Role of medical therapy in the management of deep rectovaginal endometriosis

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Defining whether medical therapy is effective in women with deep rectovaginal endometriosis and in which circumstances it 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 approximately two-thirds of women with deep rectovaginal endometriosis. Because 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 seem 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 subocclusive 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. (Fertil Steril® 2017;108:913–30. ©2017 by American Society for Reproductive Medicine.)

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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, renowned experts convey opposite messages regarding medical treatment of deep endometriosis. The above are just but 2 examples depicting the ongoing dispute on radical surgery vs. hormonal therapy for this condition. According to Pellicer and Zupi (3), "…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."

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

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used when counseling patients and making shared medical decisions in different clinical scenarios. A PubMed search has been conducted for the period 2000 to 2017 using combinations of the medical subject terms "deep endometriosis," "rectovaginal endometriosis," "pelvic pain," and "medical treatment." Only articles reporting original data on hormonal therapy for deep endometriosis, written in English, and published in peer-reviewed 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).

HISTOLOGIC 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, references [13–15]). However, as discussed by Gordts et al. in the present issue of this journal (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 histologic characteristic: 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: mucosal, fibrotic, and smooth muscular (18).

In a baboon model, induced deep endometriotic nodules were larger and more invasive when grafting specimens containing 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 whether 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, because interobserver agreement is undetermined but potentially low. 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 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 seems unlikely, although an influence of progestins on fibrosis remodeling during time cannot be excluded, owing to their demonstrated anti-inflammatory properties (33–37).

On the basis of 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: 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 lead to typical bluish nodules formation and initiate 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 coexist, 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, the occurrence of excruciating pain when a nonpainful 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