ORIGINAL RESEARCH ARTICLE

Natural progression of deep pelvic endometriosis in women who opt for expectant management

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Abstract

Introduction: The natural history of endometriosis is poorly understood, and despite numerous studies, the rate of the disease progression and optimal treatment planning in women who are asymptomatic or experience mild symptoms not requiring treatment are unknown. The aim of this study was to assess the behavior of deep endometriosis in women who are managed expectantly without any medical or surgical intervention.

Material and methods: A retrospective cohort study of women diagnosed with deep endometriosis on transvaginal ultrasound scan at the Department of Gynecology, University College London Hospitals and The Gynecology Ultrasound Centre, London, UK, from April 2007 to April 2022. All women attended for at least two ultrasound scans which were carried out by a single expert ultrasound examiner and at least 6 months apart. The number and position of endometriotic nodules were recorded, and the mean diameter of each nodule was calculated from measurements taken in three orthogonal planes.

Results: During the study period, 1922 women were found to have moderate or severe deep endometriosis on pelvic ultrasound examination. A total of 135 premenopausal women who were managed expectantly fitted the inclusion criteria. The median number of endometriotic nodules per woman at the initial visit was 2 (range: 0–7), and the median follow-up time was 666 days (181–2984). In the follow-up period, 50/135 women (37%, 95% CI: 29–46) developed additional nodules or experienced an increase in nodule size, and 17/135 women (13%, 95% CI: 8–19) had a regression in the number or size of the nodules. In the remaining 68/135 women (50%, 95% CI: 42–59) the disease remained static during the follow-up. The median change in mean diameter of nodules during the study period per woman was +0.13 mm (−11.67 − +5.83), with an annual growth rate of +0.09 mm/year (−6.65 − +6.45).

Conclusions: In our study we found evidence of deep endometriosis progression in just over a third of women. In view of this, asymptomatic or mildly symptomatic

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women diagnosed with deep endometriosis could be reassured that their disease is unlikely to worsen with time.

1 | INTRODUCTION

Endometriosis is a common, chronic benign condition, affecting mostly women of reproductive age. It is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction.[1] The true prevalence of endometriosis is unknown, with estimates ranging from 2% to 10% within the general female population.[2] In symptomatic women undergoing transvaginal ultrasound, the incidence of ovarian and deep endometriosis (DE) was reported to be 25%.[3] While some women with endometriosis experience pelvic pain or infertility, in others, there are no significant negative effects on the quality of life.[4,5]

The diagnosis of endometriosis is based on the woman's history, symptoms and signs. It is corroborated by physical examination and imaging techniques, and in women undergoing surgery, it can be confirmed by histology. However, laparoscopy is still the most commonly used method for diagnosing endometriosis in routine clinical practice.[6] Limitations of a diagnostic process which is based on surgical findings, are that only women with relatively severe symptoms are offered the diagnostic test, and there is a tendency to treat endometriosis either at the initial or at follow-up surgery. As a result, there is comparatively less experience with conservative management options such as expectant or medical treatment. This is especially significant for women who are asymptomatic or experience relatively mild symptoms, as their benefit from surgery is uncertain. Although there is a general perception that endometriosis may progress with time, there is very limited information about the triggers for the development of endometriosis and the natural progression of the disease.[7]

In recent years, it has been shown that transvaginal ultrasound is an acceptable, non-invasive method of imaging the female pelvis.[8] It has a reported 94% accuracy for diagnosing women with moderate to severe endometriosis using laparoscopy as a reference standard.[9] The ability to detect DE on imaging facilitates the use of conservative management. In addition, response to treatment can be studied without needing repeated surgical procedures. Only recently, studies have emerged using imaging to demonstrate the dynamic changes of endometriosis over time. However, this was only shown in the case of bowel endometriosis.[10,11] The aim of our study was to observe the behavior of DE diagnosed on ultrasound and managed without any medical or surgical intervention over relatively long periods of time. We studied the size and number of DE lesions and the tendency of the disease to increase in severity with time.

> **Key message**
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> In the majority of asymptomatic or mildly symptomatic women with endometriosis, who are managed expectantly, the condition is static. In view of that, active management should be primarily governed by clinical symptoms.

2 | MATERIAL AND METHODS

The study was conducted at the Department of Gynecology, University College London Hospital and the Gynecology Ultrasound Centre, London, UK. We retrospectively searched our ultrasound clinic database (PIA Fetal Database, version 2.23; Viewpoint Bildverarbeitung GmbH, Munich, Germany) between April 2007 and April 2022 to identify women aged 18 years or older who were diagnosed with moderate or severe endometriosis which was managed expectantly for ≥6 months. All women were examined at least twice by a single expert ultrasound operator (DJ). The last available follow-up information was used for the analysis. Scans were performed using the same ultrasound machine model (Voluson E8, GE Medical Systems). We excluded women who had surgical treatment of endometriosis during follow-up. We also excluded women who were using hormonal treatment, such as the combined contraceptive pill, the progesterone-only pill, Mirena intrauterine system, cyclical/continuous progesterone, hormone replacement therapy or gonadotrophin-releasing hormone agonist therapy during follow-up.

In our practice, we routinely record the indications for examination, demographic data, gynecological, obstetric, and medical history in all women who present to the clinic. All scans are performed in a standardized way. Ovarian cysts are diagnosed as endometriomas when they appear as well-circumscribed thick-walled cysts that contained homogeneous low-level internal echoes ("ground glass").[12] Endometriotic nodules are typically visualized as stellate hypoechoic or isoechogenic solid lesions with irregular outer margins fixed to the surrounding pelvic structures.[13] They are usually located in the posterior compartment of the pelvis (rectovaginal space, uterosacral ligaments, adnexa), anterior compartment of the pelvis (vesicouterine space and urinary bladder), or in the wall of the rectosigmoid colon. Endometriotic nodules located in the wall of the rectosigmoid colon tend to appear as hypoechoic thickening of the muscular layer of the bowel (muscularis propria) and sometimes protrude towards the bowel lumen. Nodules were measured in three perpendicular planes. DE was diagnosed when endometriotic nodules were detected

within the anterior or posterior compartment of the pelvis or when involving the bowel wall. Severe endometriosis was diagnosed based on the following findings: bowel and/or bladder involvement, obliteration of the pouch of Douglas and/or dense adhesions fixing the ovaries to the posterolateral aspect of the uterus. Women with evidence of endometriotic nodules, ovarian endometrioma and adhesions, in the absence of features of severe disease, were described as having moderate endometriosis.

We created an electronic database (EXCEL spreadsheet, Microsoft Corporation, Seattle, USA) and for each woman we recorded age, reason for referral, menopausal status, the time interval (T, days) between each ultrasound examination, the number and location of endometriotic lesions at each examination (endometriotic cysts and nodules). For endometriotic nodules, we recorded the mean ($[d1 + d2 + d3]/3$) diameter at visit 1 and visit 2.

The primary outcome of the study was to determine the rate of DE progression between the two consecutive visits in each woman. Progression was defined as either increase in the number of nodules or meaningful increase in nodule size. Our secondary outcome was to evaluate the growth or regression of endometriotic nodules based on their specific location. Complete regression of endometriotic lesions was reported when a previously detected endometriotic lesion was no longer visible on follow-up ultrasound examination in women who did not undergo any medical or surgical treatment that could result in regression or removal of the lesion. Endometriotic nodules were described as "de novo" when they were not visible at visit 1 but were detected at visit 2. In order to assess the rate of disease progression/regression, we calculated the difference in size of the nodules and the number of nodules seen at each visit. Based on intraobserver variability demonstrated in our previous study of ultrasound reproducibility for measurement of endometriotic lesions, a difference of 2.6 mm in the mean diameter of endometriotic nodules was considered a meaningful difference in size.[14]

2.1 | Statistical analyses

All endometriotic nodules for each woman were included in our analysis to ensure consistency of measurement and comprehensive assessment during follow-up. We used the measurements as recorded in our database at the time of examination to calculate the mean diameter of endometriotic nodules at visit 1 ($d1_{mean} = [d1a + d1b + d1c]/3$) and the mean diameter at visit 2 ($d2_{mean} = [d2a + d2b + d2c]/3$). The time difference between visits to the clinic was recorded as T (days). Yearly change in mean diameter of nodules was calculated as ($d2_{mean} - d1_{mean})/T \times 365.25$.

The change in size of endometriotic nodules was examined for each individual and each specific anatomical site. Distribution of the data was assessed using the Kolmogorov–Smirnov test. Descriptive statistics were presented as means ± standard deviations for normally distributed data, median and range for non-normally distributed data, and percentages with their 95% confidence interval (CI) for the enumerated data. The Spearman rank correlation coefficient

was used to analyze the relation between the size at presentation and the final size of endometriotic nodules. The Wilcoxon signed rank test was used to evaluate the difference in the number of nodules between both visits. Women were categorized based on whether they experienced meaningful progression or regression of the disease between both visits. A logistic regression model was used to identify the possible clinical predictors of disease progression. Age, number of nodules at initial presentation, gravidity, parity, severity of the disease, and previous surgery for endometriosis were considered as possible predictors. Next, a multivariable logistic regression model was constructed to adjust for potential confounding effects. Assuming a progression rate of 85%, with confidence level of 90% and 5% margin of error, we aimed to recruit 130 women to the study. Data analysis was performed using SPSS 28.0 (SPSS Inc., Chicago, IL, USA).

2.2 | Ethics statement

We sought advice from the Joint Research Office of University College London and University College London Hospital regarding ethical approval and were advised that formal ethics approval was not needed for this study as long as patient identifiable data was not seen by anyone outside the clinical care team.

3 | RESULTS

During the study period, 1922 women who attended our gynecology clinic were found to have moderate or severe endometriosis on pelvic ultrasound examination. We identified 725/1922 (40%, 95% CI: 36–45) women who were premenopausal and had evidence of DE nodules and at least two ultrasound scans between April 2007 and April 2022, with a minimum of a six-month interval between the scans. Of these 725 women, 421 (58%, 95% CI: 54–62) were scanned on both visits by a single expert operator (DJ). During the follow-up period, 101/421 (24%, 95% CI: 20–28) women were excluded from the study because they had surgical treatment of endometriosis, and 184/428 (44%, 95% CI: 39–49) women were excluded because they had medical treatment. One woman was excluded because she had uterine artery embolization between visits. Ultimately, 135/421 (32%, 95% CI: 28–37) women managed expectantly during the study period were included in the final analysis. The study flow is described in Figure 1. The reasons for referral to the clinic are shown in Table 1.

At the initial assessment, 19/135 (14%, 95% CI: 9–21) women were diagnosed with moderate endometriosis and 116/135 (86%, 95% CI: 79–91) with severe endometriosis. Fifty-eight women (43%, 95% CI: 34–52) had previous surgical treatment for endometriosis. The basic demographics of women in the study are described in Table 2. Of the women with moderate disease at initial presentation, 1/19 (5%, 95% CI: 0–26) experienced progression to severe disease. She developed an additional nodule in the rectovaginal space with adhesions leading to complete obliteration
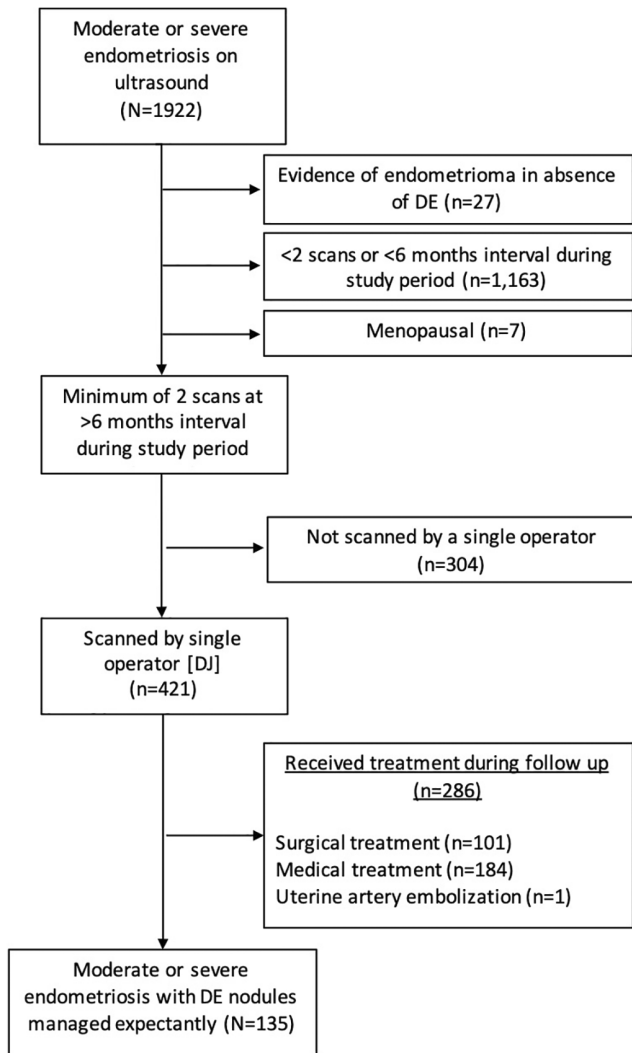
FIGURE 1 Flow diagram of the study population (*N* = 135). DE, deep endometriosis.

TABLE 1 Presenting symptoms at their first visit for women included in the study (*N* = 135)

Symptom	N	%
Chronic pelvic pain	60	44
Dysmenorrhea	35	
Dyschezia	13	
Dyspareunia	7	
Dysuria	5	
Chronic pelvic pain and abnormal uterine bleeding	16	12
Abnormal uterine bleeding	17	13
Infertility	9	7
Chronic pelvic pain and infertility	4	3
Other	29	21

TABLE 2 Characteristics of women included in the study (*N* = 135)

Demographics and ultrasound findings	Median (range)
Age (years)	40 (26–53)
Gravidity	1 (0–6)
Parity	0 (0–3)
Time between ultrasound assessments (days)	666 (181–2984)
Number of endometriotic nodules at visit 1	2 (1–7)
Number of endometriotic nodules at visit 2	3 (0–7)

consequently to the reduction in size of the rectovaginal space nodules.

The median number of endometriotic nodules per woman at the initial visit 1 was 2 (range: 1–7). At the follow-up visit 2, the median number of nodules increased to 3 (range: 0–7) ($p < 0.001$). At visit 1, all women had in total 349 nodules detected, whereas at visit 2, 133/135 women had in total 398 endometriotic nodules detected. In 38/135 (28%, 95% CI: 21–37) women, new nodules were recorded. Two women with small solitary nodules in the rectovaginal space had complete disease resolution. In addition to these, 5/135 (4%, 95% CI: 1–8) women had spontaneous regression of some of the nodules. All regressing nodules were located in the rectovaginal space.

In order to evaluate how endometriosis progressed or regressed in each woman over time, we calculated the change in mean size of the nodules detected at visit 1 over the course of time. In addition, to the 38 women who had "de novo" nodules observed at visit 2, there were 12 women who had the same number of nodules but experienced a meaningful increase in nodule size (>2.6 mm). There were 7/135 (5%, 95% CI: 2–10) women who had a lower number of nodules observed at visit 2 and additionally 10 women (7%, 95% CI: 4–13) who had the same number of nodules but experienced a meaningful reduction in nodule size. There were 68/135 women (50%, 95% CI: 42–59) who had the same number of nodules at visit 1 and visit 2 and did not experience any meaningful progression or regression in the size of the nodules. By considering the increase in nodule number or size as criteria for endometriosis progression, we have observed progression in 50/135 (37%, 95% CI: 29–46) women and regression in 17/135 (13%, 95% CI: 8–19) women. The rate of progression in reference to the number of nodules seen at visit 1 is presented in Figure 2. Women who only had one endometriotic nodule seen at visit 1 were significantly more likely to experience progression compared to women who had more than one nodule (22/43; 51%, 95% CI: 35–67 vs. 28/92; 30%, 95% CI: 21–41; $p = 0.02$). The median change in the mean diameter of nodules per woman in the follow-up was +0.13 mm (range: −11.67 – +5.83) with an annual growth rate of +0.09 mm/year (range: −6.65 – +6.45). The difference in the follow-up time between women who experienced progression and those who had not (831 days (194–2127) vs 634 days (181–2984), $p = 0.09$) was not statistically significant (Figure 3). There was also no correlation between the age of women and the rate of change in nodule size ($p = 0.67$).

of the pouch of Douglas, classifying the disease as severe. Among women with severe endometriosis, in 1/116 (1%, 95% CI: 0–4), the condition was categorized as moderate at follow-up, which was

Progression of endometriosis in reference to the number of nodules seen at initial visit (V1)
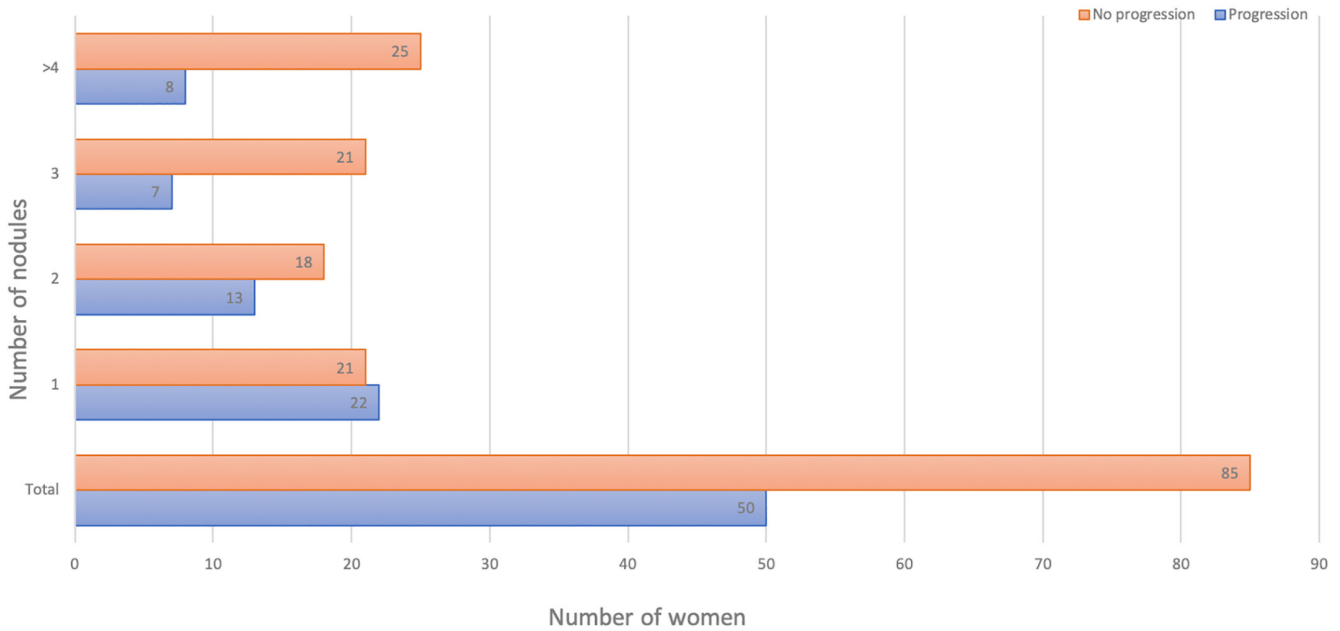

FIGURE 2 Endometriosis progression at follow up appointment (V2) in reference to the number of nodules seen at initial visit (V1).
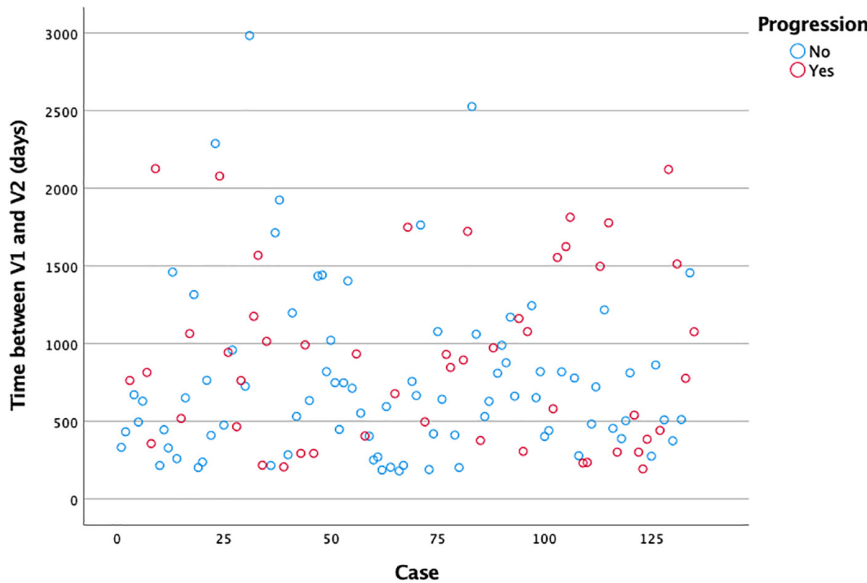

FIGURE 3 Scatter graph demonstrating follow-up time in each woman stratified according to occurrence of endometriosis progression.

Next, we focused on the specific pattern of nodule behavior considering their location. Hence, we conducted the analysis per each specific nodule as demonstrated at the first visit 1. The most common site for endometriotic nodules was the posterior compartment of the pelvis (276/349 [79%; 95% CI: 74–83]). The remaining nodules were seen in the bowel (60/349 [17%; 95% CI: 13–22]) and in the anterior compartment of the pelvis (13/349 [4%; 95% CI: 2–6]). There was no change in the median of mean diameters of all nodules during the study period (0.00mm [range: −28.67– +8.33]). The location of nodules was not significantly associated with the change in size. The median change in size for nodules in the posterior compartment was +0.33mm (range: −28.67– +8.33), compared to −0.67mm

(range: −16.33 – +3.67) ($p = 0.92$) in the anterior compartment and +0.00mm (range: −8.00 – +7.00) ($p = 1.00$) for bowel nodules. The median yearly change in size of nodules in the posterior compartment was +0.09 mm/year (range: −7.16 – +7.53), compared to −0.30 mm/year (range: −3.48 – +3.25) in the anterior compartment ($p = 0.14$). There was a moderate negative correlation between the initial size of endometriotic nodules and the change in the size of nodules. Larger nodules were more likely to decrease in size than smaller nodules (Spearman's rank correlation of −0.27, $p < 0.001$) (Figure 4).

Using logistic regression analysis, the higher number of nodules at visit 1 (OR 0.73, 95% CI: 0.56–0.95) and the cumulative size of all nodules at visit 1 (OR 0.96, 95% CI: 0.94–0.99) were significant
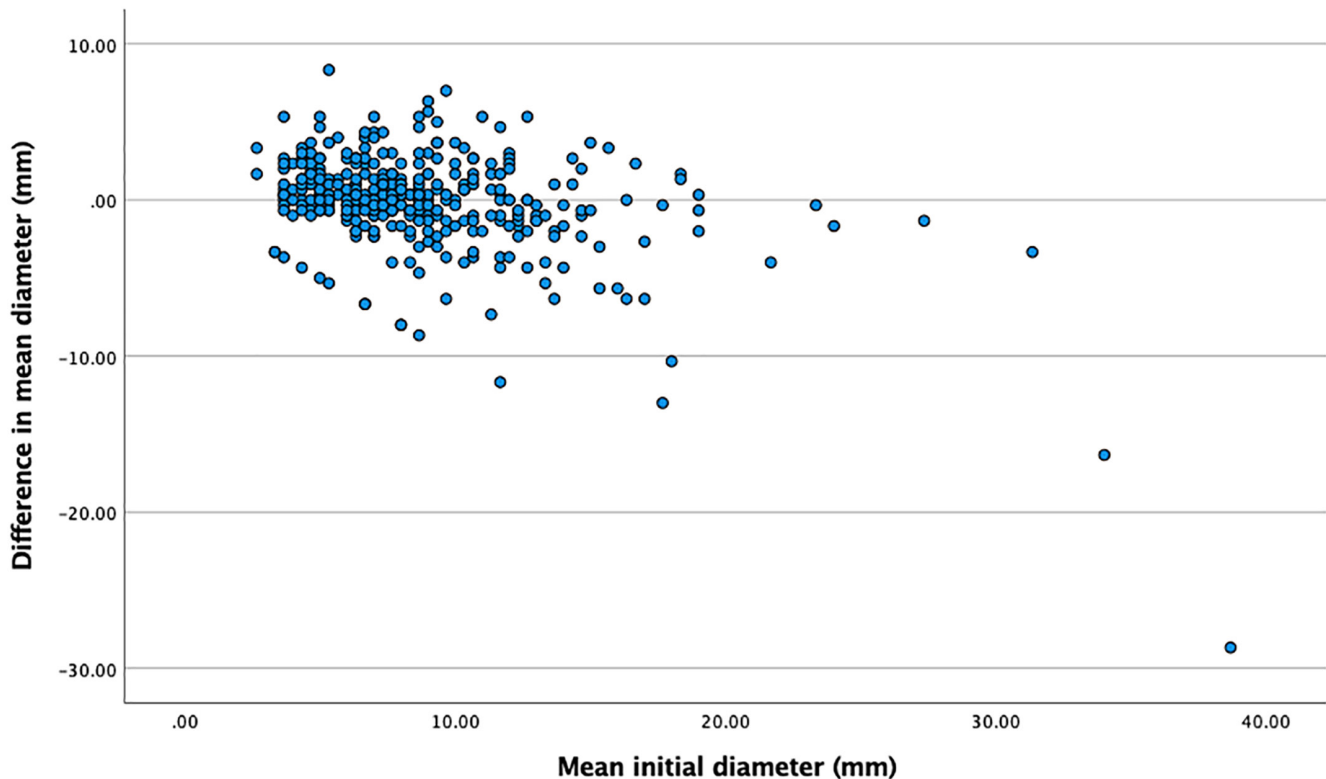
FIGURE 4 Scatter plot demonstrating the correlation between initial nodule size and change in size during follow up.

TABLE 3 Analysis of possible predictors for endometriosis progression

Characteristics	Disease progression OR (95% CI)	p-value
Age at presentation	1.02 (0.96–1.08)	0.58
Time between visits	1.00 (1.00–1.00)	0.13
Severe disease at first visit	2.46 (0.77–7.89)	0.13
Previous surgery for endometriosis	0.83 (0.41–1.68)	0.59
Gravidity	1.08 (0.83–1.41)	0.58
Parity	1.04 (0.71–1.52)	0.86
Number of nodules at first visit	0.73 (0.56–0.95)	**0.02**
Cumulative size of all endometriotic nodules at first visit	0.96 (0.94–0.99)	**0.01**

Abbreviations: 95% CI, 95% confidence interval; OR, odds ratio

Note: The bold values indicate significant results.

negative predictors for disease progression (Table 3). None of the clinical characteristics were able to predict the chance of progression or regression of endometriosis.

4 | DISCUSSION

Our study has shown that in majority of women with DE who experience mild or no symptoms, the condition is static, or even regresses.

The progression of DE was observed in just over a third of women. In one of the early studies demonstrating the natural course of endometriosis, Fedele et al. included women who underwent laparoscopic management of endometriosis, but rectovaginal nodules were managed conservatively in asymptomatic women.[15] Out of the 88 included women, only six developed either symptoms attributable to endometriosis or experienced increase in nodules size over the course of follow-up. Netter et al. carried out a retrospective analysis of 43 women who had undergone MRI to monitor their rectosigmoid endometriosis. They showed progression of bowel endometriosis in 28% of cases.[10] In this study, amenorrhea induced either medically, by pregnancy or breastfeeding was associated with lower chance of disease progression. Progression of rectosigmoid nodules was seen in 39% of women who had normal cycles, 34% with intermitted amenorrhea, in and in no women with continuous amenorrhea. In a more recent study, Abrao et al. used transvaginal ultrasound to monitor the behavior of bowel endometriosis in 164 women.[11] Their findings showed that bowel endometriosis remained stable over a prolonged period, which is consistent with our observations. However, it is important to recognize that bowel endometriosis is rarely an isolated abnormality and concomitant endometrial lesions affecting other pelvic organs are very common. In our cohort, there were only 7/135 (5.2%) women who were diagnosed with isolated bowel endometriosis. Therefore, we believe studies on the natural progression of endometriosis should include all detectable endometriotic lesions in individual patients rather than focusing on a single site.

The findings of all three studies are at odds with the widely held view that endometriosis is a progressive disease. It is possible that a single primary event or recurrent secondary events could result in the development of nodules rather than a continuously progressive disease.[16] Our study showed that larger nodules are more likely to decrease in size, which also challenges the concept of continuous progression. Early in the development of the endometriotic nodules, the main processes are probably angiogenesis and inflammation, which contribute to the formation and growth of the lesions. However, in mature lesions, this could lead to fibrotic changes and regression.[17] Hence, in advanced stages of their development, the endometriotic nodules tend to stop growing or even decrease in size. It should still be emphasized, that even in the group of women with only solitary endometriotic nodules, only half have experienced significant progression of the disease. The growth rate of endometriotic nodules was not uniform and morphological changes on ultrasound need to be correlated with the woman's symptoms and quality of life scores for the planning of management.

Two women in our study had a complete resolution of endometriotic nodules. An additional five women had resolution of some, but not all, nodules. All resolving nodules were visualized in the rectovaginal space. Complete resolution of all nodules, however, appeared to be a relatively rare occurrence. Once the deep disease was established, it tended to persist when managed expectantly. Since all resolving nodules were seen in the rectovaginal space, it could be hypothesized that similarly to the probable development of ovarian endometriosis, rectovaginal nodules may develop after episodes of acute intra-abdominal bleeding and inflammation of organized blood clots.[13] Depending on the subsequent physiological events, these could resolve or progress into true endometriotic nodules with final development of fibrosis. This means that if an ultrasound scan is performed in the early stages of these processes, organized blood clots resembling the nodules could regress on follow-up scans.

Our study included a selected population of women who were asymptomatic or experienced only mild symptoms and did not require any form of active intervention. This means that less than one third of all women seen for endometriosis and screened for inclusion were included in the final analysis. Nonetheless, the results indicate that medical or surgical treatment with the sole objective of preventing the progression of the disease in the absence of significant clinical symptoms, is unlikely to be beneficial. Surgical treatment exposes women to significant risks, including trauma to visceral structures, which may result in life-impacting morbidity.[18] The development of adhesions following surgery may result in worsening pain symptoms, bowel dysfunction, tubal factor infertility or problems with access to egg collection during fertility treatment. In addition, operative management of ovarian endometriosis has shown to be detrimental to ovarian reserve.[19] Given that, operative treatment could be reserved for women whose quality of life is impaired by their disease. The only exception are women with endometriosis of the urinary tract who may develop ureteric obstruction and hydronephrosis even when asymptomatic.[20,21] The aim of medical treatment of endometriosis is suppression of the disease using a wide variety of hormonal medications such and the combined and progesterone-only pill, Mirena intrauterine system, dienogest, aromatase inhibitors and gonadotropin releasing hormone agonists. The treatment is usually prolonged and can be associated with significant side-effects. In addition, most of the available treatment options are either contraceptives or cause suppression of ovarian activity which prevents women from trying for pregnancy for the duration of treatment.[22]

A significant limitation of our study is the lack of generally accepted criteria to define the progression of endometriosis. In a previous study, we demonstrated the reproducibility and intra-observer variability when evaluating the size of endometriotic lesions.[14] To minimize the chance of type 1 error, we have adopted our previously published 95% confidence interval limits of intraobserver variability when setting the cutoff for defining disease progression and regression. Another major limitation of this study is that it excludes symptomatic women who opt for medical or surgical management. It is more likely that women with more severe symptoms choose to have medical or surgical intervention and that this selected population may have a more progressive disease pattern. However, our study demonstrated no difference in the progression rates of the disease when comparing women that had previous surgical treatment compared to those that did not. The study is also limited by its retrospective nature. Methodologically robust, prospective studies of women who opt for expectant management of endometriosis could avoid recall bias and limit the selection bias. Women who opt for intervention may have a functionally different type of disease that lowers the clinician and woman's threshold for treatment.

5 | CONCLUSION

We have demonstrated that DE in most asymptomatic or mildly symptomatic women who opt against active treatment of endometriosis, the condition is either static or shows evidence of slow progression. A substantial change in the extent of the disease was observed in just over one third of women. Only the number of endometriotic nodules detected at the initial visit was a negative predictor of disease progression, probably representing the normal pathophysiological changes occurring in the natural development of endometriosis. There was no other demographic, clinical or anatomical factor that could allow reliable prediction of progression or regression of the disease. Hence, morphological changes in endometriosis on ultrasound should be interpreted in association with clinical symptoms when deciding on the most appropriate management of individual women affected by this common condition.

AUTHOR CONTRIBUTIONS
DJ made substantial contribution to the concept and design of the study. JK contributed to design of the study and examined the data.

JK, EB and DJ analyzed the data and wrote the article. EB, SN, TT and PC assisted in the analysis and interpretation of data. All authors contributed to revising the article for important intellectual content and approved the final version of the manuscript to be published.

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