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THE ROLE OF MEDICAL THERAPY IN THE MANAGEMENT OF DEEP RECTOVAGINAL ENDOMETRIOSIS

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CAPSULE

According to observational and randomized, controlled trials, progestins relieved pain in around two thirds of women with rectovaginal endometriosis, thus constituting an alternative to surgery in selected women.

ABSTRACT

Defining whether medical therapy is effective in women with deep rectovaginal endometriosis and in which circumstances can be considered an alternative to surgery is important for patients and physicians. Numerous observational and some randomized, controlled studies demonstrated that different hormonal drugs improved pain and other symptoms in about two thirds of women with deep rectovaginal endometriosis. As major differences in the effect size of various compounds were not observed, much importance should be given to safety, tolerability, and cost of medications when counseling patients. Progestins appear to offer the best therapeutic balance when long-term treatments are planned. Women should be informed that hormonal drugs control, but do not cure endometriosis and that, to avoid surgery, they should be used for years. Medical therapy is not an alternative to surgery in women with hydronephrosis, severe sub-occlusive bowel symptoms, and in those wishing a natural conception. A progestin should systematically be chosen as a comparator in future randomized trials on novel medications for deep endometriosis. In the meantime, the use of existing drugs should be optimized and medical and surgical treatments could be viewed as subsequent stages of a stepwise approach. In general, there is no absolute "best" choice, and women must be thoroughly informed of potential benefits, potential harms, and costs of different therapeutic options, and allowed to choose what they deem is better for them.

KEY WORDS: endometriosis; pelvic pain; dysmenorrhea; dyspareunia; medical therapy

INTRODUCTION

"*Medical therapy* [for rectovaginal and colorectal endometriosis] *has been found to be ineffective or temporary, with a rate of recurrence as high as 76%, whereas surgical excision is effective in relieving pain*".

Minelli *et al*., (1)

"*One of the main characteristics of symptoms related to deeply infiltrating endometriosis lesions is that they dramatically respond to therapeutic amenorrhea*".

Fauconnier *et al*., (2)

In high-ranking medical journals, renown experts convey opposite messages regarding medical treatment of deep endometriosis. The above are just but two examples depicting the ongoing dispute on radical surgery versus hormonal therapy for this condition. According to Pellicer and Zupi, "*excellent speakers have promoted the efficacy of hormone treatments without knowing the benefits of surgical approaches; talented surgeons are explaining the benefits of a radical removal of lesions without any experience with the medical treatment options*" (3).

Definitively disentangling this issue is difficult and, owing to the dearth of comparative effectiveness research in the specific field of deep endometriosis, even international guidelines may not be of great help. Thus, investigators perpetuate this disagreement, with potentially detrimental consequences in terms of patients' confusion and physicians' uncertainty.

Given this background, our aim was to critically appraise and summarize the available evidence on the effects of hormonal treatments in women with deep rectovaginal endometriosis, and to provide factual information to be used when counseling patients and taking shared medical decisions in different clinical scenarios. A PubMed search has been conducted for the period 2000 to 2017 using combinations of medical subjects' terms "deep endometriosis", rectovaginal endometriosis", "pelvic pain", and "medical treatment". Only articles reporting original data on hormonal therapy for deep endometriosis, written in English language, and published in peer-review journals were selected.

We believe that medical therapy should be considered as the first-line treatment in women with symptomatic deep endometriosis not seeking natural conception. At the same time, we inform readers that in our referral center the knowledge and experience is available to treat different deep endometriosis forms also surgically (4-7).

THE HISTOLOGICAL AND BIOLOGICAL BASIS OF MEDICAL THERAPY FOR DEEP ENDOMETRIOSIS

A vast body of evidence support the notion that endometriosis is primarily a peritoneal disease (8-12). If this is true, the so called "deep infiltrating endometriosis" is one manifestation of a complex disease with a single pathogenic mechanism, i.e., retrograde menstruation (see, as reviews, 13-15). However, as discussed by Gordts and colleagues in the present issue (16), other theories may explain the pathogenesis of deep endometriosis, such as the metaplasia or Müllerian rests theory.

If deep endometriosis originates from superficial endometriosis (i.e., organ infiltration starts from the serosal layer) (17), it should respond to hormonal manipulation similarly to peritoneal implants. However, compared with superficial peritoneal endometriosis, deep endometriosis has a distinct histological characteristic as, in addition to the ectopic

endometrial-like mucosa (endometrial epithelium and stroma), and the fibrotic component deriving from inflammation (caused by the metabolic activity of the ectopic endometrium and possibly also by repeated micro-hemorrhages), smooth muscle fibers are also present. This is expected because the so-called deep endometriosis infiltrates the wall of hollow viscera such has the bowel, the bladder, the ureter, and the vagina. The result is a sort of desmoplastic lesion in the form of nodules or plaques comprising the three constituents, the mucosal, the fibrotic, and the smooth muscular one (18).

In a baboon model, induced deep endometriotic nodules were larger and more invasive when grafting specimens contained the junctional zone (19). Along the invasion front, increased mitotic activity, fewer adhesion molecules (20), and higher nerve fiber density were observed (21). The progressively increasing density with time suggests a potential role of nerve fibers in the development of deep endometriotic lesions (22).

If the smooth muscular component is the histologic hallmark of deep endometriosis (18), we consider as "deep" those forms of endometriosis that infiltrate at least the muscular layer of the considered abdomino-pelvic organs and agree with Koninckx *et al*. (14) who suggest abandoning the old criterion according to which an endometriotic lesion should be defined deep when it infiltrates at least 5 mm of tissue beneath the peritoneum (23). This arbitrary definition rapidly gained popularity and has been used, untested, for decades. However, it is unclear if and how this degree of depth has been systematically and precisely measured in all the studies in which it has been adopted. Moreover, it is unknown to what extent this measurement is reproducible, as inter-observer agreement is undetermined, but potentially high. With the advent of accurate imaging techniques, identifying the endometriotic infiltration of the muscular layer of different hollow organs is feasible (17,24-28). This criterion seems valid, reliable, and reproducible, and it has been adopted by several authors when conducting studies on medical treatment of deep endometriosis (29-32).

Hormonal treatments should thus exert an effect on two out of the three components of deep endometriosis, that is, the ectopic endometrial mucosa, and the smooth muscle fibers infiltrated by it. On the other hand, a major effect of medical therapies on the fibrotic component appears unlikely, although an influence of progestins on fibrosis remodeling during time cannot be excluded, due to their demonstrated anti-inflammatory properties (33-37).

Based on these premises, medical treatment for deep endometriosis may constitute a therapeutic alternative when established fibrotic stenosis of hollow viscera, such as ureteral infiltration with hydronephrosis and intestinal infiltration with occlusive symptoms, are excluded (14,17,38). Bowel occlusion is likely when wall infiltration is associated with fixed, sharp angulation, or when the lumen is intrinsically narrow, such as in cases of involvement of the last ileal loop and the ileocecal valve (39). However, infiltration of the rectal ampulla and the posterior vaginal fornix may cause severe symptoms, but almost never constitute a surgical emergency (6).

Two pathogenic mechanisms explain pain associated with deep endometriotic lesions, i.e., chronic inflammation deriving from the metabolic activity of ectopic endometrium, and secondary fibrosis with embedding of endometriotic glands into scar tissue. Persisting ectopic micro-hemorrhages despite fibrotic burial, leads to typical bluish nodules formation and initiates a sort of desmoplastic reaction causing firm adhesion and immobilization of adjacent organs and ligaments (6,40).

Recurring release of mediators of inflammation, such as prostaglandins and cytokines, may cause a functional-type, mostly cyclic pain, such as catamenial pseudo-cystitis and irritative intestinal symptoms, whereas pressure on nodules and plaques, and traction of

inelastic tissues and immobilized pelvic structures generates an organic type of pain, such as deep dyspareunia. The two types of pain may co-exist, as in cases of catamenial dyschezia.

In addition, a downstream effect of inflammation is neurotrophism with local neo-neurogenesis and activation of sensory nerve fibers, as recently observed also in the experimental baboon model (22). This may cause hyperalgesia, that is the occurrence of excruciating pain when a non-painful stimulus is applied (41). Indeed, women with deep endometriosis generally experience major exacerbation of pain when even minor pressure is exerted on nodules or indurated lesions (41,42). A painful sensation that is out of proportion with the intensity of nociceptor stimulation is characteristic of neuropathic pain, which is usually related to nerve injury or inflammatory stimuli (42-44).

Tyrosine kinase receptor B and the mu-opioid receptor transcription, induced by pro-inflammatory cytokines synthesized and released by activated macrophages and mast cells in deep endometriotic lesions, is decreased by GnRH agonist and progestin treatment (45), whereas previous use of combined oral contraceptives (OCP) or progestins was associated with a significant reduction in the expression of nerve growth factor and of small sensory nerve fiber density (46).

Moreover, several lines of evidence support the notion that oxidative stress in the pelvic cavity is pivotal for both endometriosis development and adhesion formation (see, as a review, Donnez *et al*, (47)). In particular, an excess of erythrocytes regurgitated in the pelvis during menstrual reflux would overcome the phagocytic capacity of peritoneal macrophages. This would result in extracellular release of hemoglobin, heme, and catalytic iron, with formation of reactive oxygen species and consequent cytotoxic and genotoxic effects (47). Medical treatments inducing amenorrhea or a major reduction in the amount of uterine

bleeding, would abolish or greatly limit retrograde menstruation, thus decreasing the release of pro-oxidant and pro-inflammatory factors (48).

Therefore, a rationale exists for the use of hormonal therapy to treat both, inflammatory pain and secondary neo-neurogenesis and hyperalgesia. However, confusion seems to be present in the literature regarding the main objective of medical therapy. In fact, the usual recurrence of symptoms at variable time after drug withdrawal is still used as a demonstration that hormonal treatments are ineffective because they do not definitively cure deep endometriosis (1). This vision does not take into account two facts. Firstly, hormonal treatments can suppress but not eradicate ectopic endometrium definitively. Secondly, in general medical treatments control but rarely cure chronic disorders, whether of metabolic (e.g., diabetes), immune (e.g., autoimmune disorders), inflammatory (e.g. Crohn's disease and ulcerative colitis), or unknown (e.g., essential hypertension) origin. Therefore, medical treatments for deep endometriosis should be considered no less and no more than other treatments for several chronic medical conditions. The practical issue here is defining when is medical therapy advantageous over surgery, taking into consideration that, if chosen, hormonal treatments should be continued until a pregnancy is desired or the physiologic menopause ensues. This may mean many years of treatment, and this important aspect must be clarified during counseling, together with the fact that conservative surgery as an isolated measure does not guarantee definitive symptoms relief. The real choice is often not between medical or surgical treatment, but between medical treatment alone and surgical treatment followed by postoperative medical treatment (49).

MEDICAL THERAPY FOR DOUGLAS POUCH AND DEEP RECTOVAGINAL ENDOMETRIOSIS

Premise

An endometriotic lesion has been defined as vaginal "*when lesions infiltrate the anterior rectovaginal pouch, posterior vaginal fornix and retroperitoneal area between the anterior rectovaginal pouch and posterior vaginal fornix*" (12). In other words, rectovaginal endometriosis is a deep lesion that concurrently infiltrates the anterior rectal and the posterior vaginal walls (Figure 1). A nodule located in the posterouterine pouch that does not infiltrates the vaginal and rectal walls should be categorized as a Douglas pouch lesion, and not as rectovaginal endometriosis.

Responsiveness of the endometrium within deep lesions to gonadal steroids is the prerequisite for medical therapy aimed at inducing metabolic quiescence of ectopic glands. The presence of estrogen and progesterone receptors in peritoneal and ovarian endometriotic lesions were demonstrated by Nisolle *et al*. already several years ago (50,51). Those investigators also suggested the concept of progesterone resistance (50,51). More recently, Noël *et al*. demonstrated that estrogen and progesterone receptors were present in major histologic components of rectovaginal, bladder, and uterosacral endometriosis, including the smooth muscle fibers. Progesterone receptors were also present in endometriosis of the colon (52). Ferrero evaluated the changes in the dimension of rectovaginal endometriotic nodules during 12-month treatment with OCPs, progestins, or triptorelin plus tibolone. The volume of the nodules decreased progressively at 6- and 12-month evaluation in three out of four of the 83 women studied without statistically significant differences between subgroups of patients using different drugs (53).

Dysmenorrhea is the most frequent symptom also in women with rectovaginal endometriosis, but hormonal treatments that induce amenorrhea relieve menstrual pain by definition. Apart from dysmenorrhea, the complaint characteristically associated with vaginal and rectal endometriosis are, respectively, deep dyspareunia and dyschezia (40,54-56). Both symptoms are caused by pressure on fibrotic (inextensible) lesions, during deep-thrust

penetration in the former case, and passage of hard stools in the latter case. These organic-type pains are usually exacerbated by intra- and peri-lesional inflammatory phenomena occurring during and shortly after menstruation. Medical therapies should exert an appreciable effect on inflammatory and neuropathic pain. The effect on organic pain, likely associated with modifications in the volume of lesions, may be limited by the amount of intra- and peri-lesional fibrosis.

The results of treatment with various hormonal therapies have been reported in 10 non-comparative studies published between 2000 and 2017 in which a total of 258 patients with rectovaginal endometriotic lesions were recruited. In the same time period, nine comparative studies were published including a total of 778 participants. Two studies were randomized, controlled trials (RCT), five were patient preference trials, one was a cohort study, and one a before and after study. The main characteristics of all the identified studies are shown in Tables 1 and 2 where complete lists of adverse events associated with the use of the various medications are included. More detailed information on selected studies is provided below.

Estrogen-progestins and progestins

In the first RCT conducted specifically on women with highly symptomatic rectovaginal endometriosis, a monophasic estrogen-progestin combination (ethinyl-estradiol, 0.01 mg plus cyproterone acetate, 3 mg) and norethindrone acetate (NETA; 2.5 mg/day), both used continuously for 12 months, were compared (65). According to an intention-to-treat analysis 28/45 (62%) participants in the estrogen-progestin combination group and 33/45 (73%) in the NETA group were satisfied with the treatment received. All pain symptoms, including deep dyspareunia and dyschezia, were substantially reduced by both medications. Between-group differences in satisfaction with treatment and pain relief were not statistically different.

In a patient preference trial Ferrero *et al*. (66) compared the same dose of NETA (2.5 mg/day) combined with letrozole (2.5 mg/day; $n = 41$) with NETA used as monotherapy (2.5 mg/day; $n = 41$). The combined therapy relieved non-menstrual pain and deep dyspareunia to a greater extent compared with NETA alone but, interestingly, the satisfaction with treatment at the end of six months of therapy was similar (56% versus 63%, respectively) because of the higher incidence of adverse effects observed in the former group. As expected, pain symptoms recurred after drug discontinuation without between-group differences.

In another patient preference trial (7), NETA (2.5 mg/day for 12 months) was compared with laparoscopic surgery, in women specifically selected because of severe deep dyspareunia; 59 out of 154 participants had rectovaginal endometriosis. At 12-month intention-to-treat evaluation of these women, 54% (13/24) of those chose surgery were satisfied with the treatment received compared with 51% (18/35) of those who chose NETA. In the former group, a marked and rapid short-term improvement in dyspareunia was observed, followed by partial pain recurrence. The effect of NETA on pain at intercourse was more gradual, but progressive throughout the study period (7). Variations in sexual functioning, psychological status, and health-related quality of life followed substantially similar patterns (73).

Desogestrel (75 μg/day per os) was evaluated in two patient preference studies. Leone Roberti Maggiore *et al*. (70) compared this progestins with an estrogen-progestin vaginal ring used continuously in 143 women. After 12 months of treatment, 62% of participants who chose desogestrel were satisfied with their treatment compared with 36% of those who chose the vaginal ring. The same research group (71) compared the effect of desogestrel ($n = 62$) and that of a low-dose monophasic OCP used cyclically ($n = 82$) in women suffering from migraine without aura. Less frequent and severe migraine attacks were observed in progestin

users with respect to OCP users. At 6-month evaluation, a higher degree of patient satisfaction was observed in the former group (61%) compared with latter (38%).

The effect of dienogest (2 mg/day) was compared with that of NETA (2.5 mg/day) in a 12-month before and after study (72). A total of 64 out of 180 women had rectovaginal endometriosis. At intention-to-treat analysis in this subgroup, 67% of patients who used NETA was satisfied with the treatment received compared with 68% of those who used dienogest. The latter progestin was better tolerated, but several women discontinued it because of cost. As dienogest is much more expensive that NETA, the authors concluded that it should not be considered as the first medical approach.

Morotti *et al*. prescribed dienogest in 25 women with persistent pain associated with rectovaginal endometriosis despite NETA therapy (63). After treatment for six months, pain symptoms significantly decreased and sexual functioning and health-related quality of life improved. Given the study design adopted, a placebo effect cannot be excluded, as the rationale for such diverse effects of same-class compounds is unclear. In addition, the long-term effectiveness of NETA has been confirmed in a retrospective cohort study conducted by this research group on 103 patients with symptomatic rectovaginal endometriosis and followed for five years (64). A total of 16 women discontinued the progestin because of adverse effects. Overall, 69% of participants who completed the study (corresponding to 41% of the patients originally enrolled) were satisfied with their long-term NETA treatment. Deep dyspareunia and dyschezia improved substantially already at 1-year evaluation. Unexpectedly, the volume of the recto-vaginal nodule increased in 7 patients despite NETA treatment.

Two non-comparative studies confirmed the efficacy of dienogest in improving pain symptoms in women with rectovaginal endometriosis (31,32).

The use of the levonorgestrel-releasing IUD (LNG-IUD) for one year has been assessed by Fedele *et al*. (58) in 11 patients. At baseline, moderate to severe dysmenorrhea was referred by all women, and deep dyspareunia by eight. At the end of treatment dysmenorrhea was completely relieved and mild dyspareunia was present in five participants. The volume of the rectovaginal lesion, as assessed at vaginal ultrasonography, decreased progressively through the study period. However, a series of patients studied by Ferrero *et al*. did not respond to the LNG-IUD and required further medical therapy (62).

In particular, the effect of LNG-IUD on deep dyspareunia is less definite than that on dysmenorrhea and probably limited (74,75). In addition, the LNG-IUD does not inhibit ovulation, thus it does not seem effective in preventing endometrioma development or recurrence (75).

Danazol

Danazol was used *per vaginam* in two prospective non-comparative studies. Razzi *et al*. (60) treated 21 women with rectovaginal endometriosis with danazol, 200 mg/day for 12 months. Dysmenorrhea, dyspareunia, dyschezia and pelvic pain disappeared after 6 months of treatment and the effect persisted until the end of the study period. The volume of rectovaginal plaques decreased from a mean baseline value of 3.1 mL to 1.2 mL at 1-year assessment. Four women complained of vaginal irritation during the first month of therapy. All the participants experienced regular menstruations throughout the entire period of observation. This mandate the use of barrier contraception when this treatment modality is chosen.

Ferrero *et al*. used a lower dose of danazol (100 mg/day) for six months in 15 women with pain persisting after insertion of the LNG-IUD (62). Symptoms' intensity improved progressively and significantly during the study period, and 12 out of 15 women were

satisfied with their treatment at 6-month evaluation. The rectovaginal nodule volume decreased from 2.3 mL at baseline to 1.7 mL at the end of treatment. Adverse effects were minimal and well tolerated.

GnRH agonists

A GnRH agonist for the treatment of rectovaginal endometriosis has been used in a single, non-comparative, prospective study (57). A total of 15 patients used leuprorelide acetate in a monthly 3.75 mg depot formulation for six months. Two women dropped out of the study because of inefficacy of medical therapy and requested surgery. The remaining 13 patients showed a marked improvement in moderate to severe pain symptoms which, however, recurred soon after drug discontinuation. Apparently based on the study hypothesis of a curative effect of GnRH agonist treatment, the authors maintained that the failure rate of this treatment modality (request for further treatment) was 87% (13/15).

GnRH antagonists

GnRH antagonists prevent binding of endogenous GnRH to its pituitary receptors, which are not downregulated. Thus, titrating GnRH antagonists dosage allows modulation of inhibition of ovarian estradiol synthesis (48). Several phase I and II trials have already been conducted on GnRH antagonists, and the results of two phase III explanatory trials have recently been published demonstrating the dose-dependent superiority of elagolix, an oral, nonpeptide, GnRH antagonist, over placebo in reducing endometriosis-associated dysmenorrhea and non-menstrual pain (76). The former finding is expected by definition whenever a drug induces amenorrhea or hypomenorrhea. Unfortunately, also the reduction in bone mineral density was dose-dependent (77). Some other GnRH antagonists are currently under evaluation (48).

However, the concrete advantages of GnRH antagonists over GnRH agonists have yet to be determined. In fact, the "flare-up" effect induced by GnRH agonists can be greatly

limited administering the drugs during the luteal phase, whereas chosing a daily oral administration versus a monthly or three-monthly depot administration is a matter of personal preference. No data focusing specifically on the effect of GnRH antagonists on deep rectovaginal endometriosis are available yet. However, there is no reason to believe that they should work less than other available medications. Moreover, GnRH antagonists appears well tolerated (77).

There are several issues to be clarified here, including whether these new drugs can be used alone or necessitates add-back therapies anyway, as GnRH agonists, in order to prevent bone demineralization; whether they can safely be used for long periods of time; and whether their effectiveness and cost-effectiveness, evaluated by means of pragmatic trials, will be comparable with or superior to that of progestins. In other words, the goals will be a) investigating if the effect observed under the highly controlled conditions typical of explanatory trials will be maintained also when these drugs will be provided to unselected patients under usual circumstances of healthcare practice, and b) defining the "efficiency" of GnRH antagonists for the treatment of endometriosis, that is, the effect of these compounds in relation to the resources they consume (78).

Aromatase inhibitors

Ferrero *et al*. conducted a RCT on the use of oral letrozole (2.5 mg/day) in 35 women with symptomatic rectovaginal endometriosis (69). The aromatase inhibitor was combined with NETA (2.5 mg/day; $n = 17$) or triptorelin (depot 11.25 mg/3 months; $n = 18$) to prevent ovarian stimulation. After six months of therapy, 65% of women in the former group were satisfied with their treatment compared with 22% in the latter one. No significant between-group difference was observed in pain relief. Treatment discontinuation because of adverse effects was rare in the progestin group ($n = 1$), but frequent in the GnRH agonist group ($n =$

8). This study does not provide evidence that aromatase inhibitors work because, when hormonal medications are combined, it is not possible to discriminate the specific effect of each compound. On the other hands, aromatase inhibitors are ineffective if not associated with other drugs that inhibit ovulation.

Comment

Abundant evidence from RCTs and observational studies demonstrates the benefits of hormonal treatments in patients with symptomatic rectovaginal endometriosis. Overall, information on more than 1000 women who used hormonal medications for rectovaginal endometriotic lesions is available. This appears as an interesting body of data on which to base clinical understanding and medical decision-making. Importantly, the degree of satisfaction with treatment has been reported in most studies. This is a patient reported outcome that summarizes the global woman experience with her therapy, including pain relief, side effects, variations in health-related quality of life, psychological status, sexual satisfaction, as well as cost issues. About two thirds of patients with symptomatic rectovaginal endometriosis were satisfied with progestin treatments at intention-to-treat analyses.

However, some inconsistencies are difficult to explain. In particular, despite statistically significant reductions in pain at intercourse as measured with validated scales, only moderate improvements in general sexual function were observed during medical therapies (7,73,79). This emphasizes the notion that female sexual functioning is multifactorial, and that impacting on a single, although important, aspect of sexual life, may not affect substantially the overall sexual experience (79-80). Of relevance here, the same limitations pertain also to surgical treatment (7,73,79), and collaborating with a sexual therapist with experience in endometriosis patients may be advisable in those women who

383 complain of persistent sexual dysfunction despite considerable reduction in pain at intercourse
384 (80).

385 Also, dyschezia was substantially relieved in most patients during hormonal
386 treatments. However, defecation pain usually does not have emotional implications
387 comparable to those associated with dyspareunia, and rarely constitutes the sole indication for
388 surgery. Thus, medical therapy appears as the ideal approach in women who refer this
389 symptom as their main complaint.

390 DISCUSSION: PROMISES, PROMISES

391 Deep infiltrating endometriosis is the really severe endometriotic disease. From a therapeutic
392 point of view, and independently of different pathogenic hypotheses, clinicians and patients
393 should know if and how much medical treatments are effective when infiltrating lesions are
394 present, in which circumstances they can be used, and whether they really constitute an
395 acceptable alternative to surgery.

396 In general, hormonal drugs (or combinations of hormonal drugs) were demonstrated
397 effective in relieving pain and other associated symptoms in most women with Douglas pouch
398 and rectovaginal endometriosis. Discriminating the specific effect of medications on deep
399 lesions from that on superficial and ovarian ones is practically impossible, as the various
400 histologic phenotypes generally coexist. However, improvements in deep dyspareunia,
401 dyschezia, and several intestinal complaints, strongly suggest a specific effect of medical
402 therapies on infiltrating endometriosis, as a robust association between symptoms' type and
403 deep lesions' site has been demonstrated (12,56).

404 It is difficult to precisely define the effect size of each compound, also because very
405 few randomized, comparative effectiveness trials have been conducted selectively in patients
406 with deep endometriosis. Overall, it does not appear that major differences exist between

different medications. Therefore, much value should be given to aspects such as safety, tolerability, and cost, because medical therapies, being symptomatic and not curative, may be needed for years. In this regard, low-dose, monophasic OCPs and progestins appear to constitute the best available compromise between all the above factors, and should be proposed as the first-line medical treatment.

In general, very-low dose, monophasic OCPs may be suggested for peritoneal and ovarian endometriosis, whereas NETA and dienogest should be preferred for rectovaginal lesions. Adding aromatase inhibitors did not improve efficacy to a great extent, but increased the incidence of adverse events and raised costs. The combination of GnRH agonists and add-back therapies was demonstrated to be consistently effective in reducing pain and alleviating symptoms associated with infiltrating endometriosis, and could be considered as a second-line, long-term option in highly selected women at greatly increased surgical risk. Otherwise, conservative or definitive surgery should be carefully evaluated as a suitable and less costly alternative.

Recently Casper maintained that "*both norethindrone acetate and dienogest have regulatory approval for treating endometriosis and may be better than OCPs as a first-line therapy* [of endometriosis]" (37). Based on the available evidence (81), we are uncertain whether this should systematically apply also to patients with superficial peritoneal and ovarian forms, as the former women usually respond to low-dose, monophasic OCPs used cyclically or continuously, and the latter ones benefit from anovulation, however obtained (82-85). Treatment with progestins alone for years may impact on serum lipid profile and on bone mineral content, although a causal relation between these surrogate markers and cardiovascular events and pathologic fractures, in general, should not be given for granted (86). On the other hand, women with infiltrating endometriosis are affected by the disease form associated with the most severe pain symptoms, with the most potentially serious

clinical consequences, and with the riskiest procedures in case surgery is performed. Therefore, we concur that it appears wise here to accept minor metabolic effects with the objective of avoiding the estrogenic stimulation of deep lesions and obtaining more profound disease quiescence.

We have recently proposed a lesion-based, three-tiered risk stratification system (low-, intermediate-, and high-risk group) for an individualized management of women with, respectively, superficial peritoneal, ovarian, and infiltrating endometriosis form (81). According to this risk strata system, patients with deep infiltrating lesions should be considered a high-risk group and, when not seeking pregnancy, should use progestins instead of OCPs as a first-line medical therapy. Moreover, the contraposition between medical and surgical treatment should be overcome applying a stepwise approach, where surgery should be considered when progestins are not effective or not tolerated (Figure 2). In this regard, we fully agree with Abrao and co-workers when they conclude that "*In women with deep endometriosis, surgery is the therapy of choice for symptomatic patients when deep lesions do not improve with a medical treatment*" (17).

It has also been recently stated that, because currently used medical therapies merely control but do not cure endometriosis, "*those women who do not respond to existing therapies may benefit from new therapies with different mechanisms of action*. [...] *There remains an unmet clinical need among women with endometriosis for a specific disease-modifying therapy to provide long-term symptom relief that persists after the treatment period*" (87). Although this is undoubtedly the best imaginable future scenario for all women with endometriosis, we also deem that the clinical research conducted in the past years do not seem to support such optimistic view (87-90). The rationale for a curative effect of novel drugs is unclear, as they should exert selective cytotoxicity toward specific, autologous, benign cells. A careful balance should also be made considering adverse event and overall drug toxicity, as

endometriosis is not a cancer. Of relevance here, RCTs on novel compounds for deep endometriosis should include a progestin as a standard comparator, because women should know whether new drugs are better than those they currently use. It is unfortunate that most RCTs sponsored by pharmaceutical industries have mainly registration purposes, are designed to systematically favor the experimental compound, rarely include objectives that matter to patients, and are selectively reported (88-93).

In the meantime, we should first learn how to optimize the medical treatment of women with deep endometriosis with drugs available now, as there is already abundant and consistent evidence that about two thirds of patients can be safely and successfully managed for indefinite periods of time. This does not seem a discouraging achievement, and suggesting surgery for deep endometriosis based on the presupposition that medical treatments are ineffective, nowadays appears deceptive. In addition, existing compounds may be used differently. As an example, the vaginal route may reveal advantageous for administering medications in women with rectovaginal lesions. This understudied modality merits further developments (67,94-96). Undeniably, several issues remain unsolved, and the need for therapy discontinuation when seeking a conception is among the most important ones. Moreover, it is well known that medical therapy has no role in endometriosis-associated infertility, as it does not enhance the likelihood of conception.

Beyond debates over "old" and "novel" drugs, or medical versus surgical treatment, complete and detailed quantitative information on potential benefits, potential harms, and costs of therapeutic alternatives remains pivotal in the management of women with deep endometriosis. What may reveal difficult for us clinicians to accept is the fact that we should no longer decide for our patients (97). We may suggest considering important variables that patients may not expect or not even know (e.g., the potential complications of unoperated deep bowel endometriosis during pregnancy or when undergoing IVF) (98), and guide them

through the shared medical decision-making process, but the woman should eventually choose, as it is the woman who might experience the side effects of medications for years, or suffer the consequences of surgery in case of complications. With due exceptions, there is no absolute best choice, as different women may choose differently based on their preferences and priorities.

CONTRIBUTION TO AUTHORSHIP

Conception: PV. Literature search: LB and ES. Drafting the article: PV. Critical revision of the article for intellectual content: all authors. All the authors approved the final version of the manuscript.

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788
789 FIGURE LEGENDS

790 Figure 1. Colposcopic appearance of an endometriotic nodule in the retro-cervical area
791 (upper panel). A biopsy of the nodule is taken (lower panel).

792 Figure 2. Suggested algorithm for individualized treatment of endometriosis-associated
793 pain by means of a lesion-based, three-tiered risk stratification system and a stepwise
794 pharmacological approach (81) in women not seeking conception and preferring medical
795 therapy rather than surgery.

Table 1. Effect of danazol, estrogen-progestins, gonadotropin releasing hormone agonists (GnRHa) and progestins as assessed in non-comparative studies on the treatment of rectovaginal endometriosis (literature data, 2000–2017).

Source	**Study design**	**Patients enrolled (*n*)**	**Intervention**	**Treatment period**	**Follow-up period**	**Adverse effects (%)**	**Outcome**
Fedele *et al*., 2000 (57)	Prospective	15	Leuprolide acetate 3.75 mg i.m./28 day	6 months	12 months	NR	Improvement of pain symptoms during treatment. High rate of pain recurrence after drug suspension. Transient reduction of nodule size during treatment with return to original volume during follow-up.
Fedele *et al*., 2001 (58)	Prospective	11	LNG-IUD	12 months	No follow-up	Headache (37) Breast tenderness (37) Weight gain >1 kg (37) Seborrhea, oily hair, acne (27)	Significant improvement of dysm and CPP. Slight amelioration of deep dysp without reaching complete remission. Significant reduction of nodule size after 6-months of treatment. At the end of treatment period 9 patients were oligomenorrheic and 2 had amenorrhea.
Hefler *et al.*, 2005 (59)	Prospective	10	Vaginal anastrozole 0.25 mg/day	6 months	1 month	No severe adverse events reported during study period	Significant improvement of dysm and QoL. CPP and dysp remained unchanged during treatment. No significant changes in BMD and nodule volume size during treatment.
Razzi *et al*., 2007 (60)	Prospective	21	Vaginal danazol 200 mg/day	12 months	No follow-up	Vaginal irritation (19)	Significant improvement of dysm, dysp, and CPP. Significant reduction of nodule size after 6-months of treatment. No significant

Source	Study design	Patients enrolled (*n*)	Intervention	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							change of serum metabolic and thrombophilic parameters.
Remorgida *et al.*, 2007 (61)	Prospective	12	Letrozole 2.5 mg/day + NETA 2.5/day per os	6 months	12 months	Weight gain (33) Mood swings (33) Weakness (25) Bone and joint pain (25) Vaginal spotting (17) Muscle aches (17) Headache (17), Depression (17) Hot flushes (8) Nausea (8) Decreased libido (8)	Significant pain relief and QoL improvement during treatment. At 6-months' follow-up recurrence of pain symptoms and worsening of QoL scores in all patients. No BMD changes during treatment.
Ferrero *et al.*, 2011 (62)	Observational pilot study	15[a]	Vaginal danazol 100 mg/day	6 months	No follow-up	Seborrhea, oily hair, acne (27) Headache (20) Weight gain >3 kg (13) Vaginal irritation (13)	Significant improvement of dysm, dysp, CPP, and dyschezia and reduction of nodule size after 6 months of treatment. High satisfaction rate with the treatment (80% of women were satisfied or very satisfied).
Morotti *et al.*, 2014 (63)	Open-label prospective study[b]	25	DNG 2 mg/day per os (*n* = 25)	6 months	No follow-up	Headache (16) Nausea (8) Breast tenderness (4)	Improvement of pain symptoms, sexual function, QoL and satisfaction with DNG
Yela *et al.*, 2015 (31)	Prospective	16	DNG 2 mg/day per os	6 months	No follow-up	Headache Acne Decreased libido Breast pain Hair loss Nausea/vomit Bloating Vaginal	Significant improvement of pain symptoms (dysm, dysp, CPP, and dyschezia). No significant changes in volume size of endometriotic nodules.

Source	Study design	Patients enrolled (*n*)	Intervention	Treatment period	Follow-up period	Adverse effects (%)	Outcome
						dryness	No significant changes in QoL and sexual function.
Leonardo-Pinto *et al.*, 2017 (32)	Prospective	30	DNG 2 mg/day per os	12 months	No follow-up	Headache (63) Breast pain (43) Decreased libido (43) Nausea/vomit (23)	Significant improvement of pain symptoms (dysm, dysp, CPP, bowel pain) and QoL. No significant changes in volume size of endometriotic nodules.
Morotti *et al.*, 2017 (64)	Retrospective	103 (61 completed the 5 year follow-up)	NETA 2.5 mg/day per os[c]	5 years	--	Weight gain (30) Vaginal bleeding (23) Lipids alteration (12) Decreased libido (11) Headache (9) Bloating (8) Depression (7) Acne (5) Erythematous cutaneous reaction (1)	Significant improvement of dysm, CPP, dyschezia and dysp. At the end of study period 67% of women were satisfied or very satisfied with the treatment.

[a] This study specifically selected patients with symptomatic rectovaginal endometriosis who had pain persistence after insertion of a LNG-IUD.
[b] This study specifically selected patients with symptomatic rectovaginal endometriosis who had pain persistence and were unsatisfied after 6-months of treatment with NETA
[c] In case of breakthrough bleeding the dose of NETA was increased by 2.5 mg/day (maximum dose of 5 mg/day)

BMD = bone mineral density; CPP = chronic pelvic pain; DNG = dienogest; Dysm = dysmenorrhea; Dysp = dyspareunia; LNG-IUD = levonorgestrel-intrauterine device; NETA = norethindrone acetate; NR = not reported; OC = oral contraceptive; QoL = quality of life.

Table 2. Effect of aromatase inhibitors, estrogen-progestins, gonadotropin releasing hormone agonists (GnRHa) and progestins as assessed in comparative studies on the treatment of rectovaginal endometriosis (literature data, 2000-2017).

Source	**Study design**	**Patients enrolled (*n*)**	**Study drug**	**Comparator**	**Treatment period**	**Follow-up period**	**Adverse effects (%)**	**Outcome**
Vercellini *et al.*, 2005 (65)	RCT	90	Continuous low-dose monophasic OC (EE 0.01 + cyproterone acetate 3 mg)/day (*n* = 45)	NETA 2.5 mg/day per os (*n* = 45)	12 months	No follow-up	Group OC: Weight gain (16) Headache (7) Nausea (7) Depression (4) Decreased libido (4) Acne (2) Bloating (2) Breast tenderness (2) Hypertriglyceridemia (2) Group NETA: Weight gain (27) Decreased libido (9) Bloating (9) Depression (7) Headache (4) Acne (4) Erythematous cutaneous reaction (2)	Similar pain relief and dropout rates. Higher satisfaction with treatment in NETA group.
Ferrero *et al.*, 2009 (66)	PPT	82	Letrozole 2.5 mg + NETA 2.5 mg/day per os (*n* = 41)	NETA 2.5 mg/day per os (*n* = 41)	6 months	12 months	Group Letrozole + NETA: Weight gain (20) Joint pain (17) Myalgia (12) Spotting (10) Breakthrough bleeding (5) Migraine (5)	Greater pain relief with letrozole + NETA, but fewer side effects and higher patient satisfaction rate with NETA only. Similar pain at follow-up. No BMD changes during treatment.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							Myalgia (2) Depression (2) Hair loss (2) Decreased libido (2) Group NETA: Weight gain (17) Breakthrough bleeding (7) Spotting (7) Migraine (7) Depression (2)	
Vercellini *et al.*, 2010 (67)	PPT	59[a]	Vaginal ring (EE 15 μg + etonogestrel 120 μg) (*n* = 38)	Transdermal patch (EE 20 μg + norelgestromin 150 μg) (*n* = 21)	12 months	No follow-up	Group vaginal ring: Bloating (10) Vaginal discomfort (7) Depression (6) Weight gain (6) Headache (6) Breast tenderness (5) Decreased libido (4) Nausea (2) Group patch: Headache (18) Nausea (8) Breast tenderness (8) Weight gain (5) Depression (5) Decreased libido (5) Cutaneous reaction (5) Bloating (3) Vaginal dryness (2)	Greater pain relief and satisfaction with vaginal ring.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							Vomiting (2)	
Mabrouk *et al.*, 2011 (68)	Retrospective	106	Cyclic low-dose monophasic OC (EE 20 μg + drospirenone 3 mg)/day (*n* = 75)	No treatment (*n* = 31)	5.8 (3.7) months[a]	No follow-up	NR	No significant variations in pain scores and nodule size in OC group. Significant worsening of dysm and deep dysp scores, and enlargement of nodule size in nonuser group. No significant changes in QoL scores during study period nor between groups.
Ferrero *et al.*, 2011 (69)	RCT	35	Letrozole 2.5 mg + NETA 2.5 mg/day per os (*n* = 17)	Letrozole 2.5 mg/day per os + triptorelin 11.25 mg/3 months i.m (*n* = 18)	6 months	No follow-up	NETA group: Weight gain (12) Decreased libido (12) Spotting (12) Myalgia and arthralgia (12) Depression (6) Triptorelin group: Myalgia and arthralgia (56) Decreased libido (22) Depression (22) Hot flushes (22) Vaginal dryness (17) Insomnia (17) Hair loss (11) Headache (11)	Similar pain relief. Higher patient satisfaction with treatment in NETA group. Higher discontinuation rates in the triptorelin group. Greater nodule size reduction with triptorelin. Significant reduction of BMD in women treated with triptorelin.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							Weight gain (6)	
Vercellini *et al.*, 2012 (7)	PPT	59[b]	NETA 2.5 mg/day per os (*n* = 35)	Second-line laparoscopic excision of endometriotic lesions (*n* = 24)	12 months	No follow-up	Weight gain (34) Breakthrough bleeding (20) Decreased libido (19) Vaginal dryness (12) Spotting (11) Breast tenderness (6) Bloating (5) Headache (4) Depression (4) Nausea (2)	At the end of follow-up comparable satisfaction and improvement of deep dysp.
Leone Roberti Maggiore *et al.*, 2014 (70)	PPT	143	DSG 75 μg/day per os (n = 60)	Vaginal ring (EE 15 μg + etonogestrel 120 μg) (n = 83)	12 months	No follow-up	Group DSG: Breakthrough bleeding (8) Metrorrhagia (2) Weight gain (2) Group vaginal ring: Weight gain (6) Spotting (2)	Higher patient satisfaction with treatment in DSG group. Similar reduction in the volume of rectovaginal nodules. Comparable discontinuation rates.
Morotti *et al.*, 2014 (71)	PPT	144	DSG 75 μg/day per os (*n* = 62)	Cyclic low-dose monophasic OC (EE 20 μg + DSG 150 μg)/day (*n* = 82)	6 months	No follow-up	Group DSG: Bleeding (8) Weight gain (2) Mood changes (2) Group OC: Increased migraine (11)	Higher satisfaction with treatment in DSG group. Similar pain relief (dysp and CPP). Lower rate of migraine attacks with DSG.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							Bleeding (6) Weight gain (2) Mood changes (1) Decreased libido (1) Acne (1) Peripheral edema (1)	
Vercellini *et al.*, 2016 (72)	Before-after study	60[b]	DNG 2 mg/day per os (*n* = 29)	NETA 2.5 mg/day per os (*n* = 31)	6 months	No follow-up	Group DNG: Weight gain (16) Spotting (13) Decreased libido (9) Vaginal dryness (7) Bloating (6) Alopecia (5) Headache (3) Mood disorders (2) Breast tenderness (1) Nausea (1) Breakthrough bleeding (1) Group NETA: Weight gain (31) Spotting (22) Decreased libido (14) Vaginal dryness (13) Mood disorders (8) Breast tenderness (8) Bloating (5) Acne (4) Headache (3) Alopecia (1) Breakthrough	Similar satisfaction with treatment and pain relief.

Source	Study design	Patients enrolled (*n*)	Study drug	Comparator	Treatment period	Follow-up period	Adverse effects (%)	Outcome
							bleeding (1)	

[a] mean (SD)
[b] only the sub-group of patients with rectovaginal endometriosis was considered

BMD = bone mineral density; CPP = chronic pelvic pain; DNG = dienogest; DSG = desogestrel; dysm = dysmenorrhea; dysp = dyspareunia; EE = ethinyl estradiol; NETA = norethindrone acetate; NR = not reported; OC= oral contraceptive; PPT = patient-preference trial; QoL = quality of life; RCT = randomized controlled trial