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Medical treatment for adenomyosis: long term use of progestins

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ABSTRACT

Background: Adenomyosis is a uterine disorder causing menstruation-related symptoms such as dysmenorrhea, heavy menstrual bleeding (HMB) and dyspareunia. A long-term management of the disease is required. Hormonal drugs are the most used, including a variety of progestins, even though few data are available on their long-term use in adenomyosis.

Objective: To evaluate the long-term efficacy of different progestins, including progestin-only pills (POP), for the management of adenomyosis-related symptoms.

Methods: A total of 140 patients (18-45 years) with adenomyosis were treated with progestins for at least three years. The treatment groups included dienogest (2 mg, $n=71$), levonorgestrel-releasing intrauterine device (52 mg, $n=25$), desogestrel (75 mcg, $n=20$), and drospirenone (4 mg, $n=24$). Symptoms were assessed using the Visual Analogue Scale (VAS) for pain and the Pictorial Blood Assessment Chart (PBAC) method for bleeding.

Results: Dienogest significantly reduced dysmenorrhea, dyspareunia, and HMB, with efficacy maintained over three years in most patients. However, after the first year 49% of patients required a switch to other treatments due to side effects or contraception need. The levonorgestrel-releasing intrauterine device also effectively managed HMB and pain, with 15% of patients switching treatment due to side effects. Both drospirenone and desogestrel improved HMB and dysmenorrhea, but desogestrel had a higher discontinuation rate due to reduced long-term efficacy. Norethisterone acetate was used as a second-line treatment in cases of intolerance or inadequate response.

Conclusion: Progestins are effective for the long-term management of adenomyosis symptoms. The flexibility in switching between different progestins or routes of administration may help in optimizing outcomes.

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Introduction

Adenomyosis is a benign uterine disease characterized by the migration and implantation of endometrial-like glands and stroma into the myometrium [1,2]. The condition represents a significant healthcare challenge due to its complex pathophysiology, diagnosis, and treatment [3,4]. The ectopic endometrial implant into the myometrium is driven by a combination of inflammatory and endocrine alterations, including increased activity of estrogen receptors and progesterone resistance. These changes lead to hyperperistaltic myometrial activity, endometrial inflammation, and neuroangiogenesis, thereby facilitating the ectopic growth of endometrial cells within the myometrium [5]. These pathogenetic changes explain the main symptoms of patients with adenomyosis: dysmenorrhea, dyspareunia, abnormal uterine bleeding (AUB), heavy menstrual bleeding (HMB), and infertility. Besides, in addition to the aforementioned symptoms, endometriosis and uterine fibroids are often associated with adenomyosis [6,7].

Symptoms, age and desire for pregnancy influence the choice of treatment, however there is no universal consensus regarding the standard management of adenomyosis [8,9]. Medical treatment represents the first line approach; non-steroidal anti-inflammatory drugs, iron supplementations and hormonal drugs are commonly prescribed, although they are often used off-label [4,10]. Different surgical or radiological intervention have also been proposed, such as laparoscopic or hysteroscopic removal of adenomyotic tissue, uterine artery embolization, high-intensity focused ultrasound, or radiofrequency ablation. These treatments have been shown to be effective with good short-term efficacy; however, limited data are available on recurrence and long-term outcomes [11–13].

Hormonal treatments are the most commonly used for managing adenomyosis-related pain and HMB, including gonadotropin-releasing hormone (GnRH) agonists and antagonists, progestins, combined oral contraceptives (COC), hormone-releasing intrauterine systems (IUSs). GnRH agonists or oral GnRH antagonists block the hypothalamus-pituitary-ovary axis (HPO) by inducing a pseudo menopausal state, whereas progestins act directly on endometrial cells inducing a pseudodecidualization [4,14], thus, stopping menstruation. GnRH agonists reduce uterine volume, induce amenorrhea, and provide pain relief in patients with adenomyosis; however, they are typically used for short-term periods (3 to 6 months) due to side effects and high costs [10].

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Conversely, progestins can be used for longer periods, but there is limited data on their long-term effectiveness in the medical treatment of adenomyosis.Thus, the present study aimed to provide an overview on the long-term efficacy of a variety of progestins, including progestin-only pills (POP), for the treatment of adenomyosis-related symptoms.

Methods

This observational cohort study involved a group of reproductive age patients ($n = 140$) with adenomyosis (mean age and body mass index: 32.6 ± 8.8 years and 25.1 ± 8.4 kg/m^2, respectively), followed up at our Center for Uterine Disorders. The inclusion criteria were: age between 18 and 45 years; a clinical diagnosis of adenomyosis (imaging signs and symptoms, either HMB or dysmenorrhea, or both); medical treatment with a progestin (dienogest [DNG], desogestrel [DSG], drospirenone [DRSP], levonorgestrel-releasing intrauterine device [LNG-IUD]); follow up for at least 3 years; no desire of pregnancy during the entire duration of observation. Patients with coexisting endometriosis or uterine fibroids were excluded from the study.

The imaging diagnosis of adenomyosis was based on transvaginal ultrasound (TVUS) or magnetic resonance (MRI) findings [15]. TVUS (Voluson E8/S10, GE HealthCare, Zipf, Austria, probe frequency 5–7.5 MHz) was performed with two-dimensional and three-dimensional evaluation, and color and power Doppler assessment. According to the revised Morphological Uterus Sonographic Assessment (MUSA) criteria, a diagnosis of adenomyosis was made if at least one of the direct features was detected [16]. At the first visit most of the patients were diagnosed for the first time (60%). Diffuse adenomyosis (77%) and focal adenomyosis (23%) were the most common phenotypes. Pre- and post-treatment assessments included the use of visual analogue score (VAS) of symptoms (measurement of pain severity for dysmenorrhea, non-menstrual pelvic pain and dyspareunia). The Pictorial Blood Assessment Chart (PBAC) method was used to determine semi-objectively the amount of menstrual blood loss [17]. Most of the patients suffered from dysmenorrhea (90%) with VAS ≥7, whereas HMB was present in 62% of patients.

The primary outcome was to assess the efficacy of progestins in alleviating pain and managing HMB over a 3-year follow-up period. The treatment groups at the beginning of study were as follows:

A. DNG (2 mg/day) ($n = 71$)
B. DSG (75 mcg/day) ($n = 20$)
C. DRSP (4 mg/day) ($n = 24$)
D. LNG-IUD (52 mg) ($n = 25$).

The choice of treatment was based on the patient's age, symptomatology, and contraceptive request or need. DNG was used for treating severe dysmenorrhea, DRSP or DSG in those requesting contraception, and LNG-IUD was used in patients aged >40 years who had completed their reproductive desire. In case of side effects or the need for contraception, the treatment was switched to a different progestin. In those cases, also norethisterone acetate (NETA) (5 mg/day) was used as a replacement for the initial treatment. Follow up visits were planned every 12 months or earlier in case of side effects and/or need to change therapy.

Ethical approval

The study protocol was approved by the local Ethics Committee (n.14558_oss approved on 28 May 2019). Before being enrolled in the study, patients provided informed written consent for their clinical data to be used for scientific research purposes.

Statistical analysis

Collected data were entered in an electronic database and analyzed with SPSS software (Statistical Package for Social Science; IBM SPSS Statistics 23, IBM Corporation). Continuous data were checked for normality by using normal probability plots. A descriptive analysis was conducted with the evaluation of position measures (mean, median) and dispersion indices (standard deviation, range) for the quantitative variables. Binomial variables are described as frequencies n (%). According to normality distribution of data, the Mann Whitney U test or independent-sample T test was used to compare continuous variables. Statistical analysis was performed to compare the outcomes of patients based on their treatment regimen and to determine the overall efficacy in managing adenomyosis over time. A p value < 0.05 was considered as statistically significant.

Results

Considering the entire patient cohort, progestin treatment led to a significant reduction in dysmenorrhea, chronic pelvic pain, and dyspareunia by 76.3%, 50.0%, and 57.7%, respectively, at the three-year follow-up ($p < 0.01$) (Table 1). PBAC score decreased from 203 ± 95 to 65 ± 35 ($p < 0.01$). Mean serum hemoglobin significantly increased from 9.5 g/dL to 13.5 g/dL ($p < 0.01$).

In the group of patients treated with DNG a significant improvement of dysmenorrhea, dyspareunia and HMB was observed during and after three years of treatment. However, 49.3% of patients (35/71) required a treatment switch due to short- or long-term side effects or contraceptive needs. Among these, 45.7% (16/35) switched to another treatment due to contraception request/need, while 22.8% (8/35) changed therapy because of bleeding. Other reported adverse effects prompting treatment changes included vaginal dryness (4/35, 11.4%), mood disturbances (3/35, 8.6%), and hair loss (2/35, 5.7%). As a result, 16 patients transitioned to LNG-IUD, 5 to DRSP, 2 to DSG, and 12 to NETA, the latter mainly in response to bleeding or hypoestrogenic symptoms (Table 2).

Treatment with DSG or DRSP was associated with a significant improvement in dysmenorrhea. However, 70% of patients receiving DSG (14/20) switched to another progestin during follow-up. In most of these cases (11/14, 78.6%), the switch was prompted by a progressive decrease in efficacy, primarily related to persistent pelvic pain and breakthrough bleeding. These patients were subsequently transitioned to DNG or DRSP, which offered a more favorable bleeding profile (Table 2). In the DRSP group, 45,8% of patients (11/24) switched treatment to DNG or LNG-IUD due to bleeding (5/11, 45.4%), persistent pelvic pain (3/11, 27.3%) or reduced libido (2/11, 18.2%). Among patients treated with the LNG-IUD, a significant improvement in HMB

Table 1. Pain symptoms at starting of study, and changes at 12 months and 36 months, considering all patients with adenomyosis treated with different progestins.

	Initial VAS	VAS at 12 months	VAS at 36 months	p-value
Dysmenorrhea	7.6	2.2	1.8	<0.01
Non-menstrual pelvic pain	2.8	1.5	1.4	<0.05
Dyspareunia	5.2	3.8	2.2	<0.05

Table 2. Description of the different progestins used and the treatment switches observed during the study.

A: Dienogest ($n=71$)	Continued	36	51%
	Switch to		
	NETA	12	17%
	POP (DSG)	2	3%
	POP (DRSP)	5	7%
	LNG-IUD	16	23%
Drospirenone ($n=24$)	Continued	13	54%
	Switched to		
	DNG	8	33%
	NETA	0	0%
	LNG-IUD	3	13%
C: Desogestrel ($n=20$)	Continued	6	30%
	Switch to		
	DNG	7	35%
	DRSP	4	20%
	NETA	1	5%
	LNG-IUD	2	10%
D: LNG-IUD ($n=25$)	Continued	21	84%
	Switched to		
	DNG	4	16%

Table 3. Percentage of different types of progestins used at the beginning and at the end of the observation.

Drug	Number treated at baseline		Number treated at 3 years	
A: Dienogest	71	51%	55	39%
B: Drospirenone	24	17%	22	16%
C: Desogestrel	20	14%	10	7%
D: LNG-IUD	25	18%	40	29%
E: NETA	0	0%	13	9%

and dysmenorrhea was observed ($p<0.01$). However, in 16% of cases (4/25), AUB occurred, leading to device removal and a subsequent switching to DNG (Table 2). Despite this, the majority of patients treated with the LNG-IUD showed high adherence to therapy. At the end of the three-year follow up, considering both continuation and switching rate, DNG and LNG-IUD emerged as the most commonly used treatments, followed by DRSP, NETA, and DSG (Table 3).

Discussion

The present study demonstrated that long-term progestin therapy may provide substantial and sustained symptom relief in patients with adenomyosis, particularly in the management of pain. Progestins were found to significantly reduce dysmenorrhea, dyspareunia, and HMB. Both oral and intrauterine formulations were generally effective in controlling adenomyosis-related symptoms. Additionally, progestin-only pills (POPs) may represent a viable option for managing both pain and bleeding. However, the occurrence of side effects, diminished efficacy over time, or the need for reliable contraception may necessitate switching between different progestin types or formulations.

DNG, a 19-nortestosterone derivative, is the primary choice for patients with endometriosis [18,19] and a number of studies have shown its efficacy also in adenomyosis [20–24]. DNG showed an antiproliferative impact on endometrium, decreasing nerve growth factor expression, thus explaining the effect on pain symptoms [25]. In the present study, DNG was the most frequently used progestin, while the LNG-IUD showed the highest continuation rate. The efficacy of DNG in relieving adenomyosis-related pain has been confirmed by a short term randomized, double-blind, multicenter study [24]. DNG was successfully administered over 6- or 12-month periods [23,24,26], with a discontinuation rate of approximately 20% for AUB [27]. Diffuse adenomyosis, advanced reproductive age, severe dysmenorrhea, and low hemoglobin levels have shown to be risk factors for bleeding-related adverse events during DNG treatment in adenomyosis [28]. More recent studies have indicated that the intensity of bleeding decreases over time with continued use and the switch from DNG to other drugs was mainly due to a contraception request [29].

Our results confirm that LNG-IUD is effective in relieving both adenomyosis-related pain and HMB. The rationale for using LNG-IUD is based on the direct effect on adenomyotic foci with decidualization and increased apoptosis in endometrial glands and stroma through a down-regulation of estrogen receptors [30]. Consistent with our findings, previous studies have reported overall satisfaction with the use of the LNG-IUD. [31], noting benefits such as decreased menstrual bleeding, improved health-related quality of life, reduced uterine size and hemoglobin rise [32,33]. A randomized controlled study comparing LNG-IUD and DNG in adenomyotic patients showed that DNG is more rapid and stronger in pain relief within the first 3 months of treatment, and in terms of bleeding after 12 months [29]. Furthermore, a recent systematic review confirmed the superiority of DNG in reducing adenomyosis-associated dysmenorrhea over other hormonal treatments, including LNG-IUD. However, no significant differences were observed between DNG and LNG-IUD in the management of HMB [34].

Our study indicated that POPs containing DRSP or DSG were effective in treating adenomyosis symptoms, even though a high discontinuation rate was observed over time. In particular, DSG users switched to DNG due to a decrease in efficacy or to side effects. Patients treated with DRSP reported higher satisfaction with the treatment, with a 50% continuation rate. While no previous studies have specifically investigated the use of POPs for adenomyosis, the rationale for using DRSP in this context is based on its non-contraceptive benefits. DRSP reduces endometrial proliferation, improving AUB [35] and reduces the expression of nerve growth factor, thus decreasing pain [36]. When used as a contraceptive in the general population, DRSP was well accepted [37]. In general, the discontinuation rate was higher with DSG than with DRSP, which is consistent with our findings [38,39].

The use of NETA was limited as second line treatment for adenomyotic patients who did not respond to the other progestins. A previous study showed that NETA is effective in reducing both pain and HMB [40]. Our findings showed that the long-term use of different types and formulations of progestins in the management of adenomyosis is effective in both reducing HMB and relieving pain, being possible to switch from one to another in case of side effects or in case of contraception request or need. The pain- and HMB-relieving effects of DNG and LNG-IUD are highly valuable, and support a beneficial effect on quality of life of patients with adenomyosis.

A limitation of our study is the lack of data on the use of etonogestrel implant, which has shown to be a promising option for adenomyosis [41], although larger cohorts are needed to confirm its efficacy. Additionally, the relatively small sample size in certain subgroups (such as the LNG-IUD, DRSP, and DSG groups) may have reduced the statistical power of subgroup analyses. Moreover, since treatment selection was based on patients' clinical presentation and contraceptive needs rather than randomization, the possibility of selection bias cannot be excluded. Furthermore, given the observational nature of the study and the frequent treatment switches, an intention-to-treat analysis would strengthen future studies and help mitigate outcome attribution

bias. Despite these limitations, a key strength of our study is that, to the best of our knowledge, it is the first to present data on the long-term use of progestins for managing symptomatic patients with adenomyosis.

In conclusions, progestins are effective hormonal treatment for relieving pain and HMB in patients with adenomyosis over the long-term, even when switching between different types of compounds. Furthermore, both oral and intrauterine progestins offer the advantages of minimal side effects, low cost, and can be used as contraceptive methods at any age.

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Author contributions

CRediT: **Silvia Vannuccini**: Conceptualization, Methodology, Writing – original draft; **Francesco La Torre**: Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing; **Federico Toscano**: Data curation, Investigation, Validation; **Anna Rosa Speciale**: Data curation, Investigation, Visualization; **Milo Giani**: Data curation, Writing – review & editing; **Dilruba Tureli**: Data curation, Writing – review & editing; **Virginia Manzi**: Data curation, Investigation, Visualization; **Angela Gallone**: Data curation, Investigation, Visualization; **Felice Petraglia**: Conceptualization, Methodology, Supervision, Writing – review & editing.

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Data availability statement

The data that support the findings of this study are available from the corresponding author (Felice Petraglia) upon reasonable request.

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