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Vaginal contraception with NuvaRing decreases symptoms and uterine features of adenomyosis: A prospective evaluation☆,☆☆

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ABSTRACT

Objective: We aimed to assess the effects of contraception with NuvaRing on ultrasound signs and symptoms of women with adenomyosis.
Study design: We conducted a prospective self-controlled observational study on women with adenomyosis who required contraception with NuvaRing. Exclusion criteria were actual use or contraindications to hormonal contraception. NuvaRing was administered in a continuous regimen, one ring every 3 weeks without hormone-free intervals, to avoid menses. Adenomyosis, suggested by clinical signs, was confirmed by ultrasonography. Before and after 6 months of NuvaRing, we evaluated uterine volume, direct and indirect ultrasound signs of adenomyosis, and the severity of menstrual, intermenstrual pain, and pain during intercourse, by a 10-cm visual analog scale (VAS).
Result(s): This study included 42 women, 30.0 ± 4.5 years old, with a BMI of 22.8 ± 1.8 kg/m². All were nulliparous except one. Following 6 months of NuvaRing, uterine volume decreased of 14.4 ± 13.5% ($p = 0.001$). A similar decrease was observed in six women switching from dienogest. Direct ultrasound signs of adenomyosis per patient (total signs/n women) decreased from 0.5 (range 0–3) to 0.08 (range 0–2) ($p = 0.003$), and indirect signs, from 2.8 (range 1–5) to 1.5 (range 0–5) ($p = 0.001$). The VAS for menstrual pain decreased from 8.3 ± 1.2 to 3.9 ± 2.5 ($p = 0.001$), for intermenstrual pain from 6.6 ± 1.4 to 2.9 ± 1.7 ($p = 0.001$), and for pain during intercourse from 7.0 ± 1.4 to 2.9 ± 1.7 ($p = 0.001$). The decrease of menstrual pain was significantly associated with the reduction of uterine volume ($p = 0.003$).
Conclusion(s): Our findings demonstrate that contraception with NuvaRing is a viable contraceptive option for women with adenomyosis.
Implications: In women with adenomyosis contraception with NuvaRing is useful and can be proposed because it reduces the clinical signs and the uterine ultrasound features of adenomyosis.

1. Introduction

Adenomyosis is a common, debilitating gynecological disease characterized by ectopic endometrial glands invading the myometrium [1]. It can be either diffuse or localized in any part of the uterus. Risk factors are age, endometriosis, multiple births, uterine surgery, spontaneous miscarriage [2], as well as peculiar cervical conditions such as a highly retroflexed uterus [3] or a stiff internal cervical os [4]. Histological [5] and ultrasound [6] data indicate that the prevalence of adenomyosis ranges from 20% to 45% in asymptomatic and symptomatic women, respectively. Adenomyosis is associated with an enlarged uterus, heavy menstrual bleeding, pelvic pain, infertility, and pregnancy complications [7–9].

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Up to now, there is no specific medical management for adenomyosis. Symptoms improvement can be achieved by hormone withdrawal at adenomyotic tissue via the administration of GnRH analogs alone, in association with aromatase inhibitors, or by the administration of progestins like danazol or levonorgestrel continuously released by intrauterine systems [10–14]. Several reports suggest that the continuous administration of the progestin dienogest ameliorates adenomyosis symptoms [15]. Our previous research indicated that dienogest-based hormonal contraceptives decrease the duration of menstrual bleeding, alleviate menstrual pain, and alter the ultrasound characteristics of adenomyosis [16].

There is a notable lack of data on the effectiveness of other contraceptives or even other routes of contraceptive administration. For instance, one study found that the contraceptive vaginal ring was more effective than the transdermal patch in reducing symptoms associated with deep infiltrating endometriosis [17]; however, it did not assess the potential co-occurrence of adenomyosis.

Hormones inserted into the vagina achieve a concentration in the pelvic circulation that is likely higher than that achieved by systemic (oral or transdermal) administration [18].

Because of that, in the present study, we investigated whether contraception performed with a vaginal ring can modify ultrasound features and symptoms of adenomyosis.

2. Materials and methods

2.1. Study design and patient population

This research presents a prospective self-controlled observational analysis of women diagnosed with adenomyosis who necessitated contraception via the vaginal ring. All women participating in this study provided written informed consent. The collected data included patient management, comprising diagnostic procedures and treatments, conducted following Good Clinical Practice guidelines. Data were recorded in an electronic database and subsequently retrieved for analysis. The local ethics committee approved the study (CER Liguria 305/2022-Db id 12401, 08/03/2023). The research was conducted at a University Hospital outpatient service for contraception between March 2023 and June 2024. Premenopausal women aged 21–45 years requiring the vaginal ring for contraception (NuvaRing; Organon Italia S.r.l, importer Farmed S.r.l. Napoli, Italy) were selected based on the presence of adenomyosis. Inclusion criteria were being of reproductive age, need of contraception, preference to use vaginal contraception, and presence of adenomyosis. Exclusion criteria were contraindications to the use of hormonal contraceptives, desire to use a contraceptive other than the vaginal ring, absence of adenomyosis, and actual use of hormonal contraceptives. Ring prescription was based solely on women's preferences and choices. Six women had already a diagnosis of adenomyosis and were using dienogest for symptom control. In the remaining women, adenomyosis was initially suspected by clinical signs (heavy menstrual bleeding, intense menstrual pain, increased uterine volume at bimanual examination). In all women, the presence of adenomyosis was confirmed by an ultrasound evaluation performed by an expert sonographer (A.X.). Women received a prescription for vaginal contraception with NuvaRing in a continuous regimen (one ring every 3 weeks continuously) to induce amenorrhea and to avoid menstrual-related symptoms. A follow-up evaluation was performed after 6 months of contraceptive use, as normally scheduled in our clinical practice. All enrolled women completed the 6-month evaluation, with no participants lost to follow-up. The following information was recorded during the baseline evaluation: age, number of births, previous uterine surgery, body mass index (BMI), actual use of hormonal and non-hormonal therapies (such as dienogest and/or medicine to treat pain like non steroidal anti-inflammatory drugs or opioids), co-presence of endometriosis, and presence of heavy menstrual bleeding. Scores for menstrual pain, pain at intercourse, and intermenstrual pain were evaluated via a 10-cm visual analog scale (VAS) at baseline and after 6 months of vaginal contraception. We considered moderate and severe pain a VAS score of > 4 and > 7, respectively.

2.2. Ultrasound examination

Our experienced sonographer conducted ultrasound examinations in our outpatient gynecological imaging clinic. Our policy mandates the acquisition of blind data by ensuring that the sonographer remains unaware of the treatment the woman is undergoing during the ultrasound investigation. The ultrasound investigation was performed by a transvaginal (TVS) probe, outside the menstrual cycle period, indifferently if in the proliferative or secretory phase, using a GE E6 (GE Medical Systems, Zipf, Austria) ultrasound machine with a wideband 5–9 MHz transducer. Power Doppler was performed using fixed, preinstalled settings (frequency, 6–9 MHz; pulse repetition frequency, 0.6–0.3 kHz) to distinguish myometrial cysts from blood vessels. Uterine volume was measured using the ellipsoid formula (uterine longitudinal diameter × transverse diameter × anterior-posterior diameter × 0.5223) without considering the cervix.

Ultrasound diagnosis of adenomyosis was defined by the presence of at least one direct sign or, when absent, by the co-presence of at least three indirect signs according to the Morphologic Uterus Sonographic Assessment (MUSA) criteria [19]. The following ultrasound features were considered direct signs of adenomyosis: (1) myometrial anechoic lacunae or cysts, seen as a round anechoic area within the myometrium; (2) hyper-echogenic islands; (3) sub-endometrial lines and buds. Conversely, the indirect signs examined were the following: (4) heterogeneous myometrium, seen as irregular myometrial echo-texture with decreased or increased echogenicity; (5) hypo-echoic striation in the myometrium (fan-shaped shadowing) seen as a pattern of thin acoustic shadows not arising from echogenic foci; (6) asymmetrical myometrial thickening of the uterine wall; (7) globular uterine configuration; (8) presence of a poorly defined, thickened, irregular and interrupted endo-myometrial junctional zone (JZ). The comparison of anterior and posterior myometrial thicknesses characterized asymmetrical uterine wall thickening. We calculated the anterior-to-posterior thickness ratio, with values approaching one indicating symmetrical walls, whereas values above or below one denotes asymmetry [16]. Ultrasound diagnosis of pelvic endometriosis was performed in line with the International Deep Endometriosis Analysis (IDEA) consensus opinion by 2D-TVS [20]. Uterus volume and prevalence of direct and indirect signs were recorded at baseline and after 6 months of vaginal contraception.

2.3. Statistical analysis

Statistical analysis was performed using Stat View statistical software (version 5.01.98, SAS Institute Inc., Cary, NC, USA). Descriptive analysis was applied. Comparisons of continuous data were performed using a paired *t*-test or Wilcoxon test as appropriate. The Chi-squared test was used to compare changes in prevalence over time. Initially, we performed linear univariate regression analyses to evaluate the relationship between each candidate predictor and alterations in pain symptoms. Predictors exhibiting a significant univariate association ($p < 0.05$), along with the change in uterine volume, were eventually incorporated into a multivariate regression model to assess their independent impact on alterations in pain symptoms during vaginal ring usage. Continuous data were analyzed as collected, whereas categorical data were represented as dummy variables, assigning absence or presence of the determinant. Factors that did not show a significant relationship with uterine volume or VAS changes are systematically excluded from the analysis, retaining only those independently associated

Table 1
Characteristics of the 42 women diagnosed with adenomyosis recruited at an Italian University Hospital from 2022 to 2024

Age (years)	30.0 ± 4.5
BMI (kg/m²)	22.8 ± 1.8
Full-term pregnancies	1/42 (2.4%)
Previous uterine surgery	4/42 (9%)
Coexistence with endometriosis	29/42 (53%)
Previous use of Dienogest	6/42 (14.3%)
Moderate/Severe menstrual pain	42/42 (100%)
Moderate/Severe intermenstrual pain	40/42 (95%)
Moderate/Severe pain at intercourse	40/42 (95%)
Heavy menstrual bleedings	36/42 (86%)
Medicine for treatment of pain	37/42 (88%)
Focal adenomyosis	3/42 (7%)
Diffuse adenomyosis	39/42 (92%)
of anterior wall	5/9 (55%)
of posterior wall	4/9 (44%)
of both walls	30/39 (77%)

BMI, body mass index.

with the dependent variable. A two-tailed *p*-value of 0.05 was deemed significant. Numerical data are presented as mean ± standard deviation (SD) or minimum-maximum range.

2.4. Power of the study

The sample size was determined to identify a within-subject change in uterine volume from baseline to 6 months. According to existing literature, a medium effect size (Cohen's $d = 0.5$) was considered for sample size assessment [21]. A two-sided paired *t*-test with $\alpha = 0.05\%$ and 80% power necessitated 33 participants. The target enrollment was raised to 40 women to accommodate a potential attrition or noncompliance rate of up to 20%.

3. Results

3.1. Sample characteristics

Table 1 presents the characteristics of the women. The average age of women was 30.0 ± 4.5 years, with a BMI of 22.8 ± 1.8 kg/m². A limited number of participants had prior uterine surgery, with 29 individuals (53%) also presenting with concomitant endometriosis (Table 1). The majority of women exhibited diffuse adenomyosis affecting either the entire uterus or localized to the anterior or posterior wall. Six women (14%) underwent hormone therapy with dienogest for over 6 months before transitioning to continuous NuvaRing to address contraceptive requirements. The majority of women experienced moderate to severe menstrual pain, intermenstrual pain, or pain during intercourse, with most utilizing medication for symptom relief (Table 1). All women experienced heavy menstrual bleeding except six women on dienogest who were amenorrheic.

3.2. Ultrasound parameters

During treatment, a decline in uterine volume was observed in 39/42 (92.9%) women. Uterine volume decreased from 53.1 ± 27.3 cm³ to 45.8 ± 26.6 cm³ ($p = 0.0001$), with a net decline of −7.2 ± 7.7 cm³ (−14.5 ± 13.6%) (Fig. 1) (Table 2). The decrease was observed also in women on previous treatment with dienogest

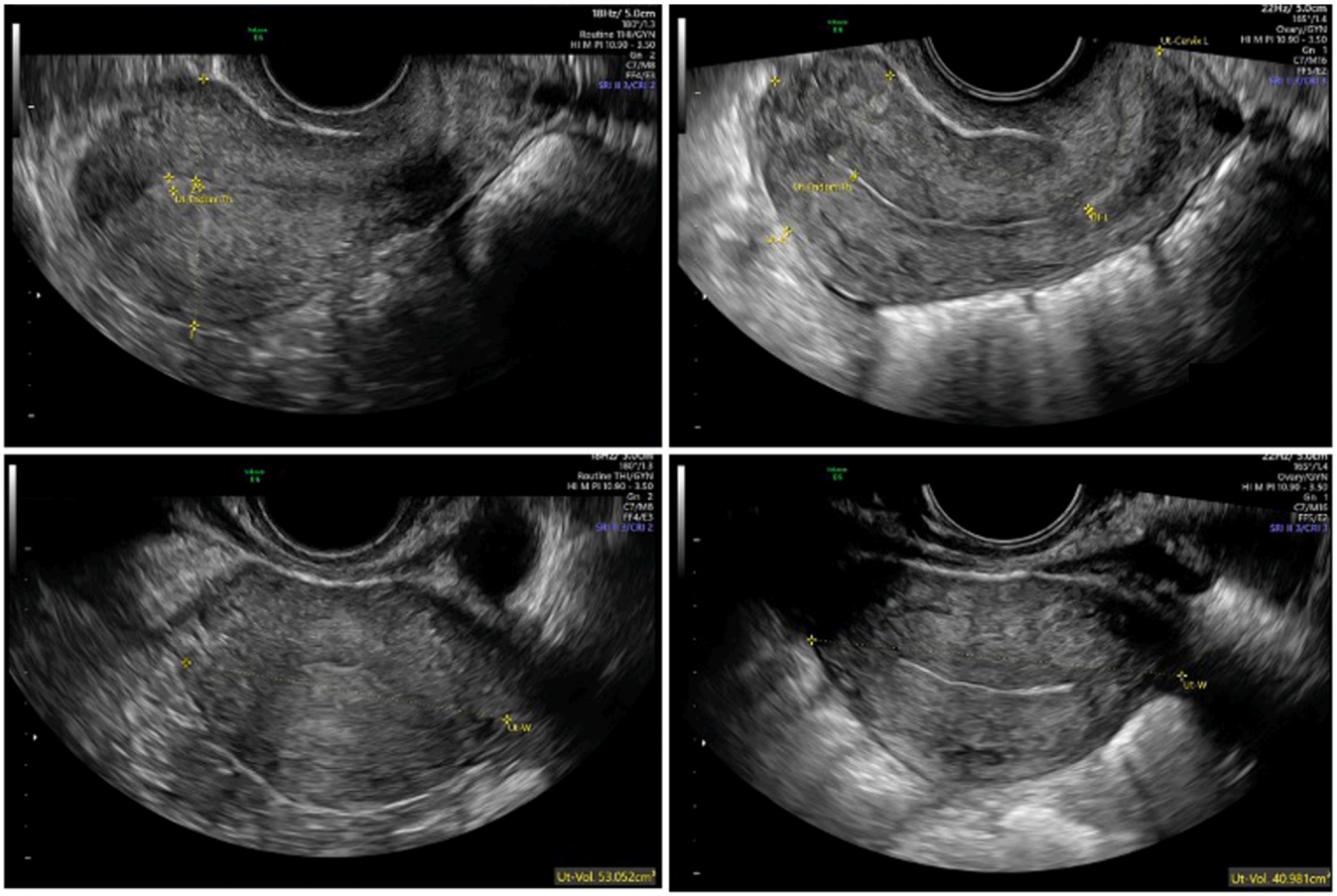

Fig. 1. Longitudinal (top) and transverse (bottom) ultrasound scans of a uterus with adenomyosis are presented before (A) and after 6 mo (B) of vaginal ring use. The scans demonstrate a reduced uterine asymmetry and volume in a woman recruited at an Italian University Hospital between 2022 and 2024.

Table 2
This analysis examines the ultrasound characteristics of the uterus and the clinical manifestations of adenomyosis before and after 6 mo of contraception using NuvaRing in 42 women diagnosed with the condition, recruited from an Italian University Hospital between 2022 and 2024

Ultrasound features	Baseline	After 6 mo	*p* value
Uterine volume cm³	53.1 ± 27.3	45.8 ± 26.1	0.001
Myometrial cysts (%)	8/42 (19%)	2/42 (5%)	0.092
Hyperechogenic islands (%)	8/42 (19%)	3/42 (7%)	0.194
Sub-endometrial lines and buds (%)	5/42 (12%)	1/42 (2%)	0.200
All direct signs	21	6	
Number of direct signs per women[a]	0.5 (0–3)	0.08 (0–2)	0.003
Wall asymmetry (%)	27/42 (64%)	12/42 (28%)	0.002
Fan-shaped shadowing (%)	22/42 (52%)	6/42 (14%)	0.004
Heterogeneous myometrium (%)	42/42 (100%)	30/42 (71%)	0.002
Uterus globular configuration (%)	19/42 (45%)	10/42 (24%)	0.065
Irregular or interrupted jz (%)	7/42 (17%)	5/42 (12%)	0.757
All indirect signs	117	63	
Number of indirect signs per women[a]	2.8 (1–5)	1.5 (0–5)	0.001
Pain symptoms			
Menstrual pain (vas)	8.3 ± 1.2	3.9 ± 2.5	0.001
Intermenstrual pain (vas)	7.0 ± 1.4	2.9 ± 2.3	0.001
Pain at intercourse (vas)	6.6 ± 1.4	2.9 ± 1.7	0.001

Statistical comparisons included paired *t*-tests for continuous variables and Chi-squared tests for categorical variables. Variables highlighted with (a) were examined using paired Wilcoxon tests rather than *t*-tests.

[a] Total number of signs/n° of women. The data are provided as mean (minimum-maximum), with *p*-values corresponding to paired Wilcoxon tests.

(−13.8 ± 12.1 cm³, $p < 0.001$). Direct signs of adenomyosis, like myometrial cysts, hyperechogenic islands, and sub-endometrial buds and lines, singularly declined, even if not significantly (Table 2). At baseline and after 6 months of NuvaRing we found 21 and six direct signs, respectively, and the mean number of direct signs per woman (total signs/n° women) significantly decreased ($p = 0.003$) (Table 2). Indirect signs of adenomyosis also showed a decline, with significant reductions observed in wall asymmetry ($p = 0.002$), fan-shaped shadowing ($p = 0.004$), and heterogeneous myometrial echogenicity ($p = 0.002$) (Table 2). At baseline and after 6 months of NuvaRing we found 117 and 63 indirect signs, respectively, and the mean number of indirect signs per woman significantly decreased ($p = 0.001$) (Table 2).

3.3. Symptoms

During treatment, we noted a significant reduction in VAS scores for menstrual pain (8.3 ± 1.2 to 3.9 ± 2.5; $p = 0.001$), intermenstrual pain (6.6 ± 1.4 to 2.9 ± 1.7; $p = 0.001$), and pain during intercourse (7.0 ± 1.4 to 2.9 ± 1.7; $p = 0.001$) (Table 2). Alterations in uterine volume directly correlated with modifications in pain symptoms (Appendix A). The net change in uterine volume correlated with a decrease in menstrual pain (R^2 0.299; $p = 0.003$). The regression analysis was binomial, exhibiting a steeper slope in the initial segment ($y = -3.317 + 0.255x + 0.007x^2$) (Fig. 2). Women who did not exhibit a reduction in uterine volume did not report an improvement in menstrual pain. We identified a notable binomial regression linking the decrease in uterine volume to the reduction in intermenstrual pain (R^2 0.178; $p = 0.039$) ($y = -3.215 + 0.162x + 0.006x^2$) and pain during intercourse (R^2 0.252; $p = 0.008$) ($y = -3.079 + 0.271x + 0.010x^2$) (Appendix A). The alleviation of symptoms such as menstrual pain, intermenstrual pain, and dyspareunia was not influenced by prior use of dienogest or the presence of deep infiltrating endometriosis (Appendix B). Age, BMI, and prior gynecological surgery did not affect the symptom reduction noted during the use of the ring (Appendix B).

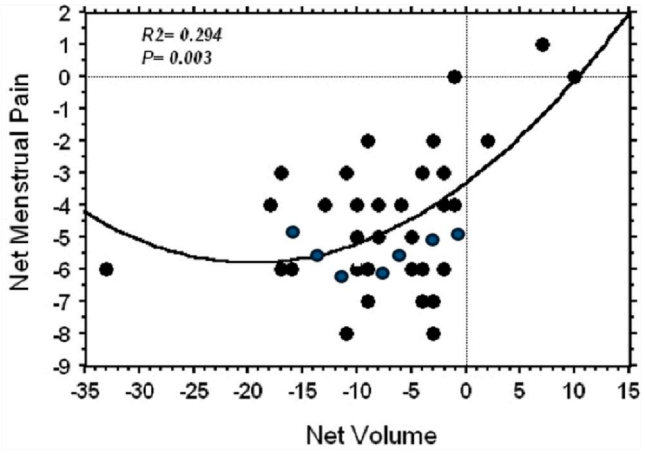

Fig. 2. Regression analysis was conducted to examine the relationship between changes in uterine volume and changes in menstrual pain VAS scores over a 6-mo period of vaginal ring administration in 42 women recruited from an Italian University Hospital between 2022 and 2024. VAS = visual analog scale.

4. Discussion

4.1. Main results

Our study shows that in women with adenomyosis, contraception with NuvaRing, administered in a continuous regimen for 6 months, determined a reduction of uterine volume and the ultrasound features of adenomyosis along with symptoms of menstrual pain, intermenstrual pain, and pain at intercourse. Only three subjects did not show a reduction in uterine volume. The reduction of pain symptoms was related to the decrease in uterine volume.

4.2. Interpretation

Ultrasound features of adenomyosis are reduced by the continuous administration of NuvaRing. A certain degree of progestin resistance in patients with adenomyosis was reported [22], but a clinical response can still be achieved by hormone modulation. Gestodene-containing oral contraceptives were effective in suppressing aromatase expression both in the eutopic and in the ectopic endometrium of adenomyotic foci [23], and effects of hormone therapy on symptoms related to adenomyosis have been well reported in the literature [16,24–26].

Recent data indicate that the severity of menstrual pain is associated with the ultrasound features of adenomyosis [27]. This finding is consistent with our data showing that pain symptoms declined in conjunction with the improvements in the ultrasound features of adenomyosis, particularly with the reduction of uterine volume. The effect was evident with mild to moderate decreases in uterine volume, followed by a plateau. The ring's effect on symptoms was not affected by age, parity, BMI, prior gynecological surgery, or deep infiltrating endometriosis. In women with adenomyosis, dienogest administration is employed to alleviate symptoms [15]; however, it does not decrease uterine volume [15,28] nor prevent uterine regrowth following GnRH analog withdrawal [29]. In our study, women on dienogest experienced a marked reduction of uterine volume when shifted to the ring. Although this analysis was based on a limited sample of six women, the results reached statistical significance and suggest that the vaginal ring may be more effective than dienogest in alleviating symptoms and improving uterine manifestations of adenomyosis.

In a prior investigation, we documented that hormonal contraceptives, particularly those based on dienogest, lead to a reduction in uterine volume by diminishing adenomyotic tissue while showing no effect on the volume of uteri devoid of adenomyosis [16]. In this study, the ring's ability to decrease uterine volume appears contingent upon its effectiveness in reducing adenomyotic tissue, as evidenced by the observed reduction in all ultrasound characteristics of adenomyosis. The ring demonstrates efficacy through its enhanced capacity to stabilize and control the endometrium [30], likely attributable to the elevated progestin concentration delivered to the uterus via the vaginal route of administration [29].

It is important to note that in ring users, the diminished ultrasound characteristics of adenomyosis may affect the diagnostic accuracy of the condition.

Multiple hormonal therapies, both with and without contraceptive purposes, can be utilized to address the symptoms of adenomyosis. These include GnRH agonists, GnRH antagonists, and levonorgestrel intrauterine devices [31]. These therapies may incur higher costs, present greater management challenges, or not be primarily designed for contraceptive purposes.

4.3. Strength and weakness

The potential weakness of the study lies in the absence of histological confirmation for the diagnosis of adenomyosis. However, transvaginal ultrasound has demonstrated sensitivity and specificity for diagnosing adenomyosis comparable to histology or magnetic resonance imaging [32–34]. Subsequent research has built upon the reliability of ultrasound diagnosis to identify medical therapies aimed at alleviating symptoms and long-term consequences of adenomyosis [35].

The follow-up period was restricted to 6 months; consequently, more extended evaluation periods are necessary to determine the long-term efficacy of the ring and its ability to mitigate the natural progression of adenomyosis [36].

Not all women exhibited severe adenomyosis, as their uterine volume was lower than that reported in other studies. This observation corresponds with the studied population, which consists mainly of young, nulliparous women. The sample size was not large yet sufficiently powered, demonstrating significant effects with consistent data.

This study lacked a control group without therapy. Adenomyosis typically advances over time [36], contrary to the findings observed in our research during the 6-month application of the vaginal ring. No other treatment group was included, making a comparative analysis of the vaginal ring against other medical remedies for adenomyosis unfeasible.

4.4. Generalizability

The data were obtained in a single center, in a population of almost exclusively White women. Although we do not expect relevant differences, these data must be confirmed in other settings and populations. The vaginal ring was used in a continuous regimen without free interval periods. It should also be evaluated whether similar benefits can be achieved with the seven-day free hormone interval.

Although other studies are needed to confirm our data, present findings indicate that contraception with continuous combined hormonal therapy by vaginal ring decreases uterine volume, improves the ultrasound features, and markedly reduces symptoms of adenomyosis.

CRediT authorship contribution statement

Isabella Perugi: Data curation, Writing – review & editing, Investigation, Writing – original draft, Conceptualization. **Mattia Francesco Ferraro:** Writing – original draft, Writing – review & editing, Conceptualization, Investigation. **Angelo Cagnacci:** Writing – review & editing, Data curation, Writing – original draft, Formal analysis, Conceptualization. **Ambrogio P. Londero:** Writing – original draft, Conceptualization, Writing – review & editing, Data curation, Formal analysis. **Anjeza Xholli:** Writing – review & editing, Project administration, Data curation, Supervision, Formal analysis, Writing – original draft, Investigation, Conceptualization. **Francesca Oppedisano:** Writing – review & editing, Investigation, Conceptualization, Writing – original draft, Data curation.

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Appendix A. Supporting material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.contraception.2025.111016.

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