteristics of DIE lesions with and without FAOM were statistically
267 different according to the factors previously described, we conducted a multiple logistic regression
268 analysis to predict the severity of DIE according to the presence of radiological FAOM, adjusted on
269 the following variables significantly associated to multiple DIE lesions in the univariate analysis:
270 tobacco use, menorrhagia, prior or current use of an intrauterine device, history of surgery for
271 endometriosis, infertility, painful symptoms duration > 5 years, VAS dysmenorrhea ≥ 7 , VAS non-
272 cyclic chronic pelvic pain ≥ 7 , VAS gastrointestinal symptoms ≥ 7 , VAS lower urinary tract
273 symptoms ≥ 7 , and the presence of endometrioma (Supplemental table 2). The presence of FAOM

274 was significantly and independently associated with multiple DIE lesions (aOR = 2.5, 95% CI [1.3
275 to 5.0]) (Supplemental table 3).

276

277 **DISCUSSION**

278

279 *Main Findings*

280 In this cross-sectional study of 255 women with histologically proven DIE, the rate of associated
281 FAOM diagnosed at the preoperative MRI was 56.5%. FAOM is associated with a greater DIE
282 severity because DIE women with FAOM are more likely to experience a longer duration of both
283 painful symptoms and infertility, as well as higher rates of a history of surgery for endometriosis or
284 OMA. Furthermore, coexisting FAOM and DIE was associated with more multifocal DIE locations,
285 more severe DIE lesions (intestine and/or ureter), more associated OMA, and higher ASRM scores.

286

287 *Strengths and Limitations*

288 The strength of this study stems largely from its methodological design: (i) DIE was histologically
289 proven for all of the patients; (ii) the clinical information was recorded prospectively through
290 structured questionnaires in face-to-face interviews for each patient in the month before the surgery,
291 and the data were compiled in a specific database managed by a clinical researcher with a low risk
292 of error; (iii) numerous parameters regarding sociodemographic variables, preoperative symptoms,
293 as well as medical and surgical histories were collected for each patient, allowing us to make
294 adjustments to limit confounding factors; (iv) during the preoperative imaging workup, the two
295 radiologists with extensive expertise in gynecological MRI (AEM and CB) were informed that
296 endometriosis and/or adenomyosis were suspected but they were blinded to the results of the
297 clinical findings and the previous imaging examinations; (v) stringent MRI criteria were used to
298 define FAOM (13), corresponding to the subtype II (extrinsic) according to the Kishi classification
299 (5); and (vi) to the best of our knowledge, this is the largest reported sample size involving
300 investigation of the association between DIE and FAOM (n = 255).

301 The main shortcoming of our study stems from the data interpretation. This monocentric study was
302 conducted in a tertiary referral center, and we may have recruited women with more severe forms of

303 DIE, which could well have affected the external validity of this study. Our study included women
304 experiencing pain who had surgically diagnosed endometriosis, while women with asymptomatic
305 endometriosis (36) were not considered in this work. Not all patients with FAOM undergo surgery.
306 This is, however, the only way to obtain a strict diagnosis based on histological findings, and the
307 population of interest is precisely those who are selected for surgery because of pain or infertility
308 (13). Our study only included women operated for DIE, and it was not designed to test whether
309 FAOM is a risk factor for DIE. However, when FAOM was present, there were multiple lesions in
310 more than 80%, and when absent, there were multiple lesions in nearly 60% of cases. While the
311 majority of women still had multiple lesions and required care in a center with high-level skills,
312 women with associated FOAM can be considered to have a greater severity of DIE than women
313 without FAOM. Another limitation relates to the lack of long-term post-operative follow-up to
314 assess whether there was a difference between the two groups, especially in terms of pain. There
315 was a statistically significant difference between the two groups regarding previous surgery for
316 endometriosis: this could represent a potential bias in the interpretation of the results. Indeed, a
317 history of surgery accelerates the development of endometriosis in mice (37), correlates with the
318 presence and severity of DIE,(38), and could increase the risk of endometriosis (39). Hence, we
319 cannot rule out an impact of surgery for endometriosis on a predisposition for the onset of FAOM.
320 Finally, the rASRM classification is one of the best known and widely used classification, easy to
321 use for clinicians, and patients can readily understand it (40). The ASRM classification nonetheless
322 suffers from a number of shortcomings. In particular, it provides limited information about deep
323 infiltrating endometriosis, and it correlates poorly with the extent of the endometriosis, without
324 considering pain and infertility. The main advantage of the Enzian classification over the rASRM is
325 the ability to provide a description of deep infiltrating endometriosis, retroperitoneal structures
326 (including adenomyosis), and other organs (7). In addition, the locations in the Enzian classification
327 correlate partially with the clinical symptoms, and the classification's severity grades correlate

328 substantially with the pain and dysmenorrhea (8). The fact that we did not use the Enzian
329 classification can be considered to be a limitation of our study.

330

331 Interpretation

332 In our previous study of the relationship between the presence of adenomyosis at preoperative
333 magnetic resonance imaging and the endometriosis phenotype in 292 patients, we observed that
334 FAOM occurred more often in endometriotic patients and it significantly correlated with the DIE
335 endometriosis phenotype. Moreover, diffuse adenomyosis was observed in one-third of the patients,
336 and diffuse and FAOM occurred in the same patient in 48 cases (16.4%) (5). The coexistence of
337 diffuse and focal adenomyosis is, therefore, not a rare occurrence. It remains unclear why
338 coexisting FAOM and DIE is associated with greater anatomical DIE severity. Refluxed ectopic
339 endometriotic cells have the potential to penetrate the pelvic retroperitoneum and colonize the
340 pelvic organs (27). Kishi et al. have already observed that posterior endometriosis and ovarian
341 endometriomas were significantly more frequent in women with FAOM (type II) compared to those
342 with subtypes I and III, which they labeled as “an extremely high coincidence” (5). We recently
343 showed that FAOM occurs more frequently in endometriotic patients and that it is significantly
344 correlated with the DIE endometriosis phenotype (13). This is in line with our recent report where
345 50% of the women with bladder DIE had focal adenomyosis of the anterior wall of the uterus (14).
346 Our present study supports the hypothesis that aggressive endometriotic lesions not only infiltrate
347 the bowel, the posterior vaginal wall, the ureters, and the bladder, but also the outer uterine wall.
348 The close association between FAOM and DIE could be a consequence of the same pathogenetic
349 pathways, partially shared, between these two entities. Such common molecular dysregulations are
350 numerous: immune system failures (41, 42), inflammation by PTGS2 (43, 44), neurogenesis by
351 neutrophilin (45, 46), vasculogenesis by VEGF (47, 48), epithelial-mesenchymal transition of
352 endometrial cells (49, 50), and oxidative stress pathway regulation by NrF2 (51, 52) or
353 ADAM17/Notch (53, 54). This supports the notion that pelvic endometriosis could be the

354 progenitor of this subtype of adenomyosis. If this is the case, these results give rise to the
355 pathophysiological question: is FAOM a DIE lesion of the myometrium? In other words, the
356 myometrial lesions could be simply named "endometriosis of the outer myometrium". When deep
357 endometriosis infiltrates the above pelvic organs, such as the bowel or the posterior vaginal wall,
358 we still refer to those lesions as "bowel endometriosis", not "bowel adenomyosis", "vaginal
359 endometriosis", or "vaginal adenomyosis". Of course, we do not speculate regarding what the
360 endometrial cells derived from menstrual fallopian reflux in the pelvic cavity indicate, but our
361 results are in line with Kishi et al. in the sense that posterior cul-de-sac endometriosis first creates
362 uterorectal adhesion (i.e., posterior cul-de-sac obliteration) and then invades posteriorly into the
363 rectum and/or anteriorly into the uterus, disrupting the uterine serosa to create subtype II
364 adenomyosis (5).

365 These results, confirming a link between the presence of adenomyosis and DIE, could represent an
366 important turning point in the diagnosis and treatment of these two diseases. The fact that FAOM
367 and DIE can coexist is of prime importance in daily practice. The presence of FAOM at the imaging
368 work-up seems to be an indication of the coexistence of extensive DIE. Imaging procedures are
369 now a suitable way to diagnose both endometriosis and adenomyosis (17, 55, 56), and they allow
370 exact mapping of the lesion without a need for laparoscopy (2). Surgery for severe DIE, with
371 multiple DIE locations (bladder, digestive, and ureteral), could be difficult with incomplete
372 procedures and entails a risk of severe complications (25, 57). Furthermore, as endometriosis can
373 recur after its surgical management (58), iterative procedures are more likely due to previous
374 unfinished surgeries (38, 57, 59). Hence, such patients should be informed of the expected benefits
375 and risks of a complete surgery strategy before they provide their informed consent, (60), and they
376 should be managed in a multidisciplinary center (38). Moreover, adenomyosis may independently
377 cause pain,(61, 62) infertility (63, 64), and bleeding (65). For these reasons, the coexistence of
378 adenomyosis and endometriosis must be part of the decision-making process for DIE patients, as
379 surgery of FAOM remains uncertain with potential severe uterine complications (66, 67). The

380 association of FOAM with DIE raises the question of whether to provide medical treatment first to
381 treat the pain and assisted reproductive technologies to treat infertility, even though surgery for DIE
382 has in fact been shown to improve reproductive outcomes (68). This is particularly relevant since in
383 our study the coexistence of FAOM and DIE was associated with more diffuse adenomyosis. In our
384 opinion, in such cases, surgery should ideally be considered only when the woman no longer wishes
385 to become pregnant, in which case surgical exeresis of all of the endometriotic lesions should be
386 associated with a concomitant hysterectomy (2).

387

388 **CONCLUSION**

389 Our study demonstrates that the coexistence of FAOM at the preoperative MRI and DIE is
390 associated with increased disease severity. Therefore, in daily practice, FAOM needs to be
391 integrated into the diagnostic strategy and in the medical decision making for the management of
392 DIE patients. Moreover, a pathogenic link between DIE and FAOM cannot be excluded.

393

394

395 **FIGURES LEGENDS**

396

397 **Figure 1.** Sagittal T2-weighted pelvic MRI. A) Bladder endometriosis in the posterior bladder wall
398 (black arrow); focal adenomyosis in the anterior uterine wall (red arrow). B) Low rectal
399 endometriosis (white arrow); focal adenomyosis in the posterior uterine wall (red arrow).

400

401

402 **TABLES**

403

404 **Table 1.** Comparison of the baseline characteristics of the 255 patients with DIE according to the
405 presence of FAOM at the preoperative MRI.

406

407 **Table 2.** Comparison of the clinical symptoms of the 255 patients with DIE according to the
408 presence of FAOM at the preoperative MRI.

409

410

411 **Table 3.** Comparison of the anatomical distribution of the histologically proven endometriosis
412 lesions in the 255 patients with DIE according to the presence of FAOM at the preoperative MRI.

413

414

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420

421 **DISCLOSURE OF INTERESTS**

422 No conflicts of interest

423

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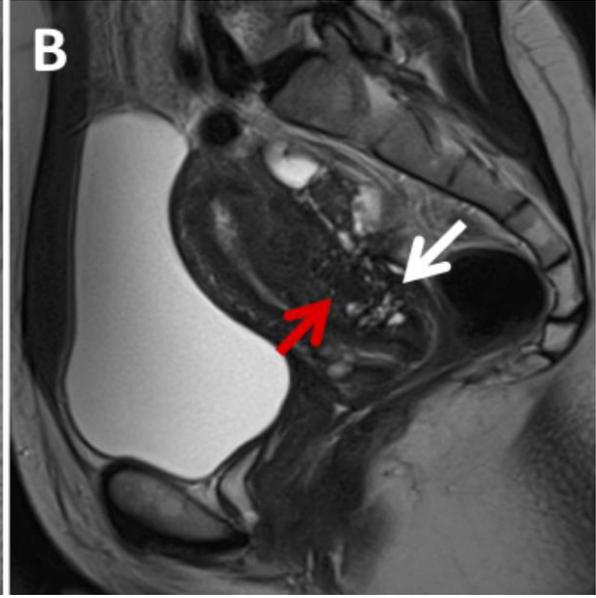
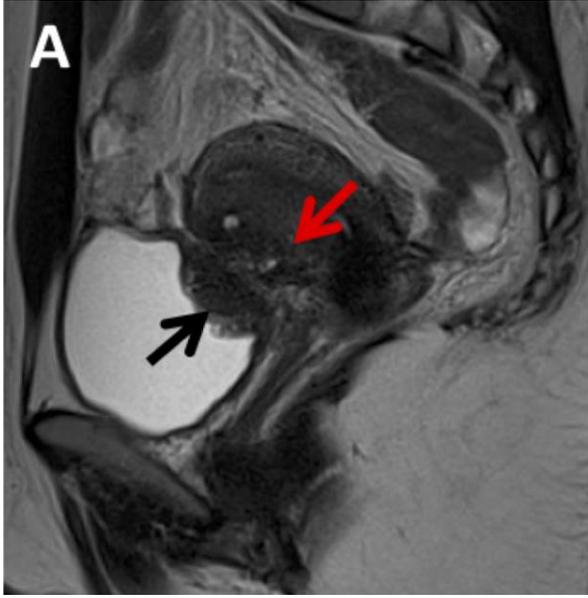


Table 1. Comparison of the baseline characteristics of the 255 patients with DIE according to the presence of FAOM at the preoperative MRI.

	Study group FAOM (+) (n = 144)	Control group FAOM (-) (n = 111)	p-value
Age (years) ^a	32.1 ± 4.5	31.3 ± 5.2	0.18
BMI (kg/m ²) ^a	22.6 ± 4.0	22.2 ± 3.3	0.12
Geographical origin, n (%)			
• <i>Caucasian</i>	110 (76.4)	96 (86.5)	0.20
• <i>Asian</i>	2 (1.4)	1 (0.9)	
• <i>African</i>	26 (18.1)	11 (9.9)	
• <i>Other</i>	6 (4.2)	3 (2.7)	
Prior or current tobacco use, n (%) [*]	56 (38.9)	45 (40.5)	0.79
History of endometriosis in a first-degree relative, n (%)	17 (11.8)	16 (14.4)	0.53
Mean age at menarche, y ^a	12.6 ± 1.4	12.7 ± 1.4	0.85
Regular menstrual cycle, n (%) [*]	107 (74.3)	92 (82.9)	0.18
Menorrhagia, n (%)	75 (52.1)	67 (60.4)	0.19
Mean length of menstruations ^a	5.4 ± 2.9	5.8 ± 2.5	0.18
OCPs treatment, n (%) [*]	107 (74.3)	92 (82.9)	0.20
• <i>Never</i>	7 (4.9)	2 (1.8)	
• <i>Prior or current use</i>	137 (95.1)	109 (97.2)	0.19
Intrauterine device, n (%)			
• <i>Never</i>	136 (94.4)	102 (91.9)	
• <i>Prior or current use</i>	8 (5.6)	9 (8.1)	0.42
Nulligravida, n (%)	102 (70.8)	71 (63.9)	0.24
Nulliparity, n (%)	119 (82.6)	82 (73.9)	0.08
History of miscarriage, n (%)	12 (8.3)	13 (11.7)	0.37
Previous surgery for endometriosis, n (%)	79 (54.8)	37 (33.3)	< 0.01
• n = 1	41/79 (51.9)	21/37 (56.8)	
• n ≥ 2	38/79 (48.1)	16/37 (43.2)	< 0.01
Previous surgery for OMA, n (%)	50 (34.7)	19 (17.1)	< 0.01
Previous uterine surgery, n (%)	17 (11.8)	8 (7.2)	0.22
• <i>Cesarean</i>	9/17 (52.9)	7/8 (87.5)	0.18
○ n = 1	7/9 (77.8)	5/7 (71.4)	
○ ≥ 2	2/9 (22.2)	2/7 (28.6)	
• <i>Myomectomy</i>	3/17 (17.6)	1/8 (12.5)	
• <i>Hysteroscopic surgery</i> ^b	5/17 (29.5)	0/8 (0)	
○ Polyps	3/5 (60%)		
○ Myoma	2/5 (40%)		

^a The data are presented as means ± the standard deviation

^b using a cutting loop to perform bipolar resection

^{*} Less than 2% missing data

DIE: deep infiltrating endometriosis, FAOM: focal adenomyosis of the outer myometrium, MRI: magnetic resonance imaging, BMI: body mass index, OCP: oral contraceptive pill, OMA: endometrioma, y: year, m: month

Table 2. Comparison of the clinical symptoms of the 255 patients with DIE according to the presence of FAOM at the preoperative MRI.

	Study group FAOM (+) (n = 144)	Control group FAOM (-) (n = 111)	p-value
Infertility, n (%)			
None	91 (63.2)	86 (77.5)	
Primary	40 (27.8)	15 (13.5)	
Secondary	13 (9.0)	10 (9.0)	0.02
Duration of infertility, m ^a	47.9 ± 28.1	37.6 ± 33.6	0.17
Duration of infertility > 5 years, n (%)	17 (11.8)	3 (2.7)	<0.01
Painful symptoms			
Pain, n (%)	136 (94.4)	105 (94.6)	0.95
Duration of pelvic pain, m	91.2 ± 82.9	62.2 ± 63.3	<0.01
Duration of pelvic pain > 5 years, n (%)	93 (64.6)	53 (47.8)	<0.01
Primary dysmenorrhea, n (%)	75 (52.1)	58 (52.2)	0.89
Secondary dysmenorrhea, n (%)	66 (45.8)	49 (44.1)	0.71
OCP administration for severe dysmenorrhea	42 (29.2)	35 (31.5)	0.62
School absenteeism, n (%)	62 (43.1)	49 (44.1)	0.86
Loss of consciousness during menses, n (%)	29 (20.1)	19 (17.2)	0.54
Painful symptoms mean VAS scores ^a			
• Dysmenorrhea	8.1 ± 1.8	7.7 ± 1.9	0.13
• Deep dyspareunia	5.1 ± 3.2	5.5 ± 5.3	0.48
• Non-cyclic chronic pelvic pain	3.5 ± 2.9	3.7 ± 2a.9	0.49
• Gastrointestinal symptoms ^b	5.8 ± 3.3	5.0 ± 3.3	0.05
• Lower urinary tract symptoms ^c	2.2 ± 3.3	2.2 ± 3.2	0.85
Severe painful symptoms (VAS ≥ 7), n (%)			
• Dysmenorrhea	121 (84.0)	90 (81.1)	0.53
• Deep dyspareunia	48 (33.3)	45 (40.5)	0.23
• Non-cyclic chronic pelvic pain	23 (16.0)	21 (18.9)	0.53
• Gastrointestinal symptoms	73 (50.7)	45 (40.6)	0.10
• Lower urinary tract symptoms	22 (15.3)	19 (17.1)	0.70

* Including multiple histories of surgery for endometriosis, duration of infertility ≥ 5 years, duration of pain ≥ 5 years, primary dysmenorrhea, OCP administration for severe dysmenorrhea, school absenteeism, and loss of consciousness during menses.

DIE: deep infiltrating endometriosis, VAS: visual analog scale; OCP: oral contraceptive pill

^aThe data are presented as means ± the standard deviation.

^bDyschezia, painful constipation, rectal bleeding

^cSuprapubic pain, hematuria, urinary tract infection

Table 4. Comparison of the anatomical distribution of the histologically proven endometriosis lesions in the 255 patients with DIE according to the presence of FAOM at the preoperative MRI.

	Study group FAOM (+) (n = 144)	Control group FAOM (-) (n = 111)	p-value
Presence of Endometrioma, n (%)	69 (47.9)	27 (24.3)	<0.01
• <i>Bilateral</i>	26/69 (37.7)	3/27 (11.1)	
• <i>Unilateral</i>	43/69 (62.3)	24/27 (88.9)	0.01
○ <i>Right</i>	14/69 (20.3)	9/27 (33.3)	
○ <i>Left</i>	29/69 (42.0)	15/27 (55.6)	0.03
• Mean OMA size	3.6 ± 2.3	4.3 ± 2.6	0.21
○ <i>Right</i>	3.4 ± 2.2	4.4 ± 3.3	0.23
○ <i>Left</i>	3.8 ± 1.8	4.3 ± 2.1	0.33
Deep infiltrative endometriosis			
• Mean total number of DIE lesions ^a	3.5 ± 2.1	2.2 ± 1.5	<0.01
• Number of lesions, n (%)			
○ <i>n = 1</i>	25 (17.4)	46 (41.4)	
○ <i>n ≥ 2</i>	119 (82.6)	65 (58.5)	<0.01
• Location, n (%)			
○ <i>USL</i>	85 (59.0)	82 (73.8)	0.01
▪ <i>Bilateral</i>	42/85 (49.4)	20/82 (24.4)	
▪ <i>Unilateral</i>	43/85 (50.6)	62/82 (75.6)	<0.01
• <i>Right</i>	21/85 (24.7)	27/82 (32.9)	
• <i>Left</i>	22/85 (25.9)	35/82 (42.7)	
○ <i>Vagina</i>	73 (50.7)	43 (38.7)	0.05
○ <i>Bladder</i>	37 (25.7)	7 (6.3)	<0.01
○ <i>Intestine DIE lesion</i>	104 (72.2)	44 (39.6)	<0.01
▪ <i>Mean total number of intestinal lesions ^a</i>	1.9 ± 1.8	0.9 ± 1.4	<0.01
▪ <i>Number of lesions</i>			
• <i>n = 1</i>	41/104 (39.4)	28/44 (63.6)	
• <i>n ≥ 2</i>	63/104 (60.6)	16/44 (36.4)	<0.01
○ <i>Ureter</i>	12 (8.3)	6 (5.4)	0.27
▪ <i>Bilateral</i>	2/12 (16.7)	0	
▪ <i>Unilateral</i>	10/10 (83.3)	6/6 (100)	0.28
• <i>Right</i>	2/10 (20.0)	2/6 (33.3)	
• <i>Left</i>	8/12 (80.0)	4/6 (66.7)	0.55
DIE surgical classification, n (%) ^b			
• <i>USL</i>	9 (6.3)	40 (36.0)	
• <i>Vagina</i>	11 (7.6)	19 (17.1)	
• <i>Bladder</i>	17 (11.8)	4 (3.6)	
• <i>Intestine</i>	95 (66.0)	42 (37.8)	
• <i>Ureter</i>	12 (8.3)	6 (5.5)	<0.01
ASRM score			
• Mean total ASRM score ^{a,c}	54.6 ± 3.2	35.5 ± 26.2	<0.01
• Mean implant ASRM score ^{a,c}	17.9 ± 15.0	9.9 ± 8.9	<0.01
• Mean adhesions ASRM score ^{a,c}	36.7 ± 27.7	15.6 ± 20.9	<0.01
• ASRM stage III/IV n, (%) ^b	112 (77.8)	45 (40.5)	<0.01
Pouch of Douglas involvement, n (%)			
• <i>Partial</i>	47/117 (40.2)	37/56 (66.1)	<0.01
• <i>Total</i>	70/117 (59.8)	19/56 (33.9)	<0.01

^a The data reported as means \pm the standard deviation.

^b According to surgical classification for DIE (Chapron et al., 2006).

^c Score according to the American Society for Reproductive Medicine classification (ASRM, 1997).

^d Sometimes more than one for the same patient.

MRI: magnetic resonance imaging, FAOM: focal adenomyosis of the outer myometrium, OMA: endometrioma; DIE: deep infiltrating endometriosis, USL: uterosacral ligaments, ASRM: American Society for Reproductive Medicine classification.