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Relationship between the magnetic resonance imaging appearance of adenomyosis and endometriosis phenotypes

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STUDY QUESTION: What is the relationship between endometriosis phenotypes superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA), deep infiltrating endometriosis (DIE) and the adenomyosis appearance by magnetic resonance imaging (MRI)?

SUMMARY ANSWER: Focal adenomyosis located in the outer myometrium (FAOM) was observed more frequently in women with endometriosis, and was significantly associated with the DIE phenotype.

WHAT IS KNOWN ALREADY: An association between endometriosis and adenomyosis has been reported previously, although data regarding the association between MRI appearance of adenomyosis and the endometriosis phenotype are currently still lacking.

STUDY DESIGN, SIZE, DURATION: This was an observational, cross-sectional study using data prospectively collected from non-pregnant patients who were between 18 and 42 years of age, and who underwent surgery for symptomatic benign gynecological conditions between January 2011 and December 2014. For each patient, a standardized questionnaire was completed during a face-to-face interview conducted by the surgeon during the month preceding the surgery. Only women with preoperative standardized uterine MRIs were retained for this study.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Surgery was performed on 292 patients with signed consent and available preoperative MRIs. After a thorough surgical examination of the abdomino-pelvic cavity, 237 women with histologically proven endometriosis were allocated to the endometriosis group and 55 symptomatic women without evidence of endometriosis to the endometriosis free group. The existence of diffuse or FAOM was studied in both groups and according to surgical endometriosis phenotypes (SUP, OMA and DIE).

MAIN RESULTS AND THE ROLE OF CHANCE: Adenomyosis was observed in 59.9% ($n = 175$) of the total sample population ($n = 292$). Based on MRI, the distribution of adenomyosis was as follows: isolated diffuse adenomyosis (53 patients; 18.2%), isolated FAOM (74 patients; 25.3%), associated diffuse and FAOM (48 patients; 16.4%). Diffuse adenomyosis (isolated and associated to FAOM) was observed in one-third of the patients regardless of whether they were endometriotic patients or endometriosis free women taken as controls (34.2% (81 cases) versus 36.4% (20 cases)); $P = 0.764$. Among endometriotic women, diffuse adenomyosis (isolated and associated to FAOM) failed

to reach significant correlation with the endometriosis phenotypes (SUP, 20.0% (8 cases); OMA, 45.2% (14 cases) and DIE, 35.5% (59 cases); $P = 0.068$). In striking contrast, there was a significant increase in the frequency of FAOM in endometriosis-affected women than in controls (119 cases (50.2%) versus 5.4% (3 cases); $P < 0.001$). FAOM correlated with the endometriosis phenotypes, significantly with DIE (SUP, 7.5% (3 cases); OMA, 19.3% (6 cases) and DIE, 66.3% (110 cases); $P < 0.001$).

LIMITATIONS, REASONS FOR CAUTION: There was a possible selection bias due to the specificity of the study design, as it only included surgical patients in a referral center that specializes in endometriosis surgery. Therefore, women referred to our center may have suffered from particularly severe forms of endometriosis. This could explain the high number of women with DIE (166/237–70%) in our study group. This referral bias for women with severe lesions may have amplified the difference in association of FAOM with the endometriosis-affected patients compared to women without endometriosis. Furthermore, according to inclusion criteria, women in the endometriosis free group were symptomatic women. This may introduce some bias as symptomatic women may be more prone to have associated adenomyosis that in turn could have been overrepresented in the endometriosis free group. Whether this selection could have introduced a bias in the relationship between endometriosis and adenomyosis remains unknown.

WIDER IMPLICATIONS OF THE FINDINGS: This study opens the door to future epidemiological, clinical and mechanistic studies aimed at better characterizing diffuse and focal adenomyosis. Further studies are necessary to adequately determine if diffuse and focal adenomyosis are two separate entities that differ in terms of pathogenesis.

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Key words: adenomyosis / diffuse adenomyosis / focal adenomyosis / endometriosis phenotype / magnetic resonance imaging

Introduction

Endometriosis is defined as the development of ectopic endometrium-like tissue outside of the uterine cavity (Sampson, 1927). In terms of clinical appearance, there are three endometriosis phenotypes: (Tosti *et al.*, 2015) superficial peritoneal endometriosis (SUP), ovarian endometrioma (OMA) and deep infiltrating endometriosis (DIE).

Adenomyosis is a neglected enigmatic (Benagiano *et al.*, 2012), benign gynecologic disease characterized by infiltration of endometrial tissues (endometrial glands and stroma) into the myometrium that causes myometrial inflammation and hypertrophy (Bird *et al.*, 1972; Siegler and Camilien, 1994). The disease leads to pain (Parker *et al.*, 2006; Guo *et al.*, 2013), infertility (Vercellini *et al.*, 2014) and uterine bleeding (Naftalin *et al.*, 2014) with a consequent negative impact on patient quality of life (Ekin *et al.*, 2013; Iacovides *et al.*, 2015). Adenomyosis is a heterogeneous disease that may present in different configuration in the myometrium: diffuse, focal and rare cases of cystic adenomyoma (Bergeron *et al.*, 2006; Gordts *et al.*, 2008; Kishi *et al.*, 2012). Adenomyosis must be considered as diffuse when numerous foci of endometrial glands and stroma are dispersed diffusely within the myometrium and focal when circumscribed nodular aggregates are observed (Van den Bosch *et al.*, 2015). Cystic adenomyoma is a rare variation of focal adenomyosis with additional compensatory hypertrophy of the surrounding myometrium (Van den Bosch *et al.*, 2015). There is a tight relationship between endometriosis and adenomyosis (Kunz *et al.*, 2005; Leyendecker *et al.*, 2015; Yasui *et al.*, 2015). In some studies (Kunz *et al.*, 2005; Larsen *et al.*, 2011), this relationship was assessed as a function of the severity of the endometriosis according to the revised American Society for Reproductive Medicine classification (rAFS) (rAFS, 1997).

The aim of our study was to investigate the relationship between endometriosis phenotypes (SUP, OMA and DIE) and magnetic resonance imaging (MRI) appearance of adenomyosis.

Materials and Methods

Ethical approval

The local ethics committee (CCPPRB: Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of our institution approved the study protocol and all of the included patients provided a signed informed consent form.

Patients

We performed a prospective observational study evaluating symptomatic women younger than 42 years of age who were undergoing surgery for benign gynecological pathologies. Indications for surgery (possibly more than one per patient) included: (i) infertility: defined as at least 12 months of unprotected intercourse not resulting in pregnancy (Marcoux *et al.*, 1997); (ii) 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 (Fedele *et al.*, 2005); (iii) a pelvic mass (e.g. uterine myomas, benign ovarian cysts, etc.); (iv) miscellaneous: e.g. uterine bleeding, request for tubal ligation, infection etc. Excluded from this population were the following: (i) patients who had undergone surgery for cancer; (ii) pregnant patients (i.e. ectopic pregnancies); (iii) endometriotic patients for whom surgical exeresis was considered as being incomplete by the surgeon (Lafay Pillet *et al.*, 2014; Sibiude *et al.*, 2014). All women underwent preoperative MRI.

For the purpose of this study, patients retained for analysis were divided into two groups: Group A (the endometriosis group) included women with histologically proven endometriosis, and Group B (the endometriosis free group) included patients without any visual endometriotic lesions as determined during the surgical procedure. Patients who were visually diagnosed as having endometriosis but lacking histological confirmation were excluded from the study (Chapron *et al.*, 2010). Histologically proven endometriotic lesions were classified into three phenotypes: SUP, OMA and DIE, as previously described (Chapron *et al.*, 2010a,b, 2011). Since the three types of endometriotic lesions (SUP, OMA and DIE), can be associated, patients were classified according to their most severe lesion. By

definition, endometriosis phenotypes were ranked from least to most severe as follows; SUP, OMA and DIE (Chapron et al., 2011).

For each patient, data were recorded during face-to-face interviews conducted by the surgeon in the month preceding the surgery, using a structured previously published questionnaire (Chapron et al., 2010a,b). For each painful symptom, the intensity was assessed using a 10-cm visual analog scale (VAS) (Peveler et al., 1996). When present during surgery, the extent of the endometriosis (e.g. stages and mean scores: total, implants and adhesions) were assessed according to the revised American Fertility Society (rAFS) classification of endometriosis (rAFS, 1997).

MRI examination

All pelvic MRI examinations were performed on a 1.5 T MRI machine (Sonata, Siemens; Erlangen, Germany). The patients were placed in a phased-array coil in a supine position. All sequences were performed with saturation bands placed anteriorly and posteriorly to eliminate artifacts from the high subcutaneous fat signal. The patients fasted for 3 h and received a bowel preparation (Microlax®: sorbitol, citrate and sodium lauryl sulfoacetate) 12 h prior to the MRI. No antiperistaltic drugs were administered. The acquisition protocols were acquired with 5 mm thick-section and a 1 mm gap, a rectangular field of view of 270×270 mm and a matrix of 320×320 pixels. The protocol always included sagittal and transverse fast spin-echo T2-weighted MR imaging, transverse gradient-echo T1-weighted MR imaging, with and without fat suppression. The fast spin-echo T2-weighted sequence was performed with the following imaging parameters: repetition time ms/echo time ms, 4000/120 (effective); echo train length, 35; and the number of signals acquired was two. T1-weighted spin-echo sequences were performed with 322/4.8 and one signal was acquired. MRI results were interpreted by a single radiologist (A-.E.M.), with expertise in gynecological MRI (10 years of referral practice and a mean of 1000 scans/year).

Three criteria were assessed on T2-weighted acquisitions (Bazot et al., 2001): (i) Maximal Junctional Zone (JZ_{max}) thickness corresponding to a low signal intensity band of myometrium lining the endometrium (Novellas et al., 2011); (ii) JZ_{max} to myometrial thickness ratio ($ratio_{max}$) using the maximal thickness of the JZ and the corresponding thickness of the myometrium obtained at the same level of measurement; (iii) the presence of high-intensity spots within the myometrium. In this study, diffuse adenomyosis was defined by the association of the two following criteria: (i) JZ_{max} of at least 12 mm (Reinhold et al., 1996; Bazot et al., 2001; Kunz et al., 2005) and (ii) $ratio_{max} > 40\%$ (Bazot et al., 2001).

Concerning focal adenomyosis, the radiologist was asked to thoroughly define the foci location within the myometrium on axial and sagittal T2 planes. The size of the lesion (length $\times$ width) was provided systematically. Three subtypes of focal adenomyosis according to the foci location in the outer, middle and inner myometrium were previously described (Gordts et al., 2008; Kishi et al., 2012). By definition, in this study, we consider as focal adenomysosis only adenomyotic foci located in the outer shell of the uterus, separated from the JZ (Arnold et al., 1995), which was kept intact and with preserved healthy muscular structures between the adenomyosis and the JZ (Kishi et al., 2012). In this study, focal adenomyosis correspond to the sub-type II (extrinsic) according to the Kishi' Classification (Kishi et al., 2012) and must be considered as focal adenomyosis located in the outer myometrium (FAOM) (Fig. 1).

The radiologist (A-.E.M.) was informed that endometriosis and/or adenomyosis were suspected, but was blinded to the results of the clinical findings and previous imaging examinations (Piketty et al., 2009).

Statistical analyses

Data were presented as the mean $\pm$ SD or as the number (percent) for continuous and categorical variables, respectively. We compared the prevalence of adenomyosis in the Group A (the endometriosis group) and in the Group B (the endometriosis free group), taking into account the endometriosis phenotypes (SUP, OMA or DIE). Between-group comparisons were performed using the Pearson's Chi^2 or Fisher's exact tests for categorical variables and the Student's t-test for numerical variables. A P-value of 0.05 was considered as statistically significant. The statistical analyses were performed using SPSS software version 15.0 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, 292 patients were enrolled. Group A (the endometriosis group) included 237 women (81.2%) with histologically proven endometriosis upon surgery, and Group B (the endometriosis free group) included 55 patients (18.8%) without any visual endometriotic lesions at the time of surgery. Indications for surgery in the endometriosis free group, which were sometimes more than one for the same patient, were the following: benign ovarian cyst (6 cases; 10.9%), uterine myomas (26 cases; 18.2%), pelvic pain (16 cases; 29.1%), tubal infertility (4 cases; 7.3%) and others (3 cases; 5.4%). The patient distribution according to their most severe endometriotic lesion was as follows: SUP (40 patients; 16.9%), OMA (31 patients, 13.1%) and DIE (166 patients; 70.0%). Among the DIE patients, 66 (39.8%) were also diagnosed with an associated OMA for a total 97 endometriotic patients (40.9%) with OMA (right 21, left 46 and bilateral 30). For DIE patients ($n = 166$), the distribution according to the main DIE location was as follows: uterosacral ligament(s) (USL) (16 patients; 9.6%), vagina (10 patients; 6.0%), bladder (12 patients; 7.3%), intestine (112 patients; 67.5%) and ureter (16 patients; 9.6%). Taking into account the bilaterality of certain DIE lesions (USL, ureter) and the multifocality of intestinal DIE, 546 histologically proven DIE lesions were observed after complete surgical exeresis. Thus, the anatomical distribution of the DIE lesions was as follows: USL (146 DIE lesions), vagina (88 DIE lesions), bladder (31 DIE lesions), intestine (261 DIE lesions) and ureter (20 DIE lesions). The patients' baseline characteristics are detailed in Table I.

The MRI adenomyosis appearance distribution was detailed in the Table II. In the total sample population ($n = 292$), adenomyosis was observed in 59.9% ($n = 175$). Diffuse and FAOM can occur in the same patient (48 cases) (Fig. 1 and Table II). The mean size of the FAOM nodule was 15.9 ± 5.2 mm (range 5–34 mm). Diffuse adenomyosis was observed in one-third of the patients whether they were endometriotic patients or endometriosis free women (34.2% (81 cases) versus 36.4% (20 cases) respectively; $P = 0.764$). For endometriotic patients ($n = 237$), diffuse adenomyosis (isolated and associated to FAOM) failed to reach significant correlation with the endometriosis phenotypes (Table II). Diffuse adenomyosis was observed more frequently in women with DIE or OMA than in women with SUP (37.0% (73/197) and 20.0% (8/40), respectively, $P = 0.032$). These relationships between diffuse adenomyosis and endometriosis were observed irrespective of the MRI criteria for severity that were used to define diffuse adenomyosis ($JZ_{max} \geq 12$ or ≥ 15 mm; JZ_{max} and/or $ratio_{max}$) (Supplementary data, Table S1). FAOM was observed significantly more frequently in the endometriosis group than in the endometriosis free group (119 cases (50.2%) versus 5.4% (3 cases); $P < 0.001$). For endometriotic patients ($n = 237$), FAOM correlated with the endometriosis phenotypes ($P < 0.001$) (Table II).
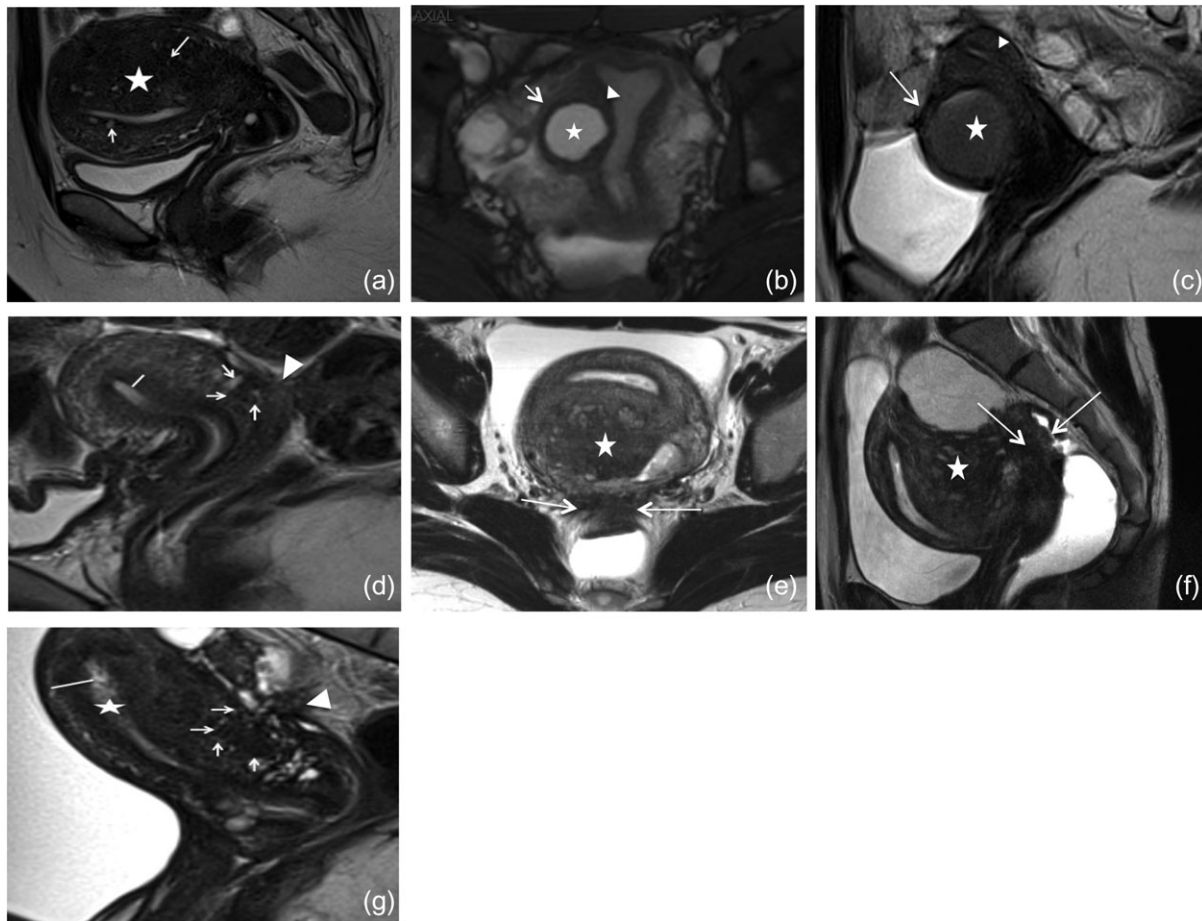
Figure 1 MRI for diffuse and/or focal adenomyosis. (**a**) MRI with Isolated diffuse adenomyosis (a 34-year-old woman). MRI sagittal T2-weighted section with an overall enlargement of the uterus, with an asymmetric wall of the myometrium, significant thickening of the JZ (white star), with numerous hyper T2 foci (white arrows), predominantly in the posterior myometrium, suggesting asymmetric diffuse adenomyosis; (**b** and **c**) MRI with isolated focal adenomyoma (sub-type III Kishi). MRI coronal T2-weighted (b) and sagittal T2-weighted (c) image of intramural adenomyosis. The focal adenomyosis (white star) is located in the right lateral edge of the uterus. Intact myometrium surrounds the lesion. The JZ (white arrowhead) and the serosa (white arrow) are preserved. (**d**) MRI with isolated FAOM (sub-type II Kishi) (Kishi *et al.*, 2012) (a 31-year-old woman). MRI sagittal T2-weighted image reveals a focal hypointense focused area in the posterior wall of the myometrium (white arrows) exhibiting focal adenomyosis located in the outer myometrium without any diffuse adenomyosis (thin Junctional Zona (white line), and no hyperintense T2 foci). The intermediate intensity reaching at least up to the fundal part of the uterine cavity, corresponds to a partial volume on the endometrium. The lesion is contiguous to a deep infiltrating lesion (white arrowhead). (**e** and **f**) MRI with isolated posterior FAOM (sub-type II Kishi) (Kishi *et al.*, 2012) (a 34-year-old woman). MRI Axial T2-weighted (e) and sagittal T2-weighted (f) image demonstrates focal hypointense focused area, located in the posterior wall of the myometrium (white star). The lesion is contiguous to a deep infiltrating bowel lesion (white arrow). (**g**) MRI with associated diffuse and FAOM (sub-type II Kishi) (Kishi *et al.*, 2012) (a 32-year-old woman). MRI sagittal T2-weighted image through the mid portion of the uterus reveals focalized posterior adenomyosis (FAOM) (white arrows) with hyperintense focal signals. Diffuse adenomyosis added as a thickening of the JZ (black area highlighted by the white line) anterior and posterior to the hyperintense normal appearing endometrium (white star). FOAM is contiguous to a deep infiltrating lesion (white arrowhead). JZ, junctional zone; MRI, magnetic resonance imaging; FAOM, focal adenomyosis located in the outer myometrium.

Discussion

This prospective study demonstrates that, in a population of symptomatic women younger than 42 years of age, FAOM was more frequently observed in women with endometriosis than in endometriosis free women taken as controls, and was significantly associated with a DIE endometriosis phenotype. Diffuse adenomyosis is observed in one-third of the patients whether they were endometriotic patients or not. Diffuse adenomyosis failed to reach significant correlation with the endometriosis phenotypes (SUP, OMA or DIE).

The strength of this study is based on the following aspects: (i) the selection of the study population was based on strict surgical and histological criteria. Women allocated to endometriosis free group were surgically explored and presented no visual endometriosis lesions. Women in the endometriosis group had histologically proven

Table I Patient baseline characteristics.

Medical history

	Endometriosis (n = 237)	Endometriosis free (n = 55)	P-value
Age (years)	31.2 ± 5.3	32.9 ± 6.2	0.050
Birth weight (g)	3240 ± 481.4	3118 ± 484.3	0.165
Weight (kg)	62 ± 11.1	64 ± 15.7	0.343
Height (cm)	166.1 ± 6.2	165.8 ± 5.8	0.747
Body Mass Index (m^2/kg)	22.5 ± 3.8	23.3 ± 5.2	0.278
Age at menarche (years)	12.7 ± 1.5	12.8 ± 1.9	0.509
Family history of endometriosis (n, %)	35 (14.9)	4 (7.3)	0.136
Previous endometriosis surgery (n, %)	103 (43.5)	n.a	
Previous surgery for endometrioma (n, %)	59 (25.2)	n.a	
Previous uterine surgery (n, %)	24 (10.2)	8 (14.5)	0.356
Gravidity	0.6 ± 1.3	0.8 ± 0.9	0.339
Parity	0.3 ± 0.7	0.6 ± 0.9	0.038
Gravidity (n, %)			0.015
0	157 (66.2)	25 (45.5)	
1	50 (21.1)	20 (36.4)	
2 and more	30 (12.7)	10 (18.2)	
Parity (n, %)			0.008
0	187 (78.9)	33 (60.0)	
1	31 (13.1)	16 (29.1)	
2 and more	19 (8.0)	6 (10.9)	
Miscarriage (n, %)	24/80 (30.0)	6/30 (20.0)	0.294
Regular menstrual cycle (n, %)			0.837
Always regular	185 (78.1)	41 (74.5)	
Often regular	3 (1.3)	1 (1.8)	
Never regular	49 (20.7)	13 (23.6)	
OCs treatment (n, %)			0.015
Never	17 (7.2)	11 (20.0)	
Current user	164 (69.5)	33 (60.0)	
Previous user	55 (23.3)	11 (20.0)	
Intrauterine device (n, %)			0.047
Never	216 (91.5)	45 (81.8)	
Current user	10 (4.2)	7 (12.7)	
Previous user	10 (4.2)	3 (5.5)	
Dysmenorrhea (n, %)			<0.001
No dysmenorrhea	15 (6.3)	16 (29.1)	
Primary	129 (54.4)	26 (47.3)	
Secondary	93 (39.2)	13 (23.6)	

Continued

Table I *Continued*

Medical history

	Endometriosis (n = 237)	Endometriosis free (n = 55)	P-value
Infertility (n, %)	75 (31.6)	9 (16.4)	0.031
Primary	56 (23.6)	5 (9.1)	
Secondary	19 (8.0)	4 (7.3)	
Length of infertility (months)	42.3 ± 30.4	38.4 ± 24.1	0.718
ASRM total score*	38.4 ± 34.2	n.a.	
ASRM implants score*	14.5 ± 4.0	n.a.	
ASRM adhesions score*	24.4 ± 26.8	n.a	
Size right-OMA (cm)	3.3 ± 2.1	n.a	
Size left-OMA (cm)	4.0 ± 2.3	n.a	
Painful symptoms (VAS score)			
Dysmenorrhea	7.5 ± 2.4	5.6 ± 2.9	<0.001
Deep dyspareunia	4.9 ± 3.3	3.9 ± 3.7	0.069
Non-cyclic chronic pelvic pain	3.2 ± 3.0	2.2 ± 3.2	0.032
Gastrointestinal symptoms	5.0 ± 3.5	2.2 ± 3.1	<0.001
Lower urinary tract symptoms	1.7 ± 2.9	0.2 ± 1.3	<0.001

n.a., not applicable; OCs, oral contraceptives; OMA, ovarian endometrioma; VAS, visual analog scale; ASRM, American Society for Reproductive Medicine.
*Score according to the American Society for Reproductive Medicine classification (rAFS, 1997).

endometriotic lesions; (ii) the results were analyzed according to the three endometriosis phenotypes, with a large number of DIE patients; (iii) the results were analyzed according to whether the adenomyosis was diffuse and/or focal; (iv) Relationships between diffuse adenomyosis and endometriosis were similar, irrespective of the MRI criteria used to define diffuse adenomyosis ($JZ_{max} \geq 12$ or ≥ 15 mm; JZ_{max} and/or $ratio_{max}$); (v) clinical data were recorded prospectively by the surgeon during face-to-face interviews in the month prior to the surgery using a structured questionnaire; (vi) during the preoperative imaging work-up, the radiologist was informed that endometriosis and/or adenomyosis were suspected, but they were blinded to the results of the clinical findings and previous imaging examinations.

Our study also has some limitations: (i) this study was performed with a patient population that required surgical intervention for symptomatic benign gynecological conditions. One can hence speculate that the results may have been affected by the nature of the patients included in the study design. Including symptomatic women, with dysmenorrhea in 39/55 (70.9%) endometriosis free women, could select women with adenomyosis and could explain the high proportion of women with adenomyosis observed in the endometriosis free group. Whether this selection could have introduced a bias in the relationship between endometriosis and adenomyosis remains unknown. (ii) The number of patients was much smaller for the endometriosis free group (55 versus 237). While it

is not possible in daily practice to provide a preoperative MRI to all of the patients presenting with suspected endometriosis, it is even more difficult to provide it to patients before they undergo intervention for another benign gynecologic indication (e.g. tubal infertility; non endometriotic benign ovarian cyst, etc.); (iii) Imaging has led to numerous types of adenomyosis being reported, thus leading to several adenomyosis classifications (Gordts *et al.*, 2008; Kishi *et al.*, 2012; Pistofidis *et al.*, 2014). In our study, the results were analyzed based on whether the adenomyosis was diffuse and/or focal, using the above reported strict MRI criteria. Furthers studies are necessary to demonstrate if our results are also observed with others adenomyosis classifications; (iv) The difference between the ZJ maximum and minimum thickness ($JZ_{max} - JZ_{min}$) seems to also be an accurate MRI criterion for the diagnosis of adenomyosis (Dueholm and Lundorf, 2007). Further work will be required to determine whether our results also hold up when $JZ_{max} - JZ_{min}$ are taken as the MRI criterion for adenomyosis diagnosis. In the future, the development of more accurate imaging criteria would optimize the diagnostic process allowing a more precocious diagnosis of adenomyosis.

Our studies show that diffuse adenomyosis is a common pathology, and that it can be encountered in young patients, including those who

Table II **MRI adenomyosis appearance distribution according to the surgical endometriosis phenotype.**

Phenotype		Adenomyosis (*n*, %)				No adenomyosis (*n*, %)
		Isolated diffuse	Associated diffuse and FAOM	Isolated FAOM	Total	Total
Endometriosis free (*n*, %)	55	19 (34.5)	1 (1.8)	2 (3.6)	22 (40.0)	33 (60.0)
Endometriosis (*n*, %)	237	34 (14.3)	47 (19.8)	72 (30.4)	153 (64.6)	84 (35.4)
P-value*		<0.001	<0.001	<0.001	<0.001	
Endometriosis phenotype						
SUP (*n*, %)	40	6 (15.0)	2 (5.0)	1 (2.5)	9 (22.5)	31 (77.5)
OMA (*n*, %)	31	9 (29.0)	5 (16.1)	1 (3.2)	15 (48.4)	16 (51.6)
DIE (*n*, %)	166	19 (11.4)	40 (24.1)	70 (42.2)	129 (77.7)	37 (22.3)
P-value**		0.170	<0.001	<0.001	<0.001	
Total (*n*, %)	292	53 (18.2)	48 (16.4)	74 (25.3)	175 (59.9)	117 (40.1)

FAOM, focal adenomyosis located in the outer myometrium; SUP, superficial peritoneal endometriosis; DIE, deep infiltrating endometriosis; MRI, magnetic resonance imaging.
*Chi^2-test *P*-value: variables are categorized into two groups (endometriosis versus no endometriosis).
**Chi^2-test *P*-value: variables are categorized into four groups: SUP, OMA, DIE and no endometriosis group.
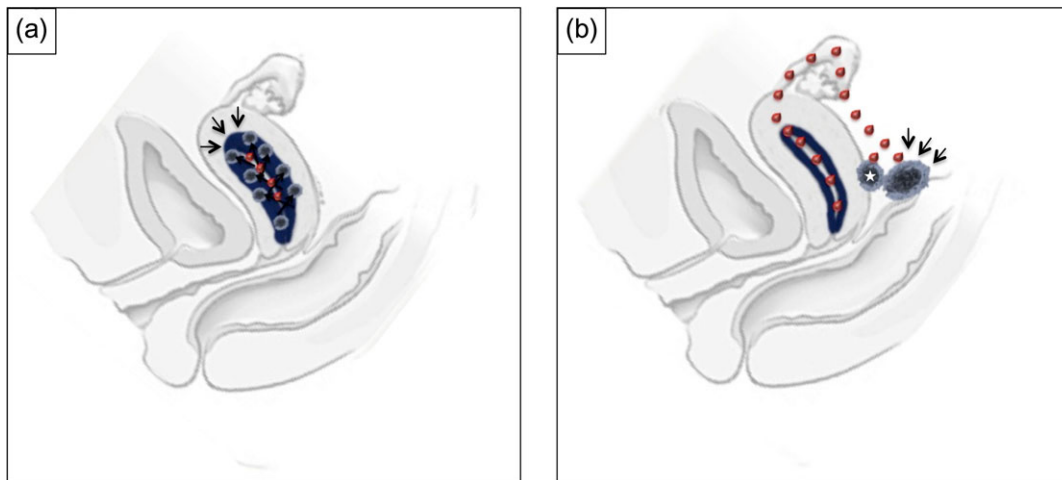

Figure 2 Adenomyosis schematic representation. (**a**) Isolated diffuse adenomyosis; (**b**) Isolated posterior FAOM (sub-type II Kishi) (Kishi *et al.*, 2012). Panel a: Schematic representation of isolated diffuse adenomyosis pathogenesis: 'from inside to outside invasion'. EMT may increase the invasiveness of endometrial cells in favor of myometrial invasion leading to significant thickening of the JZ (black arrow). Panel b: Schematic representation of FAOM pathogenesis 'from outside to inside invasion'. Through menstrual reflux, ectopic endometriotic cells may have the potential to infiltrate the posterior uterine wall (posterior FAOM) (white star) opposite to the posterior deep infiltrating lesion involving the bowel (black arrow). EMT, epithelial-mesenchymal transition.

do not have associated endometriosis. The mean age of women with isolated diffuse adenomyosis in this study was 33.2 ± 5.3 years (range 22–41 years). We found that diffuse adenomyosis occurred in one-third of the patients (34.6%, 101/292), regardless of whether they were endometriosis free or not. Diffuse adenomyosis should no longer be considered to be a disease of older multiparous patients with an associated endometriosis (Naftalin et al., 2012) as it can also be encountered in younger women (Kunz et al., 2000, 2005, 2007; Suginami, 2001; Leyendecker et al., 2006; Zacharia and O'Neill, 2006; Kissler et al., 2007), including adolescents (Brosens et al., 2015; Mansouri et al., 2015). It is paramount to bear this observation in mind in daily practice in the sense that adenomyosis is a factor in infertility, it causes pelvic pain, and it contributes to menorrhagia.

According to our results, diffuse and focal adenomyosis differ in terms of their relationship with endometriosis phenotypes. FAOM is significantly associated with endometriosis and specifically with the DIE phenotype. While the pathogenesis of endometriosis has remained elusive, retrograde menstruation remains the most commonly accepted theory (Sampson, 1927). The Sampson hypothesis provides an explanation for the anatomical distribution of endometriotic lesions (Chapron et al., 2006). Endometriotic lesions are more commonly seen in the posterior pelvic compartment and on the left pelvic side-wall (Vercellini et al., 2004; Bricou et al., 2008). Regurgitant menstrual flow in the abdominal pelvic cavity gives rise to an inflammation (McKinnon et al., 2015) responsible for an adherential process that leads to a degree of obliteration of the pouch of Douglas (Vercellini et al., 2000). While ectopic endometriotic cells have the potential to penetrate the posterior vaginal fornix, the rectovaginal septum and the rectosigmoid, there is no scientific evidence that allows for exclusion of the hypothesis that these same cells can also infiltrate the posterior uterine wall to form a posterior focal adenomyotic nodule opposite to the posterior intestinal DIE lesion (Khong et al., 2011) (Fig. 2b). For these same reasons, Fedele et al. (1997) applied this physiopathological argument at the level of the vesico-uterine pouch to explain the observation of a bladder DIE lesion in front of an anterior uterine wall adenomyotic nodule. Our findings indicate that diffuse adenomyosis is only associated to some extent with endometriosis phenotypes. Recent evidence suggests that an epithelial-mesenchymal transition (EMT) is involved in the pathogenesis of adenomyosis, thereby resulting in increased invasiveness of endometrial cells (Chen et al., 2010) by a range of pathogenic mechanisms (Leyendecker et al., 2009; Oh et al., 2013; Khan et al., 2015; Qi et al., 2015; Guo et al., 2016; Liu et al., 2016; Shen et al., 2016) (Fig. 2a).

In conclusion, based on a population of young women who underwent surgery for benign gynecological disease, our study demonstrates that adenomyosis is a common occurrence. FAOM is more commonly seen in endometriotic patients, and it is significantly correlated with the DIE endometriosis phenotype. Diffuse adenomyosis is encountered in one-third of the population (endometriotic or not) and failed to reach significant correlation with the endometriosis phenotype. These results raise the question of whether diffuse and FAOM are two different entities.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

Conflict of interest

None declared.

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