Human Reproduction, Vol.34, No.11, pp. 2144–2152, 2019
Advance Access Publication on November 4, 2019 doi:10.1093/humrep/dez188

human reproduction

ORIGINAL ARTICLE *Gynaecology*

Progression of deep infiltrating rectosigmoid endometriotic nodules

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Submitted on December 23, 2018; resubmitted on August 1, 2019; editorial decision on August 12, 2019

STUDY QUESTION: What is the risk of progression of deep endometriotic nodules infiltrating the rectosigmoid?

SUMMARY ANSWER: There is a risk of progression of deep endometriotic nodules infiltrating the rectosigmoid, particularly in menstruating women.

WHAT IS KNOWN ALREADY: Currently, there is a lack of acceptance in the literature on the probability that deeply infiltrating rectosigmoid endometriotic nodules progress in size.

STUDY DESIGN, SIZE, DURATION: We conducted a monocentric case–control study between September 2016 and March 2018 at Rouen University Hospital. We enrolled 43 patients who were referred to our tertiary referral centre with deep endometriosis infiltrating the rectosigmoid, who had undergone two MRI examinations at least 12 months apart and had not undergone surgical treatment of rectosigmoid endometriosis during this interval.

PARTICIPANTS/MATERIALS, SETTING, METHODS: MRI images were reinterpreted by a senior radiologist with experience and expertise in endometriosis, who measured the length and thickness of deep infiltrating colorectal lesions. Intra- and inter-observer reliability were tested on 30 randomly selected cases. We defined 'progression' of a nodule as an increase of ≥20% in length or in thickness and 'regression' of a lesion as a decrease of ≥20% in length or in thickness between two MRIs. Any nodule for which the variation in length and thickness was <20% was considered as 'stable'. Patients were divided into three groups based on evidence of progression, regression or stability of deep endometriotic nodules between their two MRI examinations. The total length of any period of amenorrhoea between the two MRI examinations, due to pregnancy, breastfeeding or hormonal treatment, was recorded. The total proportion of the time between MRIs where amenorrhoea occurred was compared between groups.

MAIN RESULTS AND THE ROLE OF CHANCE: Eighty-six patients underwent at least two MRIs for deep endometriosis infiltrating the sigmoid or rectum between September 2016 and March 2018. Of these, we excluded 10 patients with an interval of <12 months between MRIs, 10 patients who underwent surgery between MRIs, 17 patients for whom at least 1 MRI was considered to be of poor quality and 6 patients for whom no deep colorectal lesion was found on repeat review of either MRI. This resulted in a total of 43 patients eligible for enrolment in the final analysis. Mean time (SD) between MRIs was 38.3 (22.1) months. About 60.5% of patients demonstrated stability of their colorectal lesions between the two MRIs, 27.9% of patients met the criteria for 'progression' of lesions and 11.6% met the criteria for 'regression' of lesions. There was no significant difference in time interval between MRIs for the three groups ($P = 0.76$). Median duration of amenorrhoea was significantly lower in women with progression of lesions (7.5 months) when compared to those with stability of lesions (8.5 months) or regression of lesions (21 months) ($P < 0.001$). Median duration of amenorrhoea (expressed as percentage of total time between two MRIs) was also found to be significantly lower in the group demonstrating progression (15.1%) when compared to the group demonstrating stability (19.2%) and the group demonstrating regression (94.1%; $P = 0.006$). Progression of rectosigmoid nodules was observed in 34% of patients without continuous amenorrhoea, in 39% who had never had amenorrhoea and in no patients with continuous amenorrhoea.

LIMITATIONS, REASONS FOR CAUTION: Due to a lack of universally accepted criteria for defining the progression or regression of deep endometriotic nodules on MRI, the values used in our study may be disputed. Due to the retrospective design of the study, there may be

heterogeneity of interval between MRIs, MRI techniques used, reason for amenorrhoea and duration of amenorrhoea. The mean inter-MRI interval was of short duration and varied between patients. Our findings are reported for only deep endometriosis infiltrating the rectosigmoid and cannot be extrapolated, without caution, to nodules of other locations.

WIDER IMPLICATIONS OF THE FINDINGS: Patients with deeply infiltrating rectosigmoid endometriotic nodules, for which surgical management has not been performed, should undergo surveillance to allow detection of growth of nodules, particularly when continuous amenorrhoea has not been achieved. This recommendation is of importance to young patients with rectosigmoid nodules who wish to conceive, in whom first line ART is planned. There is a very low risk of progression of deep endometriotic nodules infiltrating the rectosigmoid in women with amenorrhoea induced by medical therapy, lactation or pregnancy.

STUDY FUNDING/COMPETING INTEREST(S): No funding was received for this study. The authors declare no competing interests related to this study.

Key words: deep infiltrating endometriosis / amenorrhoea / bowel / MRI / progression

Introduction

Although endometriosis is common among women of reproductive age, its natural history is still debated (Giudice, 2010; Gordts *et al.*, 2017). Hormonal treatments used either for treatment of infertility or for contraception may interfere with the natural evolution of the disease (Fedele *et al.*, 2000), which makes the assessment of progression of endometriotic lesions over time challenging. Thus, data on this matter are scarce in the scientific literature: only one prospective study exists. In this study, asymptomatic and untreated women with deep endometriotic lesions infiltrating the rectum were followed up for a median time of 6 years, and the study concluded that asymptomatic deep nodules are unlikely to progress (Fedele *et al.*, 2004). Other arguments against the progression of endometriosis are based only on retrospective studies conducted on indirect outcomes or on biological data (Savaris *et al.*, 2014; Zhang *et al.*, 2016a,b; González-Foruria *et al.*, 2017). In addition, there is also a paucity of literature supporting the theory of the evolution of deep infiltrating endometriosis (Gordts *et al.*, 2017). There are however various reports of evolving endometriotic lesions causing organ failure (bowel occlusion or ureteric obstruction) due to the progressive growth of nodules (Roman *et al.*, 2015). Deep infiltrating endometriosis is diagnosed only rarely in adolescent patients, while the mean age of patients undergoing management of rectal endometriosis averages 33 years. This suggests that the development of deeply infiltrating lesions may occur between 20 and 30 years of age (Roman *et al.*, 2015; Torralba-Morón *et al.*, 2016; Abo *et al.*, 2018; Vallée *et al.*, 2018). Therefore, no definitive conclusions can be drawn as to whether deep infiltrating endometriosis is a progressive disease or not. Despite this apparent lack of evidence, there is consensus about a presumed slow progression of deeply infiltrating endometriosis (Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Collinet *et al.*, 2018).

The medical treatment of the symptoms of endometriosis is based on the inhibition of ovulation, the interruption of menstruation and the stabilization of the steroid hormone milieu (Vercellini *et al.*, 2014). Various treatments can be used to achieve amenorrhoea and their efficacy in reduction of pain has been well established (Fedele *et al.*, 1993; Vercellini *et al.*, 1993; Leone Roberti Maggiore *et al.*, 2014). However, the influence of amenorrhoea on disease progression remains unknown (Vercellini *et al.*, 2011). This influence can only be argued on the basis of pathophysiology: it has been postulated that the interruption of retrograde menstruation and the inhibition of inflammation and the secretion of biosteroid hormones may prevent the progression of the disease and the occurrence of new lesions.

We conducted a retrospective study on patients with rectosigmoid endometriosis who had not undergone surgical management and had successive pelvic MRI examinations to follow the natural evolution of deep infiltrative lesions. The aim of this study was to assess the risk of progression of deep endometriotic nodules infiltrating the rectosigmoid and to evaluate the influence of continuous amenorrhoea on their development.

Materials and Methods

Study design

We conducted a monocentric case series study. Data were retrospectively and anonymously collected. The study was approved by the local ethics committee (E2018-71).

Study population

Women who were referred from September 2016 to March 2018 to two of the authors (H.R.—surgeon or I.C.-L.—fertility specialist) for advice on the management of deep endometriosis infiltrating the rectum or the sigmoid colon causing pain and/or infertility were enrolled. Women were included if they had undergone two consecutive pelvic MRIs prior to outpatient review, at an interval of >12 months, with one or more deep endometriotic nodules infiltrating the rectosigmoid muscularis layer demonstrated on at least one MRI. Exclusion criteria were as follows: any surgical management of rectosigmoid endometriosis between the two MRIs, the onset of menopause between the two MRIs, an age <20 years at the time of the first MRI, insufficient quality of one or both MRIs to allow accurate measurement of deeply infiltrating lesions (minimum requirement of three main sequences, images of high quality and without artefact hampering nodule assessment) and insufficient data in the patient medical file to assess the duration of amenorrhoea between MRIs.

MRI measurements

Digital Imaging and Communications in Medicine (DICOM) files were recorded using Osirix MD 10.0 software (Pixmeo SARL, Geneva,

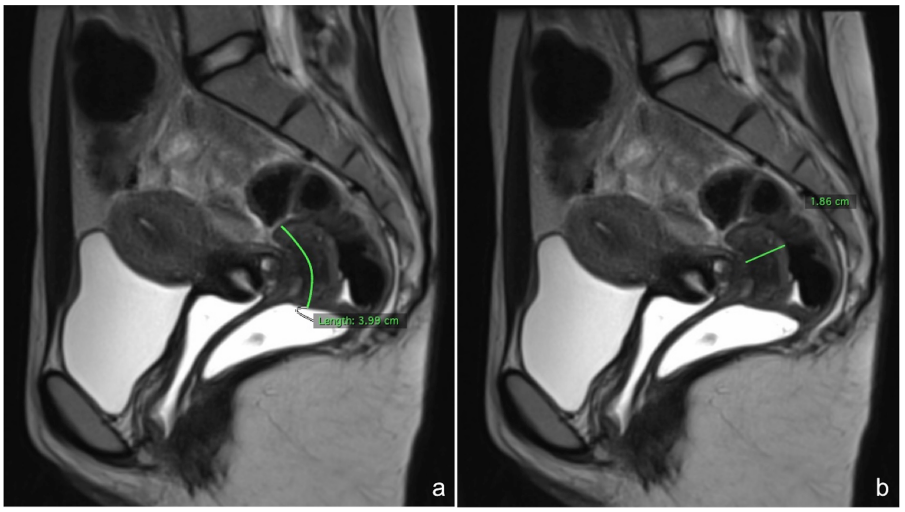

Figure 1 Measurement of the length (a) and the thickness (b) of deep endometriosis nodules infiltrating the rectosigmoid.

Switzerland). MRIs were analysed by one senior radiologist (P.d'A.-F.), specializing in women's health imaging and with experience and expertise in endometriosis. The radiologist was blinded to patient symptoms and prior hormonal treatment. The radiologist performed an initial assessment of MRI quality. MRIs where the protocol did not include at least one T1-weighted fat saturation sequence (T1 FS) and two orthogonal T2-weighted sequences were considered inaccurate and were excluded from the analysis. MRIs of poor quality, which did not allow precise measurement of endometriotic nodules, were also excluded. Poor MRI quality was determined by the presence of excessive bowel peristalsis, patient movement, excessive presence of stools or metal artefact. For patients with more than two prior MRIs, the two with the longest interval and greatest quality were selected.

Rectosigmoid involvement on MRI was based on the disappearance of the hypointense signal of the anterior wall of the rectum and/or sigmoid colon on T2-weighted images and the presence of a tissue mass forming an obtuse angle with the wall of the rectosigmoid, extending to the anterior wall of the rectum and the inferior wall of the sigmoid colon (Bazot and Daraï, 2017). The length of bowel wall infiltration was measured in millimetres from the proximal to the distal edge of involvement, along the bowel segment, using the 'open polygon' function. The thickness of the lesion was also measured in millimetres as the largest anteroposterior diameter of the nodule orthogonal to the length (Fig. 1). The height of the nodule was defined as the distance from the anal verge to the distal edge of the nodule along the rectum (millimetres), using the 'open polygon' function. Number, length, thickness and height of endometriotic rectosigmoid lesions were reviewed and recorded for each MRI. For patients who presented with more than one rectosigmoid lesion, we selected the lesion with the greatest length for review. Only deep endometriotic nodules infiltrating the rectosigmoid were included for review because their interpretation and measurement on MRI are reliably standardized.

We defined 'progression' of any nodule as an increase of $\geq$20% in length or in thickness and 'regression' of any lesion as a corresponding decrease in length or thickness, between two MRIs. Any nodules where length and thickness variations were $<$20% were considered as 'stable'.

To confirm reproducibility of results, a second measurement of rectosigmoid nodules was conducted on 30 randomly selected MRIs by the same radiologist (P.d'A.-F.) and by another experienced radiologist (M.L.). This enabled the assessment of both intra- and inter-operator reliability.

Assessment of amenorrhoea

We recorded the time (in months) between the two MRIs. To assess the duration of amenorrhoea between the two MRIs, data were extracted from the medical records of all patients included in the study. The total number of months where pregnancy or breastfeeding occurred, or hormonal treatment (GnRH agonists, macroprogestins or continuous combined oral contraception) was taken without interruption for at least 3 months, were recorded as periods of amenorrhoea.

Endpoints

The primary endpoint was the probability of progression of any rectosigmoid nodule between two MRIs.

The secondary endpoints were the total duration of amenorrhoea between the two MRIs and the proportion of time between the two MRIs where amenorrhoea occurred among the three groups of women with stable, progressive and regressive rectosigmoid nodules, respectively. The risk of progression of rectosigmoid nodules was also compared according to whether or not a pregnancy had occurred during the interval.

Statistical analyses

Statistical analysis was performed using IBM SPSS Statistics 20.0 (IBM Inc., New York, USA). The study sample was described using mean $\pm$ SD for continuous variables and number (percentage) for categorical variables. ANOVA and χ^2 tests were used to compare, respectively, continuous and categorical variables among the three groups. Intraclass correlation coefficient (ICC) was estimated to assess the inter- and intra-observer concordance of measures for the length and the thickness of rectosigmoid nodules. All statistical analyses were

Table I Epidemiological characteristics of the population ($N = 43$).

Characteristics	
Age at second MRI (years, mean ± SD)	33.1 ± 5.5
BMI (kg/m^2, mean ± SD)	22.5 ± 3.9
Details of previous surgery	*n* (%)
Number of prior surgeries	23 (53.5)
Laparotomy	2 (4.7)
Number of previous laparoscopies	21 (48.8)
1	13 (30.2)
≥2	8 (18.6)
Ovarian cystectomy	
Right ovary	6 (14.0)
Left ovary	8 (18.6)
Oophorectomy	3 (7.0)
Salpingectomy	3 (7.0)
Rectal surgery	1 (2.3)
Justification for surgery	*n* (%)
Pelvic pain	18 (41.9)
Infertility	5 (11.6)
Obstetric history	*n* (%)
Nulligravid	22 (51.2)
Nulliparous	27 (62.8)
Miscarriage	8 (18.6)
Ectopic pregnancy	0 (0)
Documented infertility	25 (58.1)

two-tailed, and results were considered to be statistically significant when $P < 0.05$.

Results

Patient characteristics

Between September 2016 and March 2018, 86 patients with deep endometriosis infiltrating the rectosigmoid, assessed by at least two pelvic MRIs, were referred for review to one of the authors. Ten patients were excluded because the interval between the two MRIs was <12 months. Ten patients were excluded because they had undergone pelvic surgery between the two MRIs. Seventeen patients were excluded because one of their MRIs was considered to be of poor quality, which would impact on accurate repeat assessment of nodules. In six patients, a colorectal lesion could not be confirmed on one or more MRIs. A total of 43 patients were enrolled in the study. Among them, 58% had a prior history of infertility. Patient characteristics and main presenting complaints are reported in Tables I and II, respectively.

Reproducibility of measurements

Our results demonstrate that our method of measurement of the length and thickness of rectosigmoid nodules on MRI is reproducible. Inter-observer reliability for nodule thickness is characterized by an ICC of 0.793 (95% CI = 0.565–0.901), $P < 0.001$; intra-observer reliability for nodule thickness: ICC = 0.956 (0.908–0.979), $P < 0.001$; inter-observer reliability for nodule length: ICC = 0.904 (0.798–0.954), $P < 0.001$; intra-observer reliability for nodule length: ICC = 0.982 (0.962–0.991), $P < 0.001$.

Table II Main symptoms related to endometriosis ($N = 43$).

Principal pain symptoms related to pelvic endometriosis	*n* (%)
Dysmenorrhea	40 (93.0)
Defecation pain	22 (51.2)
Rectorrhage	3 (7.0)
Constipation	22 (51.2)
Diarrhoea	12 (27.9)
Bloating	6 (13.9)
Urinary pain	10 (23.2)
Deep dyspareunia	32 (74.4)
Right shoulder pain	2 (4.6)
Sciatic pain	9 (20.9)
Consultation	
Referred by	
Herself	25 (58.1)
By another physician	18 (41.9)
Motive for consultation	
Aggravation of pain	30 (69.8)
Infertility	13 (30.2)

Progression of rectosigmoid lesions

Mean time between MRIs was 38.3 ± 22.1 months. The mean length of rectosigmoid nodules at first MRI was 37 ± 26 mm and the mean thickness was 11 ± 5 mm. The mean height of nodules at both first and second MRI was 86 ± 21 mm. In 26 (60.5%) women, rectosigmoid nodules were stable, in 12 women (27.9%) nodules progressed, while in 5 women (11.6%) nodules regressed (Table III and Fig. 2).

Influence of amenorrhoea

There was no significant difference in interval between MRIs between the three groups ($P = 0.76$). The median proportion of time where amenorrhoea occurred between MRIs was significantly different among the three groups: in women where progression of a rectosigmoid nodule between MRIs was demonstrated, amenorrhoea had occurred for a significantly lower proportion of time between MRIs (15.1%) than those with stable nodules (19.2%) and those with nodule regression (94.1%) ($P = 0.006$). Median number of months of amenorrhoea between MRIs tended to be lower in women with nodule progression (7.5 months, range 0–9 months) than in those with stable nodules (8.5 months, range 0–23) and nodule regression (21 months, range 13–41) ($P < 0.09$; Table IV).

Among the 36 women with ongoing menses during the interval, nodule growth was recorded in 12 patients (34%) and nodule regression was recorded in 3 patients (8%), while in 21 patients nodule size was stable (58%). Among 13 patients who did not experience any amen-

Table III MRI findings (N = 43).

Findings	
Mean time between MRI (months, mean ± SD)	38.3 ± 22.1
No. of rectal lesions at first MRI	*n* (%)
None	2 (4.6)
1	38 (88.4)
2	3 (7.0)
Other location of deep infiltrated endometriosis	*n/N* (%)
Endometrioma	26/43 (60)
Adenomyosis	31/43 (72)
Bladder	7/43 (16)
Ureteric stenosis	4/43 (9)
Sacral roots	6/43 (14)
Main rectal lesion at first MRI (mm)	Mean ± SD
Length	37 ± 26
Thickness	11 ± 5
No. of rectal lesions at second MRI	*n* (%)
None	1 (2.3)
1	39 (90.7)
2	3 (7.0)
Main rectal lesion at second MRI (mm)	Mean ± SD
Length	42 ± 25
Thickness	13 ± 5
Comparison of colorectal lesions between MRI (mm)	Mean ± SD
Length	5 ± 13
Thickness	2 ± 5
Evolution of main rectal lesion between the two MRIs	*n* (%)
Stable	26 (60.5)
Progression	12 (27.9)
Among whom, *de novo* appearance	2 (4.6)
Regression	5 (11.6)
Among whom, disappearance	1 (2.3)

orrhoea during the interval, nodules progressed in 5 patients (39%) and were stable in 8 of them (61%). Among 7 patients with continuous amenorrhoea during the whole interval, a regression of nodule size was observed in 2 cases, while in 5 cases the size of the nodule remained stable. Thus, no patients with continuous amenorrhoea demonstrated nodule progression.

De novo rectosigmoid nodules developed between the two MRIs in a total of two patients. The first patient was a 30-year-old nullipara, with an inter-MRI interval of 93 months, during which time she reported 9 months of amenorrhoea due to pregnancy. Review of the second MRI revealed a new nodule, 21 mm in diameter, infiltrating the rectum 86 mm above the anal verge (Fig. 2). The second patient was a 27-year nullipara with a history of infertility, with an inter-MRI interval of 15 months completely free of amenorrhoea. Review of her second MRI revealed a new nodule, 27 mm in diameter, infiltrating the rectum 120 mm above the anal verge.

Conversely, complete regression of a rectosigmoid nodule was recorded in a 29-year patient who had an inter-MRI interval of 34 months. During this time, she reported 32 months of amenorrhoea (15 months due to GnRH agonists and 17 months due to the continuous combined oral contraceptive pill). The first MRI revealed a nodule, 19 mm in diameter, infiltrating the rectum 104 mm above the anal verge, which was not present on the second MRI. However, this patient reported ongoing pelvic pain at the time of the second MRI.

Eight patients reported a pregnancy in the inter-MRI interval. We investigated whether or not pregnancy had a more pronounced effect on the risk of progression of endometriotic nodules than medically induced or lactational amenorrhoea (Table V); however, no significant difference was found.

No previous surgery undergone by patients enrolled in our study was for treatment of deep endometriotic nodules, but only for the purpose of diagnostic laparoscopy, treatment of superficial lesions and endometriomas or assessment of fallopian tubes. The comparison between patients who had, or had not had, prior surgery did not reveal significant differences in terms of progression or regression of deep endometriosis nodules ($P = 0.098$).

Discussion

Our results suggest that in 28% of patients who have a deep infiltrating rectosigmoid nodule, growth will occur over a 3-year period. This risk of progression is directly related to the presence of menstruation during this time, as nodule growth will occur in 39% of women free of amenorrhoea. These findings are of major importance when selecting expectant management rather than surgery or hormonal suppression for women with rectosigmoid endometriotic nodules.

Our study has several limitations. The inter-MRI interval of 3 years is of short duration, when compared to the potentially long period of development of endometriotic nodules over an average of 30 years, from menarche to menopause. We therefore cannot extrapolate our findings to nodules followed up over any period of longer duration. The sample size is small, due to exclusion criteria which eliminated half of the patients presenting for review with two consecutive MRIs. Our cut-off values defining the progression and the regression of nodules may be considered restrictive, as in the group of women with nodules demonstrating progression, mean length and thickness increased 2-fold when compared to baseline measures. Due to the absence of predefined criteria, the cut-off measurements used to confirm the progression or regression of rectosigmoid nodules were chosen according to published criteria used to define solid tumour growth (Eisenhauer *et al.*, 2009). Our findings cannot be extrapolated to asymptomatic women with rectosigmoid nodules, because all patients included in our analysis reported either pain or infertility or both.

All MRI examinations were performed externally, prior to patient review in our centre. As there is currently no international consensus regarding MRI patient preparation, protocols or reporting criteria (Bazot *et al.*, 2017), there is heterogeneity of MRI techniques, which were performed by radiologists from a range of facilities in France. Our inclusion criteria required the availability of three main sequences, images of high quality and without artefact hampering nodule assessment. These criteria were strict; thus, 17 patients, despite presenting with rectosigmoid nodules demonstrated on two MRIs, were ultimately ineligible for enrolment in our study. We cannot confirm the effect these criteria may have had on our results. However, these limitations did not allow us to monitor nodule growth, but only to demonstrate that their size may increase, particularly in patients having periods.

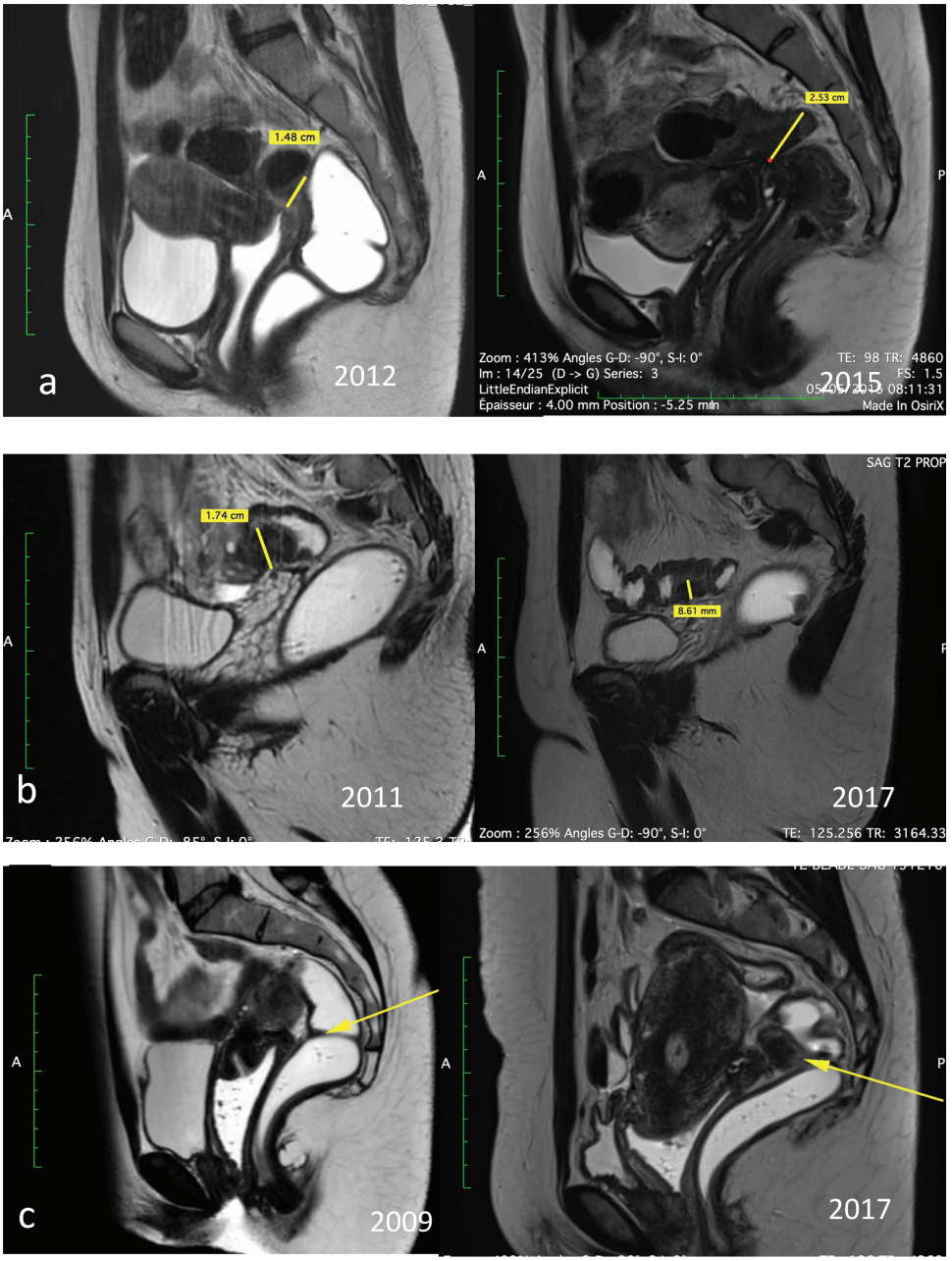

Figure 2 Evolution of rectosigmoid nodules during the interval between the two MRI examinations. (**a**) Nodule progression, (**b**) nodule regression and (**c**) occurrence of a rectosigmoid nodule (10 cm scale marker in all panels).

Another limitation of the study was the inclusion of patients with a prior history of pelvic surgery (48.8%). However, none of these patients had previously undergone surgery for deep infiltrating endometriosis; thus, it is unlikely that previous surgeries had an impact on the growth of any deep endometriotic nodules.

One may object that our study population is heterogeneous, due to the inclusion of women undergoing various hormonal treatments, women who were pregnant and/or breastfeeding and women with ongoing menses. The sample is also heterogeneous in terms of length of interval between MRIs and length of interruptions in medical treatment during the interval. In reality it is difficult, if not impossible, to conduct a long-term study in patients with endometriosis completely free of medical or surgical treatment. Symptomatic patients, who are likely to benefit from hormonal or surgical treatments, have a lower probability of eligibility for inclusion at the time of follow-up. Further studies are required to assess the risk of progression of rectosigmoid nodules over the whole 30-year reproductive period.

Our study has several strengths. As our cut-off values are restrictive, the definition and therefore confirmation of growth or regression of nodules is robust. We chose to enrol only patients with rectosigmoid nodules, because their measurement is both comprehensive and reproducible: the length is measured longitudinally while the thickness

Table IV Relationship between amenorrhoea and rectosigmoid nodules evolution.

	Evolution of the main colorectal lesion of endometriosis (N = 43)			
	Regression	Stability	Progression	*P* value
Number of women, *n* (%)	5 (11.6)	26 (60.5)	12 (27.9)	
Time between the two MRI, months, mean ± SD	31.4 ± 12.7	39.0 ± 22.5	39.7 ± 25.1	0.76
Percentage of time of amenorrhoea between MRI, %, median (IQR)	94.1% (53.9–100.0)	19.2% (.0–67.9)	15.1% (.0–41.4)	0.006
Due to pregnancy (% of total)	15	25	18	0.84
Due to GnRH agonists (% of total)	15	14	53	0.06
Due to oral contraception (% of total)	70	61	29	0.20
Duration of amenorrhoea, months, median (IQR)	21 (13–41)	8.5 (0–23)	7.5 (0–9)	0.09
Initial length of the rectal lesion, mm, mean ± SD	33.8 ± 15.0	45.1 ± 27.4	20.8 ± 17.2	0.02
Variation in length of the rectal lesion, mm, mean ± SD	−11.8 ± 6.1	0.9 ± 4.9	20.9 ± 12.3	<0.001
Initial thickness of the rectal lesion, mm, mean ± SD	11.4 ± 3.9	12.9 ± 5.0	7.6 ± 4.4	0.01
Variation in thickness of the rectal lesion, mm, mean ± SD	−3.2 ± 3.5	0.0 ± 2.5	7.1 ± 4.8	<0.001

IQR, interquartile range.

Table V Comparison of the different means of amenorrhoea.

	Pregnancy	Hormonal contraception or GnRH agonists	No amenorrhoea	*P* value
Number of patients (*N*)	8	22	13	
Time between the two MRI, months, mean ± SD	51.5 ± 26.7	36.4 ± 23.6	33.5 ± 13.1	0.164
Time with menstruations between MRI, months, mean ± SD	35.0 ± 26.4	17.0 ± 21.4	33.5 ± 13.1	0.031
Percentage of time of amenorrhoea between MRI, %, median (IQR)	34.4% (17.2–60.5)	51.1% (24.0–100.0)	0.0% (0.0–0.0)	<0.01
Initial length of the rectal lesion, mm, mean ± SD	38.5 ± 29.8	38.1 ± 23.3	34.2 ± 28.9	0.900
Variation in length of the rectal lesion, mm, mean ± SD	1.4 ± 9.9	3.8 ± 14.0	9.3 ± 13.3	0.344
Initial thickness of the rectal lesion, mm, mean ± SD	12.4 ± 7.3	11.5 ± 12.4	10.2 ± 5.4	0.619
Variation in thickness of the rectal lesion, mm, mean ± SD	0.1 ± 5.9	0.9 ± 4.1	3.8 ± 5.1	0.158
Evolution status, *n* (%)				0.541
Regression	1 (12.5)	4 (18.2)	0.0 (0.0)	
Stability	5 (62.5)	13 (59.1)	8 (61.5)	
Progression	2 (25.0)	5 (22.7)	5 (38.5)	

is measured orthogonally to the bowel wall. We were able to accurately estimate the impact of amenorrhoea on the growth, stability or regression of nodules, because all patient medical records consistently documented duration of menstruation, amenorrhoea, pregnancy, breastfeeding and medical treatment occurring in the inter-MRI interval. All MRIs were reviewed by a senior radiologist experienced in deep endometriosis.

Regarding the technique for radiological measurement of nodules, our results demonstrate good intra- and inter-observer reproducibility for measurement of both length and thickness of lesions. To our knowledge, there are no specific recommendations regarding the technique for measurement of endometriotic nodules on MRI. We deliberately chose not to measure the width, the area or the volume of deep endometriotic nodules for two reasons: (i) these measurements can be challenging and are therefore less reproducible due to the irregular shape of endometriotic nodules and (ii) the length and the thickness of nodules are clinically relevant measurements, as the length is routinely used to define the feasibility of bowel disc excision, while the thickness is employed to estimate the feasibility of rectal shaving (Abrão *et al.*, 2015; Roman *et al.*, 2016; Donnez and Roman, 2017).

It has already been proven in the field of radiology for malignancy that there is unavoidable intra- and inter-observer variability when solid tumour measurements are expressed in millimetres. For this reason, it has been recommended that confirmation of progression or regression of solid tumours be done via the use of thresholds: progression is defined as an increase in tumour diameter of >20%, regression is defined as a decrease in diameter of >30% and stability is defined as any growth or regression between these two thresholds (Eisenhauer *et al.*, 2009). To increase the strength of our study, we chose large thresholds (>20% variation in length and in thickness), which defined nodules

where size increased 2-fold as 'progressive'. Using these thresholds, the definition and therefore the statement of progression of nodules are more reliable for readers.

In our centre, we surgically manage more than 130 patients per year with deep rectosigmoid nodules; however, very few of these patients present with two prior pelvic MRIs of good quality and without surgical procedures during the interval between MRIs. In addition, despite our small sample size, we report robust data regarding the probability of growth or regression of endometriotic nodules, as well as statistically significant association between duration of amenorrhoea and progression of endometriotic nodules. The low number of patients did not allow us to compare amenorrhoea by cause (pregnancy, lactation, GnRH agonist or continuous combined oral contraception), although this may be interesting to study further in future studies.

The pathogenesis of deep infiltrating endometriosis is not yet fully understood (Vercellini *et al.*, 2014; Gordts *et al.*, 2017). Retrograde menstruation through the fallopian tubes is as yet only a theory, mostly based on indirect observations such as the common locations of lesions and the correlation between the frequency of the disease and various factors that could increase retrograde flow. Neither the mechanism of the development of deep endometriotic lesions is known nor the time at which they arise. The progression of deep endometriotic nodules has been demonstrated in three female baboons, in which nodules were induced and then followed up at 6 and 12 months, with specific analyses of gland morphology, collective cell migration and nerve fibre density. Invasion and nodule innervation increased between 6 and 12 months of follow-up. The authors suggested that nerve fibres may play a role in the development of lesions, as has previously been observed in women (Orellana *et al.*, 2017). One cohort study on 500 women who underwent laparoscopy for endometriosis showed no correlation between patient age and the stage of endometriosis (Savaris *et al.*, 2014). Fedele *et al.*, 2004 conducted a prospective cohort study on 88 women presenting with asymptomatic rectal endometriotic nodules with follow-up over 68 months. Lesions were assessed every 6 months by rectal ultrasonography. Only six patients (6.8%) demonstrated progression of nodule size. The authors concluded that progression of an asymptomatic rectal nodule is unlikely to occur. However, the findings of this study cannot be compared to ours, as our patients were symptomatic, reporting either pain or infertility or both. Several biological studies have suggested that endometriotic lesions tend to regress naturally and fibrose rather than proliferate (Zhang *et al.*, 2016a,b; González-Foruria *et al.*, 2017), which may correlate to our group of patients with stable lesions.

There is no consensus on optimal method and frequency of follow-up in women with deep rectosigmoid nodules (Leyland *et al.*, 2010; Dunselman *et al.*, 2014; Collinet *et al.*, 2018). On the basis of our results, it appears reasonable to recommend induction of continuous amenorrhoea in patients with rectosigmoid nodules in whom surgical management has not been performed. There is a very low risk of progression of deep endometriotic nodules infiltrating the rectosigmoid in women with amenorrhoea induced by medical therapy, pregnancy or lactation. In those patients who do not benefit from amenorrhoea, due to desire to conceive or refusal of medical treatment, we recommend close surveillance with symptoms and routine imaging (every 1–2 years) to allow early detection of growth and progression of rectosigmoid nodules. This recommendation also concerns young patients who wish to conceive, in whom first line IVF has been recommended. In these patients, especially if there is a long time to conception, there is often ongoing menstruation and a lack of amenorrhoea.

Finally, we did not find any previous reports in the literature describing the occurrence of a new rectosigmoid nodule, as occurred in two of the patients in our study. This observation is compatible with our demonstration of the progression of rectosigmoid endometriotic lesions.

The rationale for the assessment of progression of deep rectosigmoid lesions is based on two main concerns. First, cases of bowel occlusion in women desiring pregnancy, either spontaneously or by ART, have been reported in the literature (Roman *et al.*, 2015). Although the incidence of this serious complication is low, its consequences may be disastrous. In our opinion, physicians should consider this outcome in women with large rectosigmoid nodules, which appear to grow (Roman *et al.*, 2015). Second, the growth of nodules may change the surgical approach, render surgical procedures more challenging and increase the risk of unfavourable postoperative outcomes. In large nodules > 30 mm diameter, conservative rectal surgery is less feasible, which may subsequently impact on functional outcomes (Abrão *et al.*, 2015; Donnez and Roman, 2017). Furthermore, the increase in risk of complications is not only related to nodule size but also to the direction of extension and subsequent involvement of the ureters, splanchnic nerves or sacral roots.

The efficacy of hormonal contraception or GnRH agonists to reduce pain symptoms related to endometriosis has been widely studied (Fedele *et al.*, 1993; Vercellini *et al.*, 1993; Leone Roberti Maggiore *et al.*, 2014). Our results suggest that hormonal treatments, which induce amenorrhoea may prevent growth of nodules and may even result in the regression of lesions. Continuous hormonal treatment and induction of amenorrhoea are recommended in patients with rectosigmoid nodules in whom surgery is, for various reasons, not performed. In infertile women managed with ART, continuous hormonal treatment is recommended during the interval between two consecutive IVF cycles, especially if there is no chance of natural pregnancy (absence of fallopian tubes, sperm abnormalities, absence of sexual intercourse due to deep dyspareunia).

However, it must be emphasized that regression or stability of nodule size may not be associated with relief of pain. In our study, pelvic pain was still present in 100.0% of women with a lesion that regressed and in 92.3% of those with a stable nodule, compared to 91.7% of women with a nodule that progressed ($P = 0.807$). This means that in numerous women free of nodule progression, amenorrhoea does not allow to definitively avoid the surgery. On the other hand, even though surgery for colorectal endometriosis provides an overall improvement of pain and quality of life, complete postoperative relief of pain is not guaranteed, often due to the presence of adenomyosis. Therefore, surgery should be carefully considered especially in women with amenorrhoea presenting with troublesome symptoms such as bowel sub-occlusion, severe dyschezia and deep dyspareunia.

Acknowledgements

The authors are grateful to Amélie Bréant for the management of data and Nikki Sabourin-Gibbs, Rouen University Hospital; Dr Jennifer Pontré, King Edward Memorial Hospital, Western Australia and Dr Ilyas Arshad, John Radcliffe Hospital, Oxford, UK, for their help in editing the manuscript.

Authors' roles

H.R. and A.N. developed the original design. H.R. and I.C.-L. enrolled the patients. A.N., M.F. C.H. and A.A. performed the data analysis and interpretation. P.d'A.-F. and M.L. performed the MRI lecture. A.N. and H.R. wrote the first draft of the report. All authors contributed to the writing of the final manuscript.

Funding

No external funding was either sought of obtained for this study.

Conflict of interest

The authors declare no conflict of interest related to this study.

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