RUNNING TITLE: Stepwise endometriosis management

A STEPPED-CARE APPROACH TO SYMPTOMATIC ENDOMETRIOSIS MANAGEMENT: A PARTICIPATORY RESEARCH INITIATIVE

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CAPSULE

Two-thirds of symptomatic patients accepting a stepped-care endometriosis management were satisfied with oral contraceptives and a low-cost progestin, and few had to step up to a high-cost progestin or surgery.

ABSTRACT

Objective: To assess the proportion of patients with symptomatic endometriosis satisfied with their medical treatment 12 months after enrollment in a stepped-care management protocol.

Design: Prospective, single-arm, self-controlled study.

Setting: Academic department.

Patient(s): A cohort of 157 consecutive patients referred or self-referred to our center for symptomatic endometriosis.

Intervention(s): Systematic, detailed information process on medical and surgical treatment followed by a shared decision to start a stepped-care protocol including three subsequent medical therapy steps (oral contraception, [OC]; 2.5 mg/d norethindrone acetate, [NETA]; 2 mg/d dienogest, [DNG]) and a fourth surgical step. Stepping up was triggered by drug inefficacy/intolerance.

Main Outcome Measure (s): Satisfaction with treatment was assessed according to a five-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied). Variation were measured in pain symptoms with the use of a 0-10 point numeric rating scale (NRS), in quality of life with the use of Short Form-12 questionnaire (SF-12), and in sexual functioning with the use of Female Sexual Function Index (FSFI).

Result(s): At the end of the 12-month study period, 106 women were still using OC, 23 were using NETA, three were using DNG, and four had undergone surgery. Twenty-one (13%) participants dropped out from the study. In intention-to-treat analysis, excluding five drop-outs for pregnancy desire, the overall satisfaction rate with the stepped-care protocol was 62% (95/152; 95% CI, 55% to 70%). By 12-month follow-up, significant improvements were observed in all pain symptoms scores and in SF-12 physical and mental component summary scores, whereas FSFI scores did not vary substantially.

Conclusion(s): Most women with endometriosis-associated pelvic pain who chose a stepped-care approach, were satisfied with OC and a low-cost progestin for the treatment of their symptoms. The need to step up to an expensive progestin or surgery was marginal.

KEYWORDS: endometriosis; pelvic pain; medical treatment; surgery.

INTRODUCTION

According to the opinion of the Practice Committee of the American Society for Reproductive Medicine on treatment of endometriosis-associated pelvic pain, "*endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures*" (1).

In fact, surgery for endometriosis is reportedly effective for pelvic pain, but postoperative recurrence of symptoms and lesions is as high as 40-50% at 5-year follow-up (2-4). Moreover, removal of ovarian endometriomas is associated with reduction of ovarian reserve (5,6), and excision of deep infiltrating forms is associated with a relatively high incidence of complications, especially when rectovaginal and bowel lesions are present (3,7,8). Outcomes of complex surgical procedures are strictly operator dependent and therefore scarcely reproducible. Finally, surgery is expensive. For these reasons, many women would leave surgery as the second choice, only in case medications are ineffective or not tolerated (9).

Based on secondary research findings (10) and according to guidelines issued by several international gynecologic societies, hormonal compounds to treat endometriosis have similar effects on pain, but different metabolic and subjective side-effects and costs (1, 11-14). Therefore, in women who prefer medical rather than surgical treatment, those drugs with the most favorable therapeutic profile and lower cost should be used first, stepping up to drugs with a less favorable therapeutic profile or higher cost selectively in those patients who do not respond or do not tolerate the first-line medications.

Despite decades of intensive clinical research, the ultimate prognosis of a woman with symptomatic endometriosis who chooses prolonged medical treatment with first-line drugs instead of surgery is currently unknown. In other words, the likelihood that a woman will succeed in successfully controlling her complaints and be satisfied with her treatment without having to step-up to second-line compounds and eventually to surgery is currently undefined. The answer to this practical question seems crucial for informing patient decisions. Even women preferring medical

rather than surgical treatment may choose differently in case the risk of having to resort anyway to surgery is high.

Given this unclear scenario, we deemed it of interest to assess the trajectory of an unselected cohort of consecutive endometriosis patients through a pre-planned stepwise therapeutic protocol including three subsequent medical steps (oral contraception, [OC]; norethindrone acetate, [NETA]; dienogest, [DNG];) and a fourth, final, surgical step. The main objective of the investigation was to estimate the probability of being satisfied with this stepped medical care approach 1 year after starting the use of a low-dose OC.

MATERIALS AND METHODS

This study was conceived and designed, the results interpreted, and the report written, together with representatives of a large Italian nonprofit endometriosis patient association (Associazione Progetto Endometriosi Onlus), and it was conducted within the framework of a participatory research initiative aimed at prioritizing topics and research questions that patients consider to be important. Engaging patients in the design of a new pragmatic study model on endometriosis management was deemed to be crucial to capturing aspects of health and functioning that matter to them.

The manuscript was prepared according to the Strengthening the Reporting of Observational studies in Epidemiology guidelines for reporting observational studies (15). The investigation was performed in an academic department specializing in endometriosis management, and the relevant Institutional Review Board approved the study (Comitato di Etica Milano Area B, determination no.903/2015). Every patient signed an informed consent form before enrollment.

Design

A prospective, single-arm, self-controlled, observational study design was adopted. The main objective was to assess the degree of satisfaction with ~~a~~ stepped medical treatment care in a cohort of consecutive patients with symptomatic endometriosis starting therapy with an OC used continuously, and sequentially stepping up to NETA and then to DNG in case of drug inefficacy or intolerance. Secondary objectives were the evaluation of within-person variations in pain

113 symptoms, health-related quality of life, and sexual function after 12 months, as well as of the
114 proportion of patients eventually needing to step up to surgery. With this study design each
115 participant acted as her own control, to avoid the potential confounding caused by differences
116 between patients (16). In fact, variations in satisfaction with treatment was not assessed after a pre-
117 planned shift to another drug in a general population of patients taking OC, but specifically in those
118 patients who stepped up to a second- or third-line medication owing to dissatisfaction with,
119 respectively, OC or NETA because of inefficacy or intolerability, and who would otherwise have
120 discontinued medical therapy.

121 **Study participants**

122 We considered 18- to 40-year-old women, not seeking conception, with a surgical diagnosis of
123 ovarian and/or deep endometriosis or a current nonsurgical diagnosis of ovarian and/or deep
124 endometriosis (17), consecutively referred or self-referred to our tertiary-care endometriosis center
125 because of moderate or severe pelvic pain symptoms of >6 months'duration. Those patients who
126 were already using any type of pharmacologic therapy and were satisfied with their treatment were
127 not considered for enrollment.

128 Nonsurgical diagnoses were based on ultrasonographic criteria in patients with ovarian
129 endometriomas (18,19); on visual inspection of the posterior fornix and biopsy of vaginal lesions in
130 those with rectovaginal endometriosis (20,21); on ultrasonographic criteria (22), cystoscopic
131 findings, and biopsy of vesical lesions in those with bladder detrusor endometriosis; on physical
132 signs at rectovaginal examination and ultrasonographic criteria (23,24) in those with deep lesions
133 infiltrating the Douglas pouch and parametria; and on ultrasonographic criteria (24), double-
134 contrast barium enema, and, in some women, rectosigmoidoscopy or colonoscopy findings in those
135 with full-thickness bowel lesions. Magnetic resonance imaging was performed in selected
136 circumstances. The ultrasonographic diagnosis of adenomyosis was based on detection of
137 asymmetric thickness of the anterior and posterior uterine walls, heterogeneous myometrial

echotexture, and round anechoic areas and hypoechoic linear striations within the myometrium (25).

Patients were excluded in case of obstructive uropathy or subocclusive bowel stenosis, evidence of complex adnexal cysts or a unilocular ovarian endometrioma with a diameter > 4 cm at vaginal ultrasonography, the typical contraindications to OC and progestins, a diagnosis of concomitant disorders that may cause pelvic pain independently of endometriosis presence (e.g., pelvic inflammatory disease or pelvic varices or genital malformations at previous surgery; known urologic and orthopedic diseases), psychiatric disturbances, and history of drug or alcohol abuse. From August 2015, all new endometriosis patients consecutively referred or self-referred to our center were evaluated for eligibility, and recruiting continued until the pre-planned sample size was reached in January 2016.

The information process

In our center, all women are thoroughly informed regarding the possible treatment options for their clinical condition on the base of up-to-date literature evidence, with priority given to the best-quality primary and secondary research available (26). The information is expressed quantitatively with the use of absolute numbers (e.g., crude percentages with a consistent denominator, such as 100 treated), and avoiding the use of estimates that may not be easily understood (e.g., relative risks), and it is provided in both verbal and written form. The communication session between the physician and the patient has no predetermined time limits. Medical and surgical treatments are described in detail and both are offered as available options.

Before deciding whether to start medical therapy or undergo surgery, women were informed that OC is considered by some authors to be the first line treatment for endometriosis-associated pelvic pain, but that further medical therapy steps are available in case of inefficacy or intolerance. They were also informed that medical therapies for endometriosis are usually effective in reducing various types of pain in about two thirds of patients (27-29). However, drugs induce only temporary relief, are not expected to be definitively curative, and may cause several side effects (listed, with

percentages derived from previous studies conducted in our center). Finally, when hormonal treatments are to be continued for long periods, estrogen-progestins and progestins appear to be among the compounds that most favorably balance benefits, harms and costs (30,31). In particular, the continuous use of OC is suggested to achieve amenorrhea and relieve pain at withdrawal bleeding that may still afflict endometriosis patients using OC cyclically (32,33).

It was explained that the estrogen included in OC on one hand may prevent potentially detrimental effects of hypoestrogenizing treatments (e.g., vaginal dryness, decrease in bone mineral density, and unfavorable modifications in serum lipid pattern), but on the other hand may limit the therapeutic efficacy on endometriotic implants that, being estrogen sensitive, may retain part of their metabolic activity. Thus, in case of symptom persistence, a shift to a progestin monotherapy may improve pain. This change of medication may be of benefit also in case of intolerance to OC, because the estrogen component is generally associated with specific side-effects (e.g., headache) (34). Differences in the effect on pain and in side-effects may exist even among different progestins. Therefore, changing from NETA to DNG may relieve symptoms to a greater extent, or untoward effects may subside. However, the likelihood and magnitude of these potential variations are scarcely quantifiable owing to limited available evidence. Moreover, NETA is very cheap, whereas DNG is costly.

Women were informed that other drugs for symptomatic endometriosis were available but that, owing to important untoward effects and/or high costs, generally they were not suggested for prolonged treatment periods. Finally, patients were also informed that laparoscopic surgery was a reasonable alternative associated with a 70-80% probability of partial or complete pain relief in case they declined medical therapy or switching from OC to a progestin, but that the risk of pain and lesion recurrence was ~10% per year without long-term postoperative medical treatment (2-3), they were also informed that, in case of excisional procedures for rectovaginal lesions, surgery is associated with major complications in ~10% of cases (listed, with percentages derived from published primary and secondary research). Finally, it was explained that repeat surgery, owing to

the presence of adhesions distorting abdominal-pelvic anatomy, may become less effective against pain as well as riskier, although precise estimates may not be provided because of paucity of published data.

Interventions: the stepped care approach

Women who chose medical therapy were invited to start ~~a~~ low-dose, monophasic OC used continuously (Step 1). During the enrollment period, the OC used in our center was a monophasic formulation containing 0.015 mg ethinyl-estradiol (EE) and 60 mg gestodene or, in case of spotting, 0.02 mg EE and 150 mg desogestrel. In smokers and in those with a body mass index (BMI) ≥ 30 kg/m^2, a combination of 0.02 mg EE and 100 mg levonorgestrel was prescribed.

All patients underwent clinical and ultrasonographic evaluations at 3, 6, and 12 months after enrollment, unless required otherwise because of pain recurrence or insurgence of untoward effects. On these occasions, the women were asked to complete questionnaires on pain, quality of life, and sexual functioning. They were also asked to indicate drug tolerability and to rate the degree of overall satisfaction with their treatment. Whenever a participant was dissatisfied with OC because of inefficacy for pain or intolerable side effects, she was counseled again and invited to consider stepping up to NETA or undergoing surgery. Dissatisfied women who chose to continue with medical treatment started NETA at the dose of 2.5 mg orally once a day, (Step 2), after 4 or 7 days off OC, depending on the type being used. Norethindrone acetate, a 19-nortestosterone-derivative progestin, has been repeatedly evaluated in women with endometriosis (35-41), and has been successfully used in our referral center for several years (20,21,42).

When a participant was dissatisfied with NETA because of inefficacy for pain or intolerable side-effects, she was counseled again and invited to consider stepping up to DNG or undergoing surgery. Those women who chose to continue with medical treatment started DNG immediately at the dose of 2 mg orally once a day, (Step 3). Dienogest, a semisynthetic 19-nortestosterone-derivative progestin, has been investigated and registered also for the treatment of endometriosis. Its effect on pain was demonstrated to be significantly superior to placebo and equivalent to a GnRH

analogue (43,44). Moreover, DNG was particularly well tolerated by women with symptomatic endometriosis (43,44). Women were informed that DNG was indicated as step 3, instead of step 2, because DNG is much more expensive that NETA and may have an adverse impact on bone mineral density (43,45).

In case of prolonged spotting (≥ 7 days) or breakthrough bleeding, the patients were advised to discontinue treatment for 1 week (4 days in case of OC containing 0.015 mg EE and 60 mg gestodene). When needed, naproxen sodium was the standard nonsteroidal antiinflammatory drug prescribed (one 550-mg tablet twice a day unless contraindicated).

When a participant was dissatisfied also with DNG because of inefficacy for pain or intolerable side-effects, she was counseled again and invited to consider undergoing surgery (Step 4). However, surgery could be chosen by women also during OC or NETA use in case they declined continuing with the stepped-care protocol. Laparoscopic treatment of endometriosis was performed with mechanical and electrosurgical instrumentation according to standard and already described techniques aiming at excising all endometriotic lesions and restoring a normal pelvic anatomy (46-49). Participants who underwent surgery were regularly followed after the procedure.

Measurements

The presence and severity of dysmenorrhea, deep dyspareunia, nonmenstrual pelvic pain, and dyschezia were assessed with the use of an 11-point numeric rating scale (NRS), with 0 indicating absence of pain and 10 pain as bad as it could be. Patients were considered for enrollment if they complained of at least one moderate-to-severe pain symptom (points 6-8, moderate pain; point 9 or 10, severe pain). Irregular bleeding during treatment was defined as spotting (scanty bleeding requiring no more than one pad or tampon per day) or breakthrough bleeding (light or moderate bleeding requiring two or more pads or tampons per day). Pain during spotting or breakthrough bleeding was considered to be dysmenorrhea.

Quality of life was assessed with the use of the Short Form-12 (SF-12) health survey, a well-known and validated self-administered 12-item instrument developed from the original SF-36

questionnaire (50,51). It measures health dimensions covering functional status, well-being, and overall health. Information from the 12 items is used to construct physical and mental component summary measures (52,53), with higher scores indicating better health perception.

The Female Sexual Function Index (FSFI) questionnaire is a 19-item, multidimensional, self-report instrument for evaluating the main categories of female sexual dysfunction and sexual satisfaction (54,55). Domains include desire, arousal, lubrication, orgasm, satisfaction, and pain. Each domain is scored on a scale of 1 to 5, and the maximum transformed full-scale score is 36, with a minimum transformed full-scale score of 2.0. Women with an FSFI total score <26.55 are categorized as experiencing sexual dysfunction (56).

Patients rated the degree of satisfaction with their treatment according to a five-category scale (very satisfied, satisfied, neither satisfied nor dissatisfied, dissatisfied, very dissatisfied) by answering the following question: "Taking into consideration the variations occurring in pain symptoms, overall physical and psychologic well-being, and sexual functioning, how would you define the level of satisfaction with your current treatment?".

Data management

Based on our previous experience, the proportion of endometriosis patients satisfied with OC treatment is ~ 65% (20,57). The study hypothesis was that the application of a stepwise treatment approach, which includes the possibility of stepping up to NETA and then to DNG, could increase this proportion to 80%. In our view, decreasing the dissatisfaction rate from one out of three to one out of five women would be a clinically important difference. Based on the Wald method for a binomial distribution, 150 participants were needed to limit the confidence interval (CI) around the point estimate (80%) to 74%-86%.

Data were archived in Excel 2003 (Microsoft Corp.) and exported to SPSS 18.0, for statistical analysis. Estimate of patient satisfaction rate was performed according to the intention-to-treat principle, considering as dissatisfied all patients who dropped out of the study for any reason except conception seeking, thus including request for not pre-planned medical therapies or need for

surgery, as well as loss to follow-up. To limit the potential effect of confounding, satisfaction with treatment, was dichotomized into "satisfied" (very satisfied plus satisfied) and "dissatisfied" (neither satisfied nor dissatisfied plus dissatisfied plus very dissatisfied).

Variations in pelvic pain symptoms, health-related quality of life, psychologic status, and sexual functioning between baseline and 12-month values were evaluated by means of the paired Student *t* test for normally distributed data (age, BMI, FSFI, SF-12), the non-parametric Wilcoxon matched pairs test for nonnormally distributed data (NRS scores and number of days with considerable pain or impairment of usual activity), the McNemar test for categoric variables, and the Fisher Exact test in case of cells without numeric data. Per-protocol analyses were adopted for secondary end points. Determinants of satisfaction with treatment were investigated with unpaired tests (Student *t* test for normally distributed continuous variables, Wilcoxon test for nonnormally distributed continuous variables, and chi-square test for categoric variables). The multivariate analysis to evaluate the independent role of the variables predictive for satisfaction with treatment was performed with the use of a logistic regression model. Specifically, those variables that were found to significantly differ at univariate analysis were included in the model. All statistical tests were two sided. A P value $< .05$ was considered to be statistically significant. When appropriate, 95% CIs were calculated for the observed differences by applying a binomial distribution model.

RESULTS

A total of 186 women were deemed to be eligible during the study period, but 29 (16%) declined enrollment: 20 opted for cyclic OC use and nine for immediate surgery. The remaining 157 women were recruited for the study (Fig.1). The baseline demographic and clinical characteristics of the patients are presented in Table 1. One-Half of the women previously underwent surgery for endometriosis, and more than two-thirds previously used some medical therapies. A total of 64 patients (41%) had deep endometriotic lesions (rectovaginal, 56; other, 8), and 64 (41%) had ovarian endometriomas (unilateral, 51, bilateral, 13). The median (interquartile range [IQR]) largest

deep lesion diameter was 15(10-20) mm (largest lesion diameter, 43 mm), and the median (IQR) largest endometrioma diameter was 26 (19-38) mm (largest endometrioma diameter, 40 mm). Thirty-three women (21%) had an ultrasonographic diagnosis of uterine adenomyosis (Supplemental Table 1). No statistically significant differences were observed in baseline characteristics between women who accepted and those who declined enrollment into the study (data not shown).

Participant progress through the stepped-care protocol

Of the recruited 157 patients, 14 (9%) requested shifting to NETA (Step 2) within 3 months after start of OC use (Step 1), because of inefficacy for pain (n = 5) or drug intolerance (n = 9), and one requested surgery (Step 4) because of pain persistence. During the same time period, five participants dropped out of the study (requested cyclic OC use because of intolerance to continuous use, n = 3; declined further treatments, n = 1; lost to follow-up, n = 1; Fig.1). At 6-month assessment, 11 women had shifted from OC to NETA, and another two from NETA to DNG because of inefficacy for pain (n = 7) or drug intolerance (n = 6). Two women taking OC underwent surgery because of endometrioma growth. Seven patients dropped out between the 3- and 6-month evaluations (declined further treatment, n = 3 (OC, n = 2; NETA, n = 1); requested cyclic instead of continuous OC use, n = 2; pregnancy desire, n = 2 (OC, n = 1; NETA, n = 1)). Within the 12-month assessment, six women shifted from OC to NETA and two from NETA to DNG, because of inefficacy for pain (n = 5) or drug intolerance (n = 3) and one from DNG to surgery because of inefficacy for pain. In the same time frame, nine patients dropped out of the study (pregnancy desire, n = 3 (all OC); requested cyclic instead of continuous OC use, n = 2; declined further treatments, n = 2 (OC, n = 1; NETA, n = 1); lost to follow-up, n = 2 (OC, n = 1; NETA, n = 1)).

At the end of the 12-month study period, 106 women were still using OC, 23 were using NETA, three were using DNG, and four women had undergone surgery (including one who requested surgery at the 12-month evaluation, after completion of the pre-planned 1-year medical treatment period). Overall, 21 participants (13%) dropped out from the study, ten because of drug

intolerance (seven requested a shift from continuous to cyclic OC use and three declined further treatments), five because of pregnancy desire, three because of phychologic intolerance to hormonal therapies (they all declined further treatments), and three were lost to follow-up. The seven women who requested to use OC cyclically instead of continuously, continued a medical treatment, but not with the modality pre-planned for the stepwise protocol. For this reason, they were included among dropouts.

Pain symptoms, health-related quality of life, and sexual functioning

A per-protocol analysis was conducted on the 133 women who completed the study (132 women who continued medical treatment plus one who used medical treatment for 1 year and requested surgery only at final 12-month evaluation). Highly statistically significant reductions in NRS score were observed for all of the symptoms considered (Table 2). At the end of study period, the prevalence of moderate or severe pain decreased from 94% to 12% for dysmenorrhea, from 59% to 30% for deep dyspareunia, from 43% to 12% for dyschezia, and from 44% to 23% for nonmenstrual pelvic pain. The median (IQR) number of days with pain necessitating analgesics decreased from 7(4-10) to 0(0-2) per month, and the number of days with impairment of usual activities decreased from 2(0-4) to 0(0-0).

Significant improvements in summary scores for both~~,~~ the physical (from 41.4 ± 11.1 to 51.0 ± 8.7) and the mental (from 41.9 ± 10.5 to 47.0 ± 10.0) SF-12 components were observed ($P <$ .001). A trend toward a marginal worsening of the FSFI score was observed (Table 2).

The incidence and types of untoward effects reported at pre-planned visits by women using medical treatments are presented in Table 3. Side-effects were experienced by about four out of five patients, but their severity determined drug discontinuation in only ten participants, seven of whom requested shifting from continuous to cyclic OC use.

Satisfaction with treatment

At the 12-month assessment, 95 of the 133 participants who completed the stepwise protocol were satisfied with their treatment (71%; 95% CI, 63%-79%). At the same time point, 38 women

346 declared that they were dissatisfied (OC, *n* = 29; NETA, *n* = 8; dienogest, *n* = 1), but only two of
347 them requested surgery. An intention-to-treat analysis was conducted on 152 patients, instead of the
348 157 enrolled, because five women dropped out of the study before the 12-month evaluation not
349 because of drug inefficacy or intolerance, but because of pregnancy desire. Considering all
350 remaining drop-outs and women who underwent surgery as dissatisfied, the overall satisfaction rate
351 was 62% (95/152; 95% CI, 55%-70%). However, seven drop-outs continued using OC, though
352 cyclically instead of continuously and six of them were satisfied with their treatment at 12-month
353 follow-up. Considering those seven women still under treatment would result in a less conservative,
354 but more realistic satisfaction rate of 66% (101/152; 95% CI, 59%-73%).
355 Baseline demographic and clinical characteristics of the 95 satisfied and 57 dissatisfied
356 patients in the intention-to-treat analysis, were substantially similar. In univariate analysis,
357 statistically significant differences were observed only for BMI and the SF-12 mental component
358 summary score, which were, slightly higher and lower, respectively, in the group of dissatisfied
359 women (Supplemental Table 2). In the logistic regression model, both BMI and the SF-12 mental
360 component summary score remained significantly associated with satisfaction with treatment (*P* =
361 .033 and .043, respectively).
362
363 DISCUSSION
364 According to the findings of this self-controlled study conducted prospectively on a cohort of
365 consecutive patients with symptomatic endometriosis who chose medical therapy as their preferred
366 treatment, the probability of stepping up to an expensive progestin (Step 3) because of intolerance
367 to NETA or to undergo surgery (Step 4) for any reason, was very limited. About two participants
368 out of three were satisfied with the proposed stepped medical care approach after 12 months. This
369 result was obtained with OC used continuously in the entire cohort of 157 women, NETA in 31
370 (20%), and DNG in four (3%). Surgery was needed in four women (3%), but in two of them the
371 indication was the unexpected growth of an ovarian endometrioma, not inefficacy of the drugs.

Unexpectedly, of the 38 women who declared themselves to be dissatisfied with medical treatment, only two requested surgery, and the other 36 preferred to tolerate reduced but persistent pain or some side-effects rather than undergo surgery. However, when pragmatically considering the impact of medical treatment at large, also those 29 women who did not accept the stepped-care protocol and requested cyclic OC use (n = 20) or immediate surgery (n = 9) should be considered. Based on this conservative approach, surgery was eventually required in 13 (4 + 9) out of 186 (157 + 29) patients (7%). Moreover, when planning the study, we hypothesized that 80% of women would had been satisfied with the stepped-care medical approach, but this was not the case. In the best scenario, that is, not excluding women who shifted from continuous to cyclic OC use, the proportion of satisfied women was 66%, thus not superior to that repeatedly observed by us when evaluating monotherapies. We recruited a series of consecutive women with endometriosis seeking care for their pain symptoms, and what we have observed might provide an overall representation of what unselected women can expect from medical treatment in the real world. These figures will now be used in our practice when informing patients during the shared decision-making process, specifying that the above estimates do not apply to the general population of women with symptomatic endometriosis, but specifically to those women who choose medical rather than surgical treatment.

We excluded women with endometriomas >4 cm. However, the maximum cyst diameter for which surgery may be safely avoided in patients aged ≤ 40 years is currently undefined. Until a consistent cutoff is indicated in guidelines issued by major scientific societies, the diameter of 5 cm suggested by Muzii *et al*. (58) may be more appropriate in women with typical endometriomas. Periodic evaluations are nevertheless recommended to detect in a timely manner possible modifications of ultrasonographic cyst characteristics or unexpected growth during ovarian suppression (58).

We deemed it to be important to describe in detail the information provided to patients, as well as the standard shared decision-making process systematically adopted in our center, because a

strong relationship seems to exist between the characteristics of specific "centers of expertise", and the treatment chosen (i.e., medical or surgical) by patients referred to those centers. It may not be excluded that the type of information provided largely determines the final patient decision (26,59,60). According to Head *et al*. (61) "*certain details of* alternate *treatments can intentionally or unintentionally be omitted, resulting in a failure to allow the patient to make a well informed decision*". Therefore, in our view, the description of the information process should be included in the methodologic section of future interventional trials for symptomatic endometriosis. In our experience, when thoroughly informed on potential benefits, harms, and drawbacks of medical and surgical treatments, most women not seeking conception express their preference for the former option (21), thus confirming that patients who engage in shared decision-making tend to choose nonsurgical treatment alternatives (62). Of relevance here, both medical and surgical treatments for all endometriosis forms are available in our center and offered to patients.

The self-controlled design may appear to be a limitation of our study. However, this model was chosen because our aim was not to conduct head-to-head comparisons between available treatment options, but rather to evaluate sequentially the effect of different drugs used as a second- or third-line therapy specifically in nonresponders to OC. In this setting, participants acted as their own control, thus limiting the effect of confounding associated with different distribution among patients of relevant characteristics that can influence study outcomes (16). Moreover, the adoption of an intention-to-treat analysis to assess patient satisfaction, and including as dissatisfied all participants who underwent surgery and all drop-outs except women who discontinued treatment to seek a conception should have avoided overoptimistic results which are generally associated with observational study designs.

Theoretically, the "regression toward the mean" phenomenon could have affected the observed data, because extreme values are frequently influenced by random variation and, when remeasured they tend to be closer to the mean of the original population from which the study subjects were drawn (32,63). Therefore, when the patients' conditions are worse than average and

standard therapies seem to have lost efficacy, some general amelioration may occur that has nothing to do with improved treatment (32,63). However, the magnitude of this effect should have been limited here, because we recruited women complaining of chronic and fairly stable pain symptoms that were measured on more than one occasion during the pre-enrollment phase and throughout the study period (63). Also, a carry-over effect could not be excluded when stepping up because of drug inefficacy or intolerance. However, in such a case the effect would have been negative and led to a decrease in the patient satisfaction rate.

Selection bias could have influenced our findings, because choosing to enter the stepped-care protocol in fact created a self-selection favoring hormonal therapy. This limits the generalizability of our results to those women who prefer medical rather than surgical treatment. On the other hand, recruiting consecutively all eligible patients referred to our center in a defined study period should have limited these study drawbacks. Furthermore, the demographic and clinical characteristics of women who accepted and refused entering the stepwise protocol were similar.

More in general, it may not be excluded that patients self-referring to our center are not representative of the general population of women with endometriosis, because they may be more prone to start medical therapies rather than request surgery. In fact, many patients may now easily identify through the Internet and patient association websites those referral centers that are in favor of medical treatment. However, this is a problem also for studies conducted in centers adopting mainly a surgical approach. In addition, the attitude of the personnel of our center toward discussing benefits and harms of all available treatment options, and the systematic application of a shared decision-making process, may have had per se a psychologic effect, because women likely felt understood and supported, although we did not measure such aspects. In theory, outcomes may vary in centers applying different approaches regarding patient information and decision-making. Nevertheless, a mere placebo effect, typically lasting no longer than a few weeks (64), seems unlikely, given the relatively prolonged treatment period.

Health-related quality of life and sexual functioning were measured with the use of widely used and reliable scales. The clinical validity and internal consistency of the SF-12 have been demonstrated in large samples in many countries, including Italy (53,65). Both the physical and the mental components of health-related quality of life, as measured by this instrument, were substantially improved with the use of medical treatment.

The FSFI also has been validated and demonstrated acceptable internal consistency and test–retest reliability (55,56). A marginal worsening of the FSFI scores from baseline to 12-month assessment was observed. In our experience, significant improvements of sexual functioning as measured by the FSFI were associated with progestin monotherapy (42,66). However, deep dyspareunia persisted in ~30% of our patients. We speculate that OC, used by most of the study participants, may exert a smaller effect on pain at intercourse owing to the estrogen component that may impede complete metabolic inhibition of endometriotic foci (67). Moreover, it has been demonstrated that OC may adversely affect desire, arousal, and pleasure (68).

The incidence of side effects of OC and progestins was surprisingly high. However, occurrence of side-effects associated with medical treatments was actively investigated by research fellows, and this may have lead (non è LED?) to listing even mild disturbances that otherwise would not have been reported. Overall, untoward effects caused drug discontinuation in fewer than one out of ~~10~~ ten patients, so most complaints were not severe enough to induce women to request surgery.

Finally, representatives of a major national endometriosis patient association were coinvestigators in this study. Partnership between patient associations and clinical investigators seems to be important to move forward patient-centered research and ameliorate patient care. Engaging patients for research on endometriosis management may help in defining those priorities that are most important to them, at the same time advancing truly shared decision making (69-71).

CONCLUSIONS

The results of this prospective, self-controlled study suggest that most women with symptomatic endometriosis were satisfied with OC and a low-cost progestin, and that only a small minority of them actually needed a costly progestin or requested surgery to control pelvic pain. Replication of our findings by other investigators is advisable, because the observed results may be valid only for patients who prefer medical rather than surgical treatment, and may not be generalizable to all patients with endometriosis.

In Italy, the yearly cost of treatment with the OC combinations used in our study is $188-197 / €159-167 / £146-154, with NETA is $20 / €17 / £16, and with DNG is $861 / €730 / £672. Thus, the use of low-dose OC and low-cost progestins for endometriosis management may be termed "high-value care" (72). The value of a medical intervention is the balance between its potential benefits, potential harms, and costs, combined with the priorities and preferences of individual patients. Value also conveys the dimension of the amount of care gained per each dollar spent (72).

When correctly used in women without major contraindications, OC is very safe (73-76). Thus, despite some limited drawbacks in terms of efficacy and tolerability (34,67), OC could retain its role in the current therapeutic armamentarium for women with endometriosis (77,78). However, those OC combinations with the lowest estrogen content (79-81) and associated with the smallest amount of withdrawal bleeding (33) should be used and further investigated (77). Progestins may be preferred in patients with deep infiltrating lesions (82).

According to the Institute of Medicine, clinical practice and research must be integrated to define "*what work best for whom in order to inform decisions that lead to safe, efficient, effective, and affordable care*" (83). The results of explanatory randomized controlled trials (RCTs) aimed at defining the effect of experimental treatments may not be directly transferable to all patients, because when treating a chronic disorder for years, the effect on pain is one among several factors to be considered. Safety, tolerability, as well as costs for individual women and for the health care system also should be taken into account. In other words, if a new drug has a demonstrated large

effect on pain, this does not mean that all patients with endometriosis should use that drug if its safety and tolerability are no better than those of existing alternatives, but its cost is much higher. In the words of Greenhalgh "*randomised controlled trials may constitute the ideal of experimental design, but they alone* can not *prove that the right intervention has been provided to the right patient at the right time and place*"(84). Moreover, patients encountered in everyday practice may have different characteristics from those enrolled in explanatory RCTs.

The advent of new drugs for endometriosis (85-88) is very welcome, because this means that patients will have another treatment option for managing their pain as an alternative to surgery. Nevertheless, if new drugs are less safe or more expensive than existing ones, they should not be prescribed to all women with symptomatic endometriosis, but solely in those who do not respond or do not tolerate low-dose OC and low-cost progestins. Therefore, the evaluation of various stepwise treatment protocols may be suggested with the objective of increasing the value of care for women with endometriosis.

AUTHOR CONTRIBUTIONS

PV: conception and design of the study, interpretation of data, manuscript preparation; AD, FO, and MPF: acquisition and analysis of data; AF, JF, and VN: conception and design of the study,

interpretation of data; AR and PM: analysis and interpretation of data; ED: design of the study, analysis and interpretation of data; all the authors: critical revision of the article for important intellectual content, and approval of the final version of the manuscript.

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CONFLICT OF INTEREST

PV, AD, FO, AF, JF, VN, MPF, AR, and PM declare that they have no conflicts of interest. ES received grants from Ferring and Serono.

ETHICAL APPROVAL

All procedures performed in this study were in accordance with the ethical standards of the local institutional review board that approved the protocol on May 14, 2015 (Comitato Etico Milano Area B, determination #903/2015)..

544 FIGURE LEGENDS

545 Figure 1. Flowchart showing recruitment and progress of participants through the study.

546

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Table 1. Baseline demographic and clinical characteristics of the 157 women enrolled in the study.

Characteristic	Data
Age (y)	32.9 ± 5.7
Age (y) at first diagnosis	27.4 ± 5.4
BMI (kg/m^2)	21.6 ± 3.5
Previous deliveries	34 (22)
Previous interventions for endometriosis	
None	78 (50)
1	58 (37)
2	15 (9)
≥ 3	6 (4)
Previous medical therapy [a]	
None	35 (22)
Estrogen-progestins [b]	115 (73)
Progestins [b]	23 (15)
GnRH analogues	3 (2)
Dysmenorrhea	
NRS	9 (8-10); 8.6 ± 4.5
NRS > 5	148 (94)
Dyspareunia [c]	
NRS	6 (0-8); 5.1 ± 3.3
NRS > 5	85 (61)
Dyschezia	
NRS	2 (0-8); 3.7 ± 3.9
NRS > 5	65 (41)
Nonmenstrual pelvic pain	
NRS	5 (0-7); 3.9 ± 3.5
NRS > 5	67 (43)
No. of days per month with considerable pain [d]	6 (3-10)
No. of days per month with impairment of usual activity	2 (0-4)
SF-12 questionnaire	
Physical Component Summary Score	41.6 ± 10.8
Mental Component Summary Score	41.8 ± 10.6
FSFI total score [c]	26.4 ± 5.6

Note: Data are reported as mean ± standard deviation, n (%), or median (interquartile range). BMI = body mass index; FSFI = Female Sexual Function Index; GnRH = gonadotropin-releasing hormone; NRS = numeric rating scale (0-10); SF-12 = Short-form 12.

[a] The sum does not add-up to the total because 17 women previously used more than one therapy.

[b] Estrogen-progestins and progestins used previously were different from those used in the present study or were used with a different modality.

NRS = 0-10-point Numeric Rating Scale.

[c] Refers to 140 women because 17 did not have sexual intercourses at study entry.

[d] Pain necessitating analgesics.

Table 2. Per-protocol analysis of pain symptoms, health-related quality of life and sexual functioning scores variation between baseline and 12-month evaluation (*n* = 133).

Symptom/Questionnaire	Baseline	12-mo follow-up	*P* value
Dysmenorrhea			
NRS	8 (8-10); 8.6 ± 4.8	0 (0-0); 1.2 ± 2.6	<.001
NRS > 5	125 (94)	16 (12)	<.001
Dyspareunia [a]			
NRS	6 (0-8); 4.9 ± 3.4	0 (0-6); 2.6 ± 3.3	<.001
NRS > 5	70 (59)	35 (30)	<.001
Dyschezia			
NRS	4 (0-8); 3.8 ± 3.9	0 (0-0); 1.2 ± 2.6	<.001
NRS > 5	57 (43)	16 (12)	<.001
Nonmenstrual pelvic pain			
NRS	5 (0-7); 3.9 ± 3.6	0 (0-5); 2.5 ± 3.1	<.001
NRS > 5	58 (44)	31 (23)	<.001
No. of days per month with considerable pain [b]	7 (4-10)	0 (0-2)	<.001
No. of days per month with impairment of usual activity	2 (0-4)	0 (0-0)	<.001
SF-12 questionnaire			
Physical Component Summary Score	41.4 ± 11.1	51.0 ± 8.7	<.001
Mental Component Summary Score	41.9 ± 10.5	47.0 ± 10.0	<.001
FSFI total score [a]	26.4 ± 5.6	25.3 ± 6.1	.07

Note: Data are reported as median (interquartile range), mean ± standard deviation, or n (%). Women who withdrew (*n* = 21) or underwent surgery (*n* = 3) before 12 month follow-up assessment were excluded. FSFI = Female Sexual Function Index; NRS = numeric rating scale (0-10); SF-12 = Short Form 12.

[a] Fifteen women did not have sexual activity either at baseline or at the pre-planned follow-up evaluations.

[b] Pain necessitating analgesics.

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Table 3. Side-effects in estrogen-progestins and progestins users during the study period.

Side-effect	3 mo (n = 151)	6 mo (n = 142)	12 mo (n = 133)
None	28 (18)	29 (20)	27 (20)
Headache	31 (20)	27 (19)	23 (17)
Spotting	55 (36)	36 (25)	30 (22)
Weight gain	43 (28)	44 (31)	46 (34)
Decreased libido	53 (35)	51 (36)	47 (35)
Vaginal Dryness	37 (24)	35 (25)	34 (25)
Mood disorders	23 (15)	22 (15)	20 (15)
Breast tenderness	16 (10)	12 (8)	11 (8)
Water retention	6 (4)	4 (3)	4 (3)
Acne	5 (3)	5 (3)	5 (4)
Others	10 (7)	8 (6)	10 (7)
Weight increase (Kg), mean ± SD	2.7 ± 0.5	2.0 ± 0.9	3.1 ± 1.2

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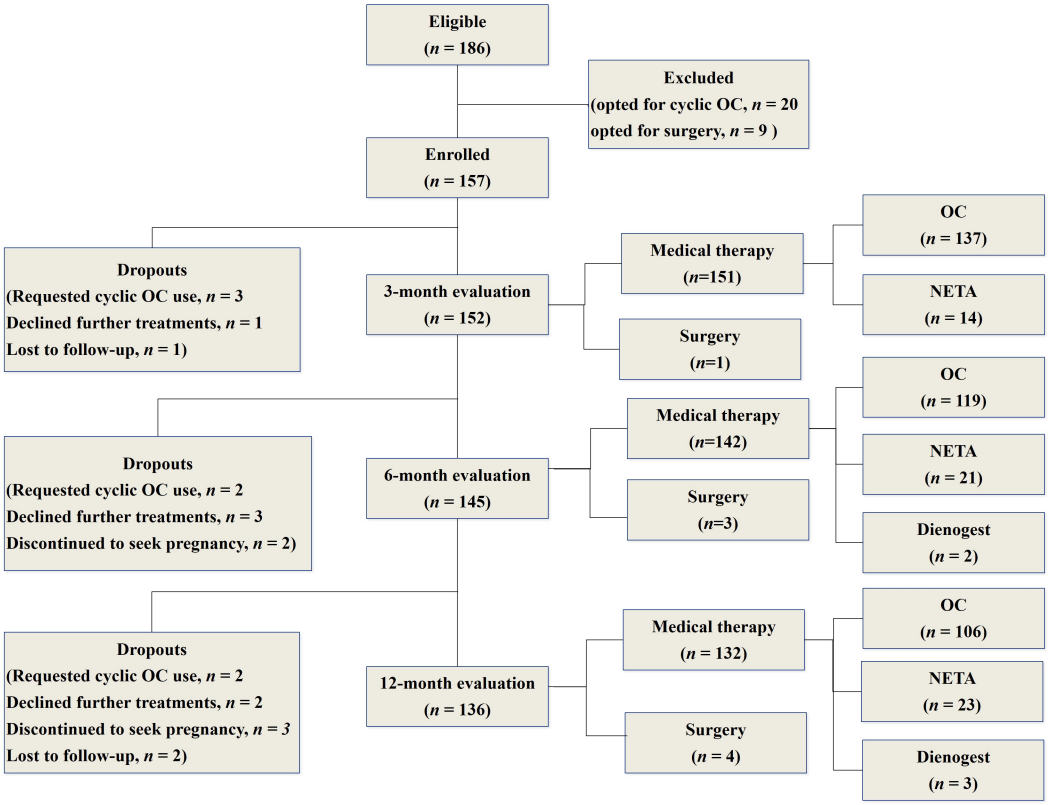

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Supplemental Table 1. Baseline ultrasonographic characteristics of study patients as assessed at transvaginal and/or transrectal examination.

Ultrasound findings	Participants (*n* = 157)
Ovarian endometriomas	
Absent	93 (59%)
Unilateral	51 (33%)
Bilateral	13 (8%)
Largest cyst diameter (mm)	26 [19-38]
Deep invasive endometriosis	
Absent	93 (59%)
Rectovaginal	56 (36%)
Other localizations	8 (5%)
Largest lesion diameter (mm)	15 [10-20]
Adenomyosis	33 (21%)

Data is reported as number (percentage), or median [interquartile range].

Supplemental Table 2. Comparison of baseline demographic and clinical characteristics of women who were or were not satisfied at 12-month follow-up evaluation (n = 152)[a].

Characteristic	Satisfied (n = 95)	Not satisfied[b] (n = 57)	P
Age (years)	32.9 ± 6.0	32.8 ± 5.5	0.94
Age at first diagnosis (years)	27.4 ± 5.2	27.0 ± 5.5	0.67
BMI (kg/m^2)	21.1 ± 3.2	22.4 ± 3.8	0.03
Previous deliveries	23 (24%)	11 (19%)	0.55
Previous interventions for endometriosis	45 (47%)	32 (56%)	0.32
Lesions detected at transvaginal and/or transrectal ultrasonography			
Deep invasive endometriosis	39 (41%)	24 (42%)	1.00
Endometriomas	37 (39%)	23 (40%)	0.87
Adenomyosis	24 (25%)	8 (14%)	0.15
Pain symptoms (NRS > 5)			
Dysmenorrhea	88 (93%)	56 (98%)	0.26
Dyspareunia	48 (56%) [c]	36 (72%) [d]	0.10
Dyschezia	40 (42%)	24 (42%)	1.00
Non-menstrual pelvic pain	38 (40%)	28 (49%)	0.31
No. of days per month with considerable pain [e]	6 [3-10]	7 [3-15]	0.20
No. of days per month with impairment of usual activity	2 [0-4]	2 [1-5]	0.20
SF-12 questionnaire			
Physical Component Summary Score	41.8 ± 11.2	41.2 ± 10.4	0.71
Mental Component Summary Score	43.0 ± 10.1	39.5 ± 11.4	0.048
FSFI total score	26.3 ± 5.3 [c]	26.4 ± 6.3 [d]	0.92