Gynecological Endocrinology

ISSN: 0951-3590 (Print) 1473-0766 (Online) Journal homepage: https://www.tandfonline.com/loi/igye20

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To cite this article: Anjeza Xholli, Gabriele Filip, Francesca Previtera & Angelo Cagnacci (2019): Modification of endometrioma size during hormone therapy containing dienogest, Gynecological Endocrinology, DOI: 10.1080/09513590.2019.1703942

To link to this article: https://doi.org/10.1080/09513590.2019.1703942

Published online: 16 Dec 2019.

GYNECOLOGICAL ENDOCRINOLOGY
https://doi.org/10.1080/09513590.2019.1703942

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ORIGINAL ARTICLE

Modification of endometrioma size during hormone therapy containing dienogest

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ABSTRACT

The aim of the present study was to evaluate whether hormone therapy containing dienogest is effective in reducing endometrioma size. A retrospective observational study was conducted on 116 women with endometrioma which was evaluated after 6 and 12 months of either no treatment ($n = 46$), or hormonal therapy containing dienogest ($n = 70$), without (DNG; $n = 34$) or with ethinylestradiol (DNG/EE; $n = 36$). Median (interquartile range) cyst diameter (23.0 mm (21.0 mm)) and volume (9941.2 mm^3 (14240.1 mm^3)) of untreated were similar to cyst diameter (25.0 mm (14.5 mm) and volume (7587.7 mm^3 (13806.2 mm^3)) of treated women. After 12 months, endometrioma volume did not vary in untreated women (-34.0 mm^3 (55595.0 mm^3); -0.77% (93.9%)) while it significantly decreased (-5400 mm^3 (15378.7 mm^3); -100.0% (27.7%); $p<.0001$) during hormone therapy. Volume decrease was linearly related to endometrioma volume ($y = 318.8 - 0.756x$; $R^2 = 0.899$, $p<.0001$). The effect tended to be greater during DNG alone than DNG/EE (-100.0% (0.0%) vs. -87.9% (47.7%); $p<.0004$). Cyst disappearance was observed in 4.4% of untreated cases and in 57.1% of cases on hormone therapy ($p<.0001$) (38.9% with DNG/EE and 76.5% with DNG; $p<.03$). The early diagnosis and treatment of endometrioma with dienogest-based hormone therapy may be effective in controlling cyst growth and in reducing the need for surgery.

ARTICLE HISTORY
Received 13 August 2019
Revised 12 November 2019
Accepted 9 December 2019
Published online 16 December 2019

KEYWORDS
Endometriosis; contraception; dysmenorrhea; ultrasound; infertility

Introduction

Endometriosis is a common condition, affecting approximately 5-10% of women during their fertile life [1]. It is defined as a pathology characterized by the presence of endometrial tissue outside the uterine cavity, such as in the pelvis, abdomen and extra-abdominal sites [2]. Ovarian endometriotic cyst or endometrioma are a common manifestation of the disease [3,4]. The exact pathogenesis that leads to the development of endometrioma is still unclear, with three main theories being proposed. Endometrioma may derive by an endometriotic transformation of a functional cyst, by the invagination of the ovarian cortex secondary to the bleeding of superficial implants, or by the invagination of the ovarian cortex secondary to metaplasia of celomatic epithelium [5]. Identification of an endometrioma is important because it may have an impact on woman fertility [6–8]. Surgical removal of an endometrioma has a negative impact on ovarian reserve [9–15] and should be individualized based on patient choice, age, ovarian reserve, associated symptoms, and the risk of repeat surgery [16]. An appropriate approach is its clinical follow-up by ultrasounds [16–18]. Ultrasonography may miss some (sensitivity from 68 to 89%), but it is highly specific in endometrioma definition (specificity about 91–98%) [19]. Reduction of endometrioma growth was tentatively tried with GnRH-analogs [20,21], aromatase inhibitors [19,22], and seldom, with hormonal contraceptives [23,24]. On no occasion, hormonal therapies containing DNG were used, apart from two studies with DNG alone [25,26]. In the present study, it was investigated whether DNG, one of the most appropriate progestins for the treatment of endometriosis [27], administered alone or in contraceptive associations containing ethinylestradiol (DNG/EE), can control endometrioma growth.

Materials and methods

A retrospective observational study was performed between June 2015 and December 2017 on women who were referred to a university hospital outpatient service for chronic pelvic pain and endometriosis. An ultrasonographic diagnosis of endometrioma was necessary to be included into the study. Out of 164 women, 130 were included. Exclusion criteria were lack of ultrasound diagnosis of endometrioma, amenorrhea for 2 or more months, suspected or confirmed diagnosis of malignancy, women within 2 years of menarche, women already in therapy with GnRH analogs, use of estrogen-progestin associations or progestins, women in menopause. Forty-nine women did not start any treatment either because they suffered from slight symptoms, they were in search of pregnancy or were afraid of hormonal treatments. Vice-versa, 81 women received hormones; 40 women a commercially available contraceptive containing DNG (2 mg) and ethynyl-estradiol 30 mcg (DNG/EE) and 41 received the oral administration of commercially available DNG (2 mg) alone. Therapies were selected on the basis of woman preference and contraceptive needs. In all cases, DNG was selected as progestin because effective in the treatment of symptoms associated with endometriosis [27]. At inclusion, women underwent an interview, a physical and gynecological examination, an ultrasound investigation, and filled self-rated questionnaires investigating pain [28]. Menstrual pain was defined as pelvic pain occurring

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Table 1. Mean ± standard deviation (SD) or median and interquartile range (IQR) baseline characteristics of women evaluated in the trial, of baseline endometriomas size and of its modification at the 12-month follow-up evaluation depending on whether women received no treatment (untreated) or dienogest-based hormone therapy (treated).

	Untreated ($n = 46$)	Treated ($n = 70$)
Age (yrs.)	32.6 ± 6.2	33.4 ± 5.1
BMI (m/Kg^2)	22.1 ± 2.3	21.6 ± 2.3
Nulliparous (%)	73.9	74.3
Median Cyst Diameter (mm)(IQR)	23.0 (21.0)	25.0 (14.5)
Net change at follow-up (mm) (IQR)	−1.0 (8.1)	−17.4 (16.6)***
% Change at follow-up (IQR)	−6.89 (29.9)	−100.0 (70.0)***
Median Cyst Volume (mm^3) (IQR)	9941.2 (14240.1)	7587.7 (13806.2)
Net change at follow-up (mm^3) (IQR)	−34.0 (5595.0)	−5400 (15378.7)***
% Change at follow-up (IQR)	−0.77 (93.9)	−100.0 (27.7)***

***$p<.0001$ vs. baseline and untreated.

during or shortly before/after a menstrual period. Intermenstrual pelvic pain was defined as recurrent or constant pelvic pain, unrelated to menstrual periods, or intercourse. Pain at intercourse was defined as deep pelvic pain occurring during sexual intercourse or within the 24 h thereafter. The intensity of each type of pain was evaluated separately by a 100 mm visual analog scale (VAS). An experienced sonographer performed transvaginal ultrasound scans, during the proliferative phase of the menstrual cycle (days 3–7), with a GE E6 (General Electric Medical Systems, Zipf, Austria) ultrasound machine, using a wideband 5–9 MHz transducer with 3 D capability. Power Doppler was performed using fixed preinstalled settings (frequency, 5–9 MHz; pulse repetition frequency, 0.6–0.3 kHz) for the assessment of ovarian cyst. The sonologist closely followed the protocol and used the IOTA terminology to describe the ultrasound findings [29]. In previous endometrioma cases, confirmed at histology, diagnostic sensibility and specificity of our ultrasound evaluation performed by the same sonologist was 92 and 98%, respectively. Diagnosis of endometrioma was based on pattern recognition. Several studies reported the ultrasound features of endometriomas [30–33]. In a premenopausal woman, the characteristic ultrasound aspect of a typical endometrioma is represented by a mass with regular margins, with ground glass echogenicity, one to four cyst locules and no papillation with detectable blood flow on color or power Doppler. A concomitant ipsilateral ovarian pathology or extraovarian endometriosis may or may not be present. Hyperechogenic wall foci may be found in up to a third of endometriomas and thick walls, usually poorly vascularized, are often present.

We measured the three dimensions of the cyst and the volume was then calculated by the ellipsoid formula (longitudinal x anteroposterior x transverse x 0.5233) [18]. Maximal cyst diameter was also recorded. Ultrasound evaluation was performed at baseline and repeated after a period of treatment of about 6 and 12 months. All evaluations were performed by the same sonologist who was blind on treatment the woman was receiving. This is because in order to have a more objective evaluation, in our clinical practice we had decided to keep the dedicated sonologist blind on whether or not a woman has been assigned to any type of therapy.

Statistical analysis

The main goal of the study was to demonstrate a reduction of endometrioma size, at ultrasound. For sample size calculation a type I error a 0.05 and type II error at 0.20 was set. Twelve subjects were necessary to show a reduction of mean cyst volume higher than one standard deviation of the difference between baseline and last follow-up visit. In order to evaluate the efficacy of treatment vs. control, we considered effective a treatment that reduced cyst volume of more than 50%. Assuming a difference of at least 50% between treatment and control, 18 women for controls and for hormone treated were necessary. Statistical analysis was blindly performed using the statistical package StatView (version 5.01.98, SAS Institute Inc., Cary, North Carolina, USA). Descriptive analysis was used. Comparisons within and among groups were performed by the Wilcoxon signed rank test and the Mann-Whitney U test, respectively for data on cysts, and by paired and unpaired t-test, respectively for the other data. The chi-squared test was used to compare prevalence. Linear regression analysis was used to evaluate whether the extent of volume change (net change; dependent variable) was related to the volume of endometrioma, age, body mass index (BMI) or months of treatment (independent variables). In order to avoid the regression to the mean phenomenon, initial endometrioma volume was corrected by the Oldham formula (volume at baseline + volume at follow-up/2) [34]. A two-tailed p-value $<.05$ was considered significant. Data are expressed as mean ± standard deviation (SD) or as the median and interquartile range (IQR).

Ethical approval

At evaluation, each patient had signed a consent, previously approved by the Institutional Review Board, for the anonymous use of her data in scientific publications. Data were anonymously retrieved from an electronic database and then blindly evaluated in statistical analyses.

Results

Main characteristic

In fourteen women we cannot retrieve follow-up data, because they were lost at follow-up (2 cases) or women had stopped treatment for the need of a pregnancy (4 cases), economic reasons (4 cases with DNG), or side effects (4 cases; 2 cases with DNG and 2 with DNG/EE). Analyses were performed on 116 cases of which 46 on no treatment, and 70 on hormone therapy (36 with DNG/EE and 34 with DNG alone). Seventy-four percent of women were nulliparous, they were 32.4 ± 5.6 years old and had a BMI of 21.8 ± 2.3.

Main findings

At baseline, the cyst dimension was similar in the two groups of women (Table 1). The range of cyst diameter was 12.3–46.4 mm and, 10.1–60.6 mm in untreated and treated women, respectively. At the 12 months follow-up evaluation, mean endometrioma diameter and volume did not change in untreated women (Table 1). In women receiving DNG-based hormone therapy, endometrioma diameter and volume decreased ($p<.0001$) both vs. baseline and vs. untreated women (Table 1).

Among all the parameters considered the extent of volume change was associated only to initial endometrioma volume. The relation was positive in untreated women (y=-882.0 + 0.200x; R^2=0.244; $p = .0007$) and negative in hormone-treated women ($y = 313.8 - 0.756x$; R^2=0.899, $p<.0001$) (Figure 1). No endometrioma of untreated women decreased in volume of more than 50%, apart from two cysts (4.4%) that disappeared. In hormone-treated women the percentage of cysts with a volume reduction >50%, >75% or of 100% was 88.5, 68.5 and 57.1%

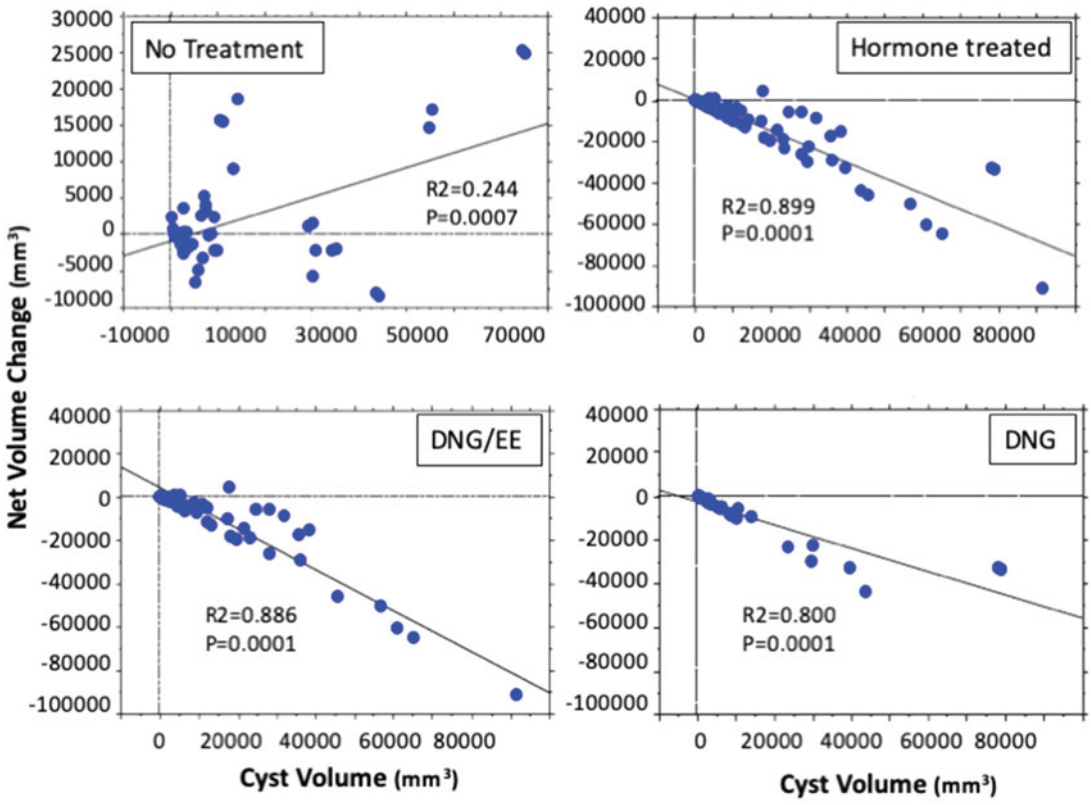

Figure 1. Linear regressions between endometrioma volume and net volume change during no treatment ($n = 46$) or the administration of dienogest-based hormone therapy (hormone treated; $n = 70$). The two graphs below show the data of hormone treated cases divided as contraceptive association containing dienogest with ethinylestradiol (DNG/EE; $n = 36$), and dienogest alone (DNG; $n = 34$).

($p<.0001$ vs. untreated women), respectively. In only 4 cases (5.7%) cyst volume did not decrease. All cases were in the group of treatment with DNG/E (4/36; 11.1%).

At baseline a higher score of menstrual (7.7 ± 2.3 vs. 4.3 ± 1.4; $p<.0001$) and intermenstrual (4.7 ± 2.6 vs. 1.9 ± 1.4; $p<.0001$) pain and pain at intercourse (4.2 ± 3.0 vs. 1.9 ± 1.3; $p<.0001$) was observed in women who received hormone therapy. Menstrual pain (-5.4 ± 2.7), intermenstrual pain (-3.6 ± 2.6) and pain at intercourse (-2.6 ± 2.2) decreased ($p<.0001$) during treatment whereas they did no change in untreated women.

Subgroup analysis

Baseline characteristics and changes during treatment with DNG/EE and DNG are reported in Table 2. At baseline, the range of cyst diameter was 11.2–60.3 mm and 10.3–51.4 mm in women who then received DNG/EE and DNG, respectively. During DNG/EE, both the diameter and the volume of the cysts decreased ($p<.0001$) (Table 2). Volume decrease was linearly related to endometrioma volume ($y = 4136.6 - 0.952x$; R^2=0.886, $p<.0001$) (Figure 1). In DNG/EE treated women, the percentage of cysts with a volume reduction >50%, >75% or of 100% was 77.7, 55.5, and 38.9% ($p < 0.007$ vs. untreated), respectively.

During DNG alone the diameter and the volume of the cysts decreased ($p<.0001$) (Table 2). Volume decrease was linearly related to endometrioma volume ($y = -2579.7 - 0.533x$; R^2=0.800, $p<.0001$) (Figure 1). In DNG treated women, the percentage of cysts with a volume reduction >50%, >75% or of 100% was 100, 82.3, and 76.5% ($p<.0001$ vs. untreated women), respectively.

Table 2. Mean (± standard deviation) or median and interquartile range (IQR) baseline parameters of women evaluated in the trials, of baseline endometriomas size and of its modification at the 12-month follow-up depending on whether women received a contraceptive association of dienogest with ethinylestradiol (DNG/EE) or dienogest alone (DNG).

	DNG/EE ($n = 36$)	DNG ($n = 34$)
Age (yrs.)	32.3 ± 4.3	32.4 ± 6.1
BMI (m/Kg^2)	21.7 ± 2.6	21.6 ± 1.9
Nulliparous (%)	77.7	70.6
Cyst Diameter (mm)(IQR)	25.0 (23.0)	20.1 (20.0)
Net change (mm)(IQR)	−11.5 (16.1)*	−18.0 (10.0)*
% Change (IQR)	−45.7 (86.7)	−100.0 (0.0)$^{\$\$}$
Cyst volume (mm^3)(IQR)	12613.1 (21986.0)	5474.9 (7357.2)
Net change (mm^3)(IQR)	−6856.9 (16659.5)*	−3747.3 (6454.0)*
% Change (IQR)	−87.9 (47.7)	−100.0 (0.0)$^{\$}$

*$p<.0001$ vs. baseline; $^{\$}p<.004$; $^{\$\$}p<.0003$ vs. DNG/E.

At statistical analysis, a percent decrease of cyst diameter ($p<.0003$), of cyst volume ($p<.004$) (Table 2), and percentage of cyst disappearance (76.5 vs.38.9%; $p<.002$) was greater during DNG than DNG/EE. Net cyst volume reduction and coefficients of linear regression analyses were not significantly different among the two groups of treatment. Similarly, no significant difference between the two groups was observed for the induced decrease of menstrual pain ($p = .51$), intermenstrual pain ($p = .61$) or pain at intercourse ($p = .91$).

Discussion

The present study shows that DNG-based hormone therapy, administered for one year, reduces endometrioma volume. The time course of the effect highlights the feasibility of reducing endometrioma volume in a relatively short period of time.

For years the most appropriate treatment of ovarian endometrioma was considered its surgical removal. This view has changed [18] with the accumulating evidence of adverse effects induced by surgery on ovarian reserve [9–15], and the high rate of endometrioma recurrence after its removal (21.5% and 40–50% at 2 and 5 years, respectively) [35]. ESHRE guidelines indicate that surgery of endometriomas with a 3 to 6 cm diameter is not indicated in order to improve the outcome of assisted reproduction techniques [16]. Accordingly, patient-associated symptoms, age, comorbidity, desire of pregnancy are factors that should be considered in the clinical management of endometriosis. With the improvement of ultrasonography and sonographers' skill, endometriomas may be detected earlier, when they are small, less fibrotic and more responsive to medical therapy. Whether effective therapies are available, early treatment may help to reduce the risk of surgery and preserve woman fertility. Reduction of endometrioma volume was reported with GnRH analogs (up to -51%) [20,21] or aromatase inhibitors (up to -75%) [19,22]. The associated hypoestrogenism limits the long-term use of these therapies. Progestins such as danazol [20,21] or northisterone acetate [23] proved to reduce endometrioma volume of about -50%. Studies using contraceptive combination of ethinylestradiol and drospirenone showed a very modest reduction of cyst diameter in one case [23] and an about -40% volume reduction in another case [24]. DNG in contraceptive associations with estrogens was never investigated, and DNG alone was evaluated in two studies. In one study including women with long-term endometriomas, previously treated with other hormonal therapies [25], a maximal endometrioma reduction of about -70%, was achieved after 15 months of treatment. In another study [26] the effect at 12 months the effect seemed less pronounced [26]. In the present study, DNG-containing hormonal therapies induced a marked volume reduction of naïve endometriomas and their disappearance in more than half of the cases within 12 months of treatment. Interestingly, in the subgroup of women receiving DNG alone endometrioma volume decreased almost completely and cyst disappeared in 76% of cases, an effect that is greater than that previously reported [25,26]. Likely, spontaneous regression of endometrioma did not play a relevant role. Spontaneous reduction of pelvic endometriotic lesions, without mentioning endometrioma, was reported in up to 42% of cases [36]. A single study performed in older women, some approaching menopause, reported a 30% spontaneous resolution of endometrioma in a mean follow-up period of 40 months [37]. In the present study, spontaneous regression of an endometrioma was observed only in 5.7% of untreated women. Vice-versa, in those women receiving DNG-based hormone therapies endometrioma disappearance was much higher and twice as greater (57%) than previously reported. In addition, cyst volume reduction greater than 50% was observed in about 90% of the cases. Interestingly, comparison of spontaneous endometrioma modifications vs. those induced by treatment is lacking in most of the previous studies [19,22–26]. Treatment suspension might be associated with a recrudescence of endometrioma growth, as previously reported with aromatase inhibitors [22] and also with DNG [25]. The advantage of DNG or DNG/EE is that, if initially accepted and well-tolerated, it can be indefinitely continued. On the basis of our data, it cannot be claimed that DNG can exert its effect in the long-term. This possibility was previously shown [25], but more long-term studies are necessary.

In accordance with the aim of the study, all included women on treatment received hormone therapy containing DNG. Accordingly, the patient-preference design of the study, some women receiving DNG and others DNG/EE, did not impact on the main results of the investigation. Subsequent analyses comparing DNG vs. DNG/EE were probably not sufficiently powered. The evidence of greater efficacy of DNG alone vs. DNG/EE on endometrioma growth indicated by some calculations needs to be confirmed but could be the consequence of an estrogenic stimulus induced by EE on endometrioma cells that was not completely counteracted by DNG. The present study was not aimed to compare different progestins, different estro-progestin associations or different routes of administration. Accordingly, the data are limited to DNG given either alone or in association with EE. It cannot be excluded that similar or better results can be obtained with other hormonal formulations. The diagnosis of ovarian endometrioma was not histological and it was based on ultrasound that for its high accuracy [38], is considered a reliable method of endometrioma diagnosis. In a previous case series comparing endometrioma histology with ultrasonography, the sensibility and specificity of our sonographic investigation were 92 and 98%, respectively. Finally, the data we obtained were based on the treatment of relatively small endometrioma. The linear relation observed between volume size and its reduction, with the greater reduction being associated with greater cysts volume, may indicate that similar to small, also larger endometrioma may respond to therapy. This possibility needs to be further explored in dedicated clinical trials.

Conclusions

Besides some limits, the present study suggests that DNG-based hormone therapy is effective in reducing symptoms and the volume of ovarian lesions. The early diagnosis of ovarian endometrioma and the immediate and prolonged medical treatment with DNG alone but also with contraceptive associations containing DNG, never investigated before, may prevent endometrioma to reach values that may pose a clinical dilemma between medical treatment or surgery. By reducing the need for surgery and its potential damage on the ovary, early diagnosis and appropriate medical treatment may help to preserve ovarian reserve and woman's future fertility. However, the efficacy of DNG-based hormone therapy in the long-term needs to be further explored.

Disclosure statement

The authors Anjeza Xholly, Gabriele Filip, and Francesca Previtera have no conflict of interest. Angelo Cagnacci has received fees by MSD, Bayer Italia, Gedeon-Richter, TEVA, Exeltis for advisory boards or congress presentations.

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