

Dienogest-based hormonal contraception induced changes in the ultrasound presentation of the uterus and menstrual pain

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Background: In young women, combined hormonal contraceptives can ameliorate menstrual pain and reduce menstrual loss, but their efficacy in adenomyosis has not been proven. The aim of this study was to investigate whether ultrasound features of adenomyosis are modified by a combined hormonal contraceptive containing dienogest. **Methods:** Fifty-eight out of 173 premenopausal women consecutively attending our university hospital outpatient service for contraception were enrolled in this observational study. Women with menstrual pain or heavy menstrual bleeding underwent ultrasonography. An expert sonographer diagnosed or excluded adenomyosis and fibroids via morphological uterus sonographic assessment (MUSA). The intensity of menstrual pain was quantified by each patient on a visual analogue scale (VAS). A total of 38 women with and 20 without ultrasound features of adenomyosis received dienogest-based hormonal contraceptive and had a follow-up ultrasound after 6 months of treatment. **Results:** During treatment, uterine volume decreased by $-13.1 \pm 22.1\%$ ($p = 0.001$) in women with adenomyosis features, while it tended to increase in controls. Hypochoic striation of myometrium present in 95% of cases and myometrial cysts in 5% of cases, respectively, at baseline, had completely disappeared by 6 months. Asymmetry of uterine walls decreased, with the anterior/posterior wall ratio declining from 2.8 ± 0.8 to 1.9 ± 0.7 ($p = 0.0001$). Heterogeneous myometrial texture, globous uterine morphology, and junctional zone alteration remained unchanged. In women with baseline adenomyosis, VAS score for menstrual pain decreased by -4.0 ± 3.6 ($p = 0.0001$). During treatment, a VAS score for menstrual pain close to 0 was found in all women without adenomyosis. Days of menstrual flow decreased in women with ($p = 0.0001$) and without ($p = 0.003$) adenomyosis. **Conclusions:** Dienogest-based hormonal contraceptives improve the sonographic features of adenomyosis and improve symptoms. Prospective data are needed to confirm these findings.

Keywords

Dienogest; Hormonal contraception; Ultrasonography; Adenomyosis; Chronic pelvic pain; Heavy menstrual bleeding

1. Introduction

Adenomyosis is a common, debilitating, yet poorly understood gynaecological disease, characterized by ectopic endometrial glands invading the myometrium [1]. It can be either diffuse (adenomyosis), focal or cystic, and localized in any part of the uterus. Risk factors are age, endometriosis, multiple births, uterine surgery, and spontaneous miscarriage [2]. Histological [3] and ultrasound [4] data indicate that the prevalence of adenomyosis ranges from 20% to 45% in asymptomatic and symptomatic women, respectively. Signs and symptoms of the disease are non-specific, and include uterine tenderness and enlargement, abnormal uterine bleeding, menstrual pain and infertility [5, 6].

Recent data indicate that diagnosis of adenomyosis by 2D trans-vaginal ultrasound has sensitivity and specificity comparable to that of histology or MRI [7–11]. Diagnosis by sensitive imaging techniques has favoured the tentative search for an effective medical therapy.

However, thus far there is no specific therapy for adenomyosis. Symptom improvement has been achieved by hormone withdrawal at adenomyotic tissue via the administration of GnRH analogues alone [12–14], or in association with aromatase inhibitors [15], and with an intrauterine system continually releasing levonorgestrel [16–18] or danazol [19]. Several reports also indicate that the continuous administration of the progestin dienogest reduces symptoms associated with adenomyosis [20–24].

However, the effect of dienogest on such lesions has scarcely been investigated. In one study, dienogest reduced, to some extent, adenomyotic lesions after 53 weeks of administration [25], while in another it failed to completely block adenomyosis re-growth after suspension of a GnRH-analogue [26]. In young women, combined hormonal contraceptives can ameliorate menstrual pain and reduce menstrual loss, but their efficacy in adenomyosis has not been proven [27–29]. In this study we therefore set out to in-

investigate whether a medical approach to adenomyosis via the use of hormonal contraceptives containing dienogest actually changes the ultrasound features of the uterus in women with ultrasound signs of adenomyosis, as compared to those without.

2. Materials and methods

2.1 Study design and patient population

This is retrospective observational study on premenopausal women, 18 to 50 years of age, attending university hospital outpatient contraception services, each of whom received dienogest-based hormonal contraceptives for at least 6 months. All patients in our clinic routinely sign informed consent to the anonymous use of their clinical data in scientific publications. Data refer to patient management (diagnostic procedures and treatments), performed in accordance with good clinical practice. Diagnostic procedures and treatments are paid partially or completely by the Italian national health system. No incentive is given to the patient. Data are recorded in an electronic database, from where they can be retrieved for retrospective analyses as necessary. Publication of results is approved, as in this case, by the hospital's internal review board.

For the purposes of this study, retrospective data pertaining to 173 women consulting the outpatient service for contraception in the period December 2016–October 2018 was retrieved. Among the women in question, 95 had been suffering from menstrual pain or abnormal uterine bleeding and had been referred for an outpatient ultrasonographic evaluation to be performed in the follicular phase (days 4 to 9) of the menstrual cycle (Fig. 1). For these women, the following information were retrieved from the electronic database: age, number of births, previous uterine surgery, presence of abnormal uterine bleeding, duration of menstrual cycle in days, menstrual pain scored on a 0–10 cm visual analogue scale (VAS) [28], ultrasound uterine features, presence of pelvic endometriosis, and type of contraceptive prescribed. On the basis of their request and medical eligibility, each woman received either a combined hormonal contraceptive, a levonorgestrel intrauterine system (IUS), an etonorgestrel implant, or a progestin only pill (desogestrel). Data from a follow-up visit and ultrasound investigation performed after 6 months of treatment were also retrieved. On the basis of baseline ultrasound investigation, the women were divided into those with ultrasound features of adenomyosis ($n = 55$) and those without ultrasound features of adenomyosis ($n = 40$). Women already on hormones at baseline were excluded ($n = 3$ with and $n = 2$ without adenomyosis). Similarly, women who did not have a follow-up ultrasound at six months were not considered in this analysis ($n = 4$ with and $n = 8$ without adenomyosis). Among those with follow-up ultrasound, the vast majority of women received combined hormonal contraception containing dienogest in association with ethinylestradiol or in a quadriphasic association with 17β -estradiol. In order to ensure greater homogeneity of

data, we excluded women who received levonorgestrel-IUS ($n = 4$ with and $n = 4$ without adenomyosis), etonorgestrel implant ($n = 3$ with and $n = 3$ without adenomyosis), vaginal ring ($n = 1$ with and $n = 3$ without adenomyosis) or progestin-only pill ($n = 2$ with adenomyosis). Accordingly, analysis was performed on 38 women with ultrasound features of adenomyosis and 20 women without ultrasound features of adenomyosis, all receiving dienogest-based combined hormonal contraception (Fig. 1).

2.2 Ultrasound examination

Ultrasound investigations were performed in an outpatient service for gynaecological ultrasound investigation by one experienced sonographer (A.X.), who was blind to the type of treatment the woman was receiving. In our clinical practice, blindness is routine so that ultrasound investigations are as objective as possible [30]. Specifically, ultrasound was performed by a trans-vaginal ultrasound (TVS) probe during the proliferation phase of the menstrual cycle (days 5–10), using a GE E6 (GE Medical Systems, Zipf, Austria) ultrasound machine and 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 by means of the ellipsoid formula (uterine longitudinal diameter \times transverse diameter \times anterior–posterior diameter \times 0.5223), without considering the cervix. Endometrial thickness was also measured.

Ultrasound diagnosis of pelvic endometriosis was performed, in line with the IDEA consensus opinion, by 2D-TVUS [31]. Ultrasound diagnosis of diffuse adenomyosis was defined, according to MUSA criteria [11], as the contemporaneous presence of at least two or more of the following features: (1) heterogeneous myometrium, seen as irregular myometrial echo-texture with decreased or increased echogenicity; (2) hypo-echoic striation in the myometrium (fan-shaped shadowing), seen as a pattern of thin acoustic shadows not arising from echogenic foci and/or leiomyoma (Fig. 1); (3) myometrial anechoic lacunae or cysts, seen as a round anechoic areas within the myometrium, hyper-echogenic islands, and sub-endometrial lines and buds (Fig. 2); (4) asymmetrical myometrial thickening of the uterine wall (Fig. 2); (5) globular uterine configuration; and/or; (6) increased uterine volume; (7) presence of a poorly defined, thickened, irregular, interrupted endo-myometrial junctional zone (JZ) [8] (Fig. 2). Information regarding other additional signs such as uterine tenderness and the question-mark or the ear sign were not available in the records [30]. Asymmetrical thickening of uterine walls was defined as thicker posterior or anterior uterine wall, unrelated to leiomyoma. To this end, the ratio between the anterior and posterior wall thickness was calculated. A ratio around 1 indicates that the myometrial walls are symmetrical, while a ratio well above or below 1 indicates asymmetry [11] (Fig. 2). In the selected sample there was no case of focal adenomyosis. The concomitant presence of fibroids was also

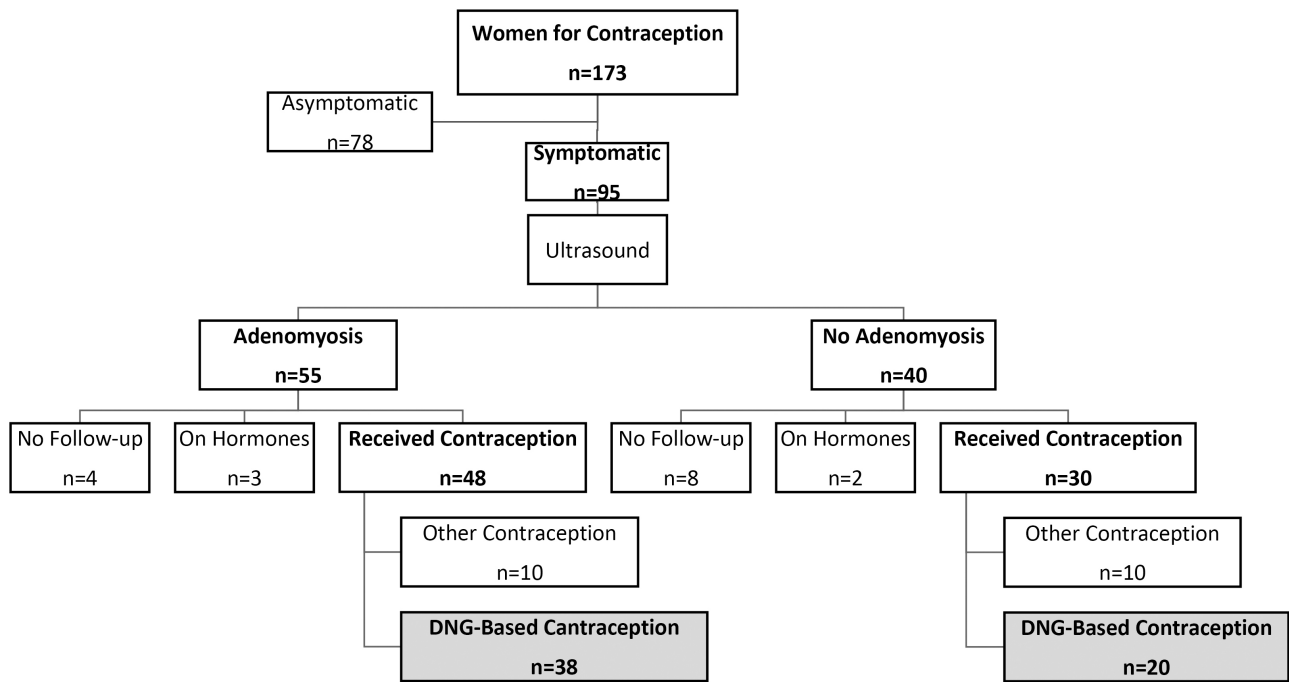


Fig. 1. Flow-chart of study design. DNG, dienogest.

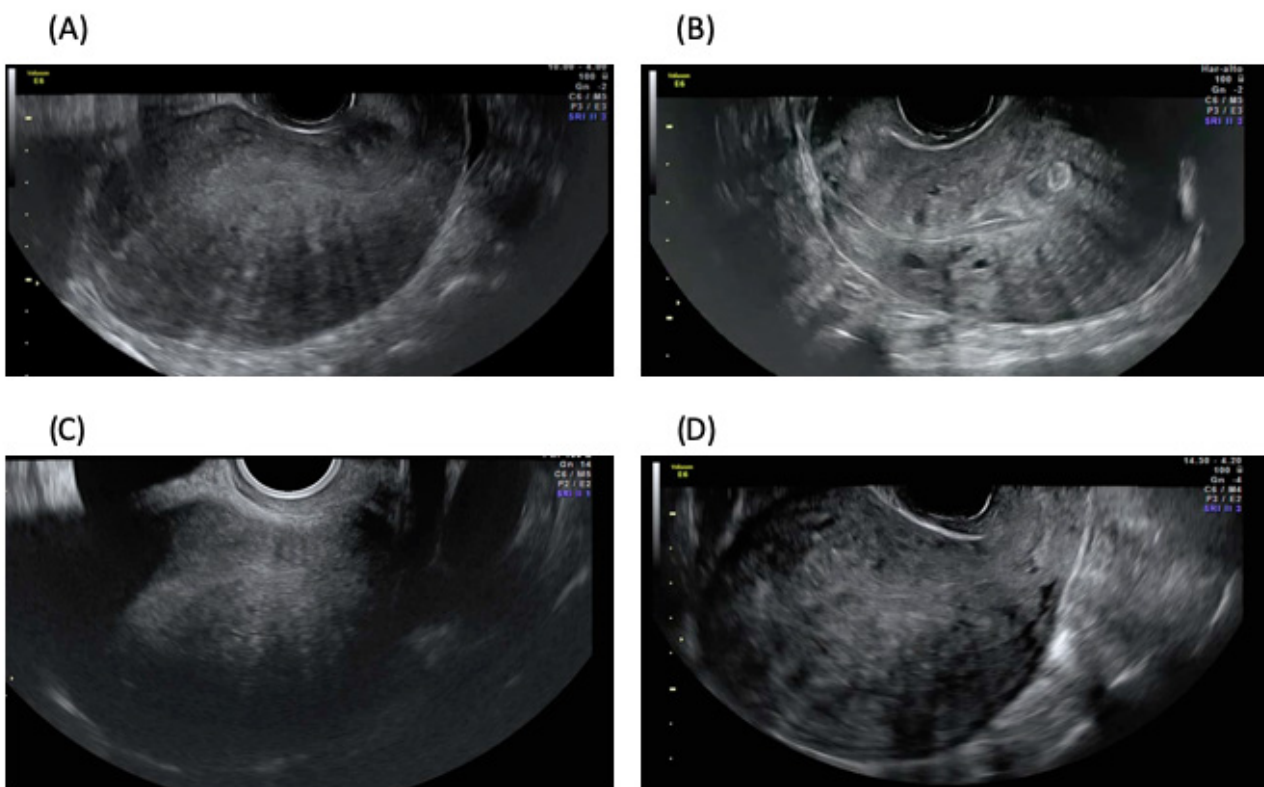


Fig. 2. Ultrasound features of adenomyosis. (A) Hypoechoic striation in the myometrium (parallel shadowing), seen as a pattern of thin acoustic shadows. (B) Myometrial anechoic lacunae or cysts, seen as round anechoic areas within the myometrium. (C) Asymmetrical myometrial thickening of the uterine wall. (D) Poorly defined endo-myometrial junctional zone (JZ).

assessed [11], and the volume of each fibroid was measured by means of the ellipsoid formula.

The study was focused on detecting modification of ultrasound parameters of adenomyosis during treatment. A secondary outcome was the clinical response in terms of VAS score for menstrual pain and length of menstrual cycles.

2.3 Statistical analysis

Statistical analysis was performed using StatView statistical software (version 5.01.98, SAS Institute Inc., Cary, NC, USA). Descriptive analysis was applied. Comparisons within groups were performed by paired *t* test. The chi-squared test was used to compare changes in prevalence over time. As applicable, means or prevalence in the two groups were compared via the Student's *t* test or chi-squared test, respectively, as a secondary statistical analysis. A two-tailed *p* value < 0.05 was considered as significant. Numerical data are expressed as mean ± standard deviation (SD).

2.4 Power of the study

The study was powered to document a within-group difference in volume between prior to and after 6 months of treatment that was greater than or at least equal to one standard deviation (SD) of the difference. In such a setting, if type I error is 0.05 and type II error is 0.2, 11 cases are sufficient to document an intragroup difference.

A secondary analysis evaluated other ultrasound features and compared data between women with and without concomitant pelvic endometriosis or with and without adenomyosis.

3. Results

3.1 Sample characteristics

Among the 95 women whose records were retrieved, 55 had ultrasound features consistent with adenomyosis, while 40 women displayed inhomogeneous echo-textured myometrium with no ultrasound features of adenomyosis (Fig. 1). Analysis was performed only on those women with a baseline and 6-month scan who had received dienogest-based hormonal contraceptives (*n* = 58) (Fig. 1). Among these 58, 38 had ultrasound features of adenomyosis and 20 did not. Women received either estradiol valerate and dienogest (*n* = 22 women with adenomyosis and *n* = 8 women without adenomyosis) or ethinyl estradiol and dienogest (*n* = 16 with adenomyosis, and *n* = 12 without adenomyosis). The mean age was 36.2 ± 7.3 years and 40.3 ± 7.8 years (*p* = 0.06) in women with and without adenomyosis, respectively, and the number of to-term pregnancies in these groups was 0.8 ± 0.9 and 1.0 ± 1.1 , respectively. Eleven women with adenomyosis (29%) and none of those without had undergone previous uterine surgery, such as laparotomic myomectomy or caesarean section (Table 1).

3.2 Ultrasound parameters

Uterine volume was 84.509 ± 53.695 mm³ and 80.513 ± 38.424 mm³ (Table 1), and endometrial thickness was 7.7 ± 0.5 mm and 7.5 ± 0.7 mm in women with and without adeno-

myosis, respectively. Twenty-six percent (*n* = 10) and 20% (*n* = 4) of women with and without adenomyosis had sub-serous or intramural uterine fibroids (Fig. 2). Mean fibroid volume was 12666 ± 35023 mm³, (diameter range 10–68 mm) and 6110 ± 3102 mm³ (diameter range 25–35 mm), respectively. No ultrasound feature of adenomyosis was detected in the uteri of women without a diagnosis of adenomyosis. Inhomogeneous myometrial echo-texture was present in 38/38 (100%) and globular configuration in 33/38 (87%) of the uteri of women with adenomyosis. Hypo-echoic striation of the myometrium (parallel shadowing) was present in 36/38 (95%) (Fig. 3), intra-myometrial cysts in 3/38 (8%), asymmetric uterine walls in 8/38 (21%), and poorly defined endomyometrial junctional zone (JZ) in 34/38 (89%) of adenomyotic uteri. Pelvic endometriosis was detected at ultrasound in 22/38 (58%) women with adenomyosis and in no woman without adenomyosis.

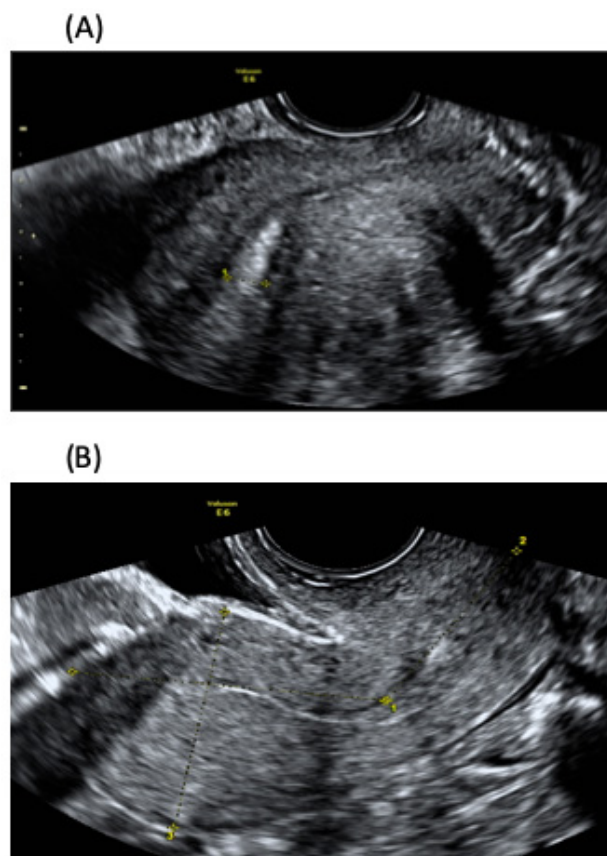


Fig. 3. Modification of Ultrasound Features of Adenomyosis. Ultrasound of the uterus before (A) and after 6 months (B) of therapy.

3.3 Changes of ultrasound uterine parameters

During the six-month period, in women with adenomyosis uterine volume decreased significantly by -10.601 ± 18.513 mm³ (*p* = 0.001) ($-13.1 \pm 22.1\%$) (Table 2). In women without adenomyosis, uterine volume increased, but not significantly so, by $+24.367 \pm 53.073$ mm³ (*p* = 0.07, $+28.0 \pm$

Table 1. Characteristics of women with and without adenomyosis.

	Adenomyosis (n = 38)	No adenomyosis (n = 20)
Age (yrs.)	36.2 ± 7.3	40.3 ± 7.8
Full-term pregnancies (n)	0.8 ± 0.9	1.0 ± 1.1
Women with uterine surgery (n)	11 (29%)	0.0 (0%)
Uterine volume (mm ³)	84568 ± 52985	80154 ± 37997
Women with fibroids (n)	10 (26%)	4 (20%)

Table 2. Ultrasound characteristic of the uterus and clinical signs in women with and without adenomyosis prior to and after 6 months of treatment with dienogest-based hormonal contraceptive.

	Before	During treatment	<i>p</i> value
Adenomyosis (n = 38)			
Ultrasound features			
Uterine volume (mm ³)	84509 ± 53625	73906 ± 58963	0.001
Wall asymmetry (ratio; mm)	2.8 ± 0.8	1.9 ± 0.7	0.0001
Parallel shadowing (%)	95	0	0.0001
Myometrial cysts (%)	8	0	0.0001
Inhomogenous myometrium (%)	100	100	0.999
Uterus globular configuration (%)	87	87	0.999
Poorly defined junctional zone (%)	89%	89%	0.999
Clinical signs			
VAS score for menstrual pain	7.3 ± 3.2	1.9 ± 2.8	0.0001
Cycle length	5.3 ± 1.2	4.1 ± 0.5	0.0001
No Adenomyosis (n = 20)			
Ultrasound features			
Uterine volume (mm ³)	80513 ± 38424	104891 ± 86755	0.07
Wall asymmetry (ratio; mm)	1.1 ± 0.3	1.2 ± 0.4	0.894
Parallel shadowing (%)	0	0	0.999
Myometrial cysts (%)	0	0	0.999
Inhomogenous myometrium (%)	75	75	0.999
Uterus globular configuration (%)	10	10	0.999
Poorly defined junctional zone (%)	0	0	0.999
Clinical signs			
VAS score for menstrual pain	1.3 ± 0.8 ^a	0.5 ± 0.4	0.0001
Duration of menstrual flow (days)	4.2 ± 0.3 ^b	3.8 ± 0.2	0.0001

^a *p* < 0.001; ^b *p* < 0.005 vs. adenomyosis.

35.0%). Upon secondary statistical analysis, volume changes in uteri with and without adenomyosis were found to be significantly different (*p* = 0.001). Changes in uterine volume were not conditioned by fibroid modifications. Indeed, fibroid volume did not change significantly during the six months of treatment (from 12.666 ± 35.023 mm³ to 14.273 ± 33.368 mm³—a net change of +1.606 ± 4.203 mm³; *p* = 0.16). Mean endometrial thickness decreased to 3.4 ± 0.3 mm and 3.2 ± 0.3, in women with and without adenomyosis features with no difference between them.

Some sonographic features of adenomyosis were modified by treatment. Hypo-echoic striation of the myometrium (parallel shadowing) was present in 95% of cases and myometrial cysts in 8% at baseline, but both had disappeared completely after 6 months of hormonal contraception (*p* = 0.0001) (Table 2). The prevalence of uterine-wall asymmetry (8/38; 21%) was unchanged after treatment, but mean asymmetry decreased from a ratio of 2.8 ± 0.8 to 1.9 ± 0.7 (*p* =

0.0001). The prevalence of poorly defined endo-myometrial junctional zone (JZ) (34/38; 89%), inhomogeneous myometrial echo-texture (38/38; 100%), and globular uterus configuration (33/38; 87%) were not altered by treatment.

3.4 Symptoms

The mean VAS score for menstrual pain was 7.3 ± 3.2 and 1.3 ± 0.8 in women with and without adenomyosis (*p* = 0.0001). In women with adenomyosis, there was no difference in VAS score between those with and without pelvic endometriosis (7.6 ± 2.9 vs. 6.7 ± 3.8, *p* = 0.433). The duration of menstrual bleeding was 5.3 ± 1.2 days and 4.2 ± 0.3 days in women with and without adenomyosis, respectively (*p* = 0.0002).

3.5 Changes in symptoms

During treatment, VAS score for menstrual pain decreased to 1.9 ± 2.8 (−4.0 ± 3.6; *p* = 0.0001) in women with adenomyosis, and to 0.5 ± 0.4 in women without ultrasound

features of adenomyosis. In women with adenomyosis the reduction of menstrual pain was similar in women with and without pelvic endometriosis (-5.0 ± 3.6 vs. -5.6 ± 3.7 ; $p = 0.655$), and reached similar post-treatment values in both, specifically 2.57 ± 3.2 vs. 1.13 ± 1.95 , respectively ($p = 0.133$).

Menstrual flow duration declined significantly in women both with (from 5.3 ± 1.2 to 4.1 ± 0.5 days; $p = 0.0001$) and without (from 4.2 ± 0.3 to 3.8 ± 0.2 days; $p = 0.0001$) ultrasound features of adenomyosis.

3.6 Side effects

Side effects were few and minor among women who completed the 6 months of therapy. Spotting and breakthrough bleeding occurred in 9.6% of women, with no need for discontinuation. Twelve women on dienogest-based contraceptive did not return at follow-up. Considering the worst-case scenario that all these women had withdrawn due to side effects related to the treatment, continuation rate at 6 months of dienogest-based hormonal contraceptives was 83%.

4. Discussion

This study shows that treatment with dienogest-based hormonal contraceptive changes ultrasound features of adenomyotic uteri, improving menstrual pain and reducing menstrual flow duration. A certain degree of progesterone resistance in patients with adenomyosis has been reported [32]. Nevertheless, gestodene-containing oral contraceptives are effective in suppressing aromatase expression in the ectopic endometrium of adenomyotic foci, similar to that exerted in the eutopic endometrium [27], and effects of hormone therapy on symptoms related to adenomyosis have been reported in the literature [28, 29].

Recent data indicate that severity of menstrual pain is associated with ultrasound features of adenomyosis [33]. This is supported by the fact that we detected changes in ultrasound features of adenomyosis and lessened menstrual pain with dienogest-based hormonal contraceptives. Volume reduction of adenomyotic uteri was about -13%. This shrinkage was not the consequence of alterations in any concomitant fibroids, whose volume tended to increase.

Hence, dienogest-based hormonal contraceptives appeared to modify uterus volume by a selective action on adenomyotic tissue. This is supported by the fact that the uterine volume of women without adenomyosis features was not affected. The uterine shrinkage observed was accompanied by the disappearance of the hypo-echoic striation present in 95% of uteri with adenomyosis. Similarly, myometrial cysts, seldom present, completely disappeared, while uterine asymmetry, an indicator of asymmetrical adenomyotic infiltration, was significantly decreased. Concomitantly, endometrial thickness was reduced to below 4 mm.

All these findings are consistent with the capability of dienogest treatment to control and reduce the activity of functional endometrium, including that displaced either within the myometrium [32] or outside the uterus [34].

Eighty-three percent of women completed the 6 months of combined treatment, and only 9% reported minor menstrual abnormalities. This contrasts with that recently reported with dienogest alone, where the rate of menstrual abnormalities was considerably higher [35].

Our findings suggest that dienogest-based hormonal contraceptives can be safely used for long-term treatment of symptomatic adenomyosis, as an alternative to treatments such as GnRH-agonists or aromatase inhibitors, capable of inducing a marked hypo-estrogenic state [12–15]. A clinical implication of the apparent ability of dienogest-based hormonal contraceptives to alter, though not completely abolish, sonographic landmarks of adenomyosis is that ultrasonographic diagnosis of the disease will be more difficult and less accurate in women taking them. This is information relevant to both clinical and research settings.

A potential weakness of the study is the lack of histological confirmation of the diagnosis of adenomyosis. However, sensitivity and specificity of ultrasound seems to be comparable to that of histology or MRI [7–11]. All ultrasound scans were performed using top-of-the-range equipment. In addition, although the study is retrospective, the sonographer was blind to the women's treatment, as is routine in our clinical practice.

The follow-up period was only 6 months, and a longer evaluation period is therefore warranted. The number of cases was limited, although not negligible. Women were treated with two different types of dienogest-based contraceptives, and further research will be necessary to establish whether there are any differences between the two.

5. Conclusions

Although prospective studies are needed to confirm our data, present findings indicate that dienogest-based hormonal contraceptives improve the ultrasound features of adenomyosis, and reduce menstrual pain and bleeding.

Author contributions

AX, AC, GG designed the research study. AX, AB performed the research. AC, GG analysed the data. AX wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Retrospective data collection was approved by the internal review board (IRB 7/2019) at our hospital, and each woman signed her consent to the anonymous use of her data in scientific publications.

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Conflict of interest

The authors declare no conflict of interest.

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