Estrogen-progestins and progestins for the management of endometriosis

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Endometriosis is characterized by frequent recurrences of symptoms and lesions even after extirpative surgery. Because medical therapies control but do not cure the disease, long periods of pharmacologic management may be needed until pregnancy desire or, sometimes, physiologic menopause. Hormonal drugs suppress ovulation and menstruation and have similar beneficial effects against pain. However, only estrogen-progestins and progestins have safety/tolerability/cost profiles that allow long-term use. These compounds induce atrophy of eutopic and ectopic endometrium, have antiinflammatory and proapoptotic properties, and can be delivered via different modalities, including oral, transdermal, subcutaneous, intramuscular, vaginal, and intrauterine routes. At least two-thirds of symptomatic women are relieved from pain and achieve appreciable improvements in health-related quality of life. Progesterone resistance may cause nonresponse in the remaining one-third. When using estrogen-progestins continuously, individualized, tailored cycling should be explained to improve compliance. All combinations demonstrated a similar effect on dysmenorrhea, independently from progestin type. Estrogen-progestins with the lowest possible estrogen dose should be chosen to combine optimal lesion suppression and thrombotic risk limitation. Progestins should be suggested in women who do not respond or manifest intolerance to estrogen-progestins and in those with dyspareunia and/or deep lesions. Progestins do not increase significantly the thrombotic risk and generally may be used when estrogens are contraindicated. Estrogen-progestins and progestins reduce the incidence of postoperative endometrioma recurrence and show a protective effect against endometriosis-associated epithelial ovarian cancer risk. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)

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Pain has an element of blank;
It cannot recollect
When it began, or if there was
A time when it was not.

It has no future but itself,
Its infinite realms contain
Its past, enlightened to perceive
New periods of pain.

—Emily Dickinson (1)

Endometriosis is a chronic inflammatory disorder associated with pelvic pain symptoms and infertility (2, 3). About 5% of women of reproductive age suffer from the disease (4–6). However, the manifestations of endometriosis are extremely heterogeneous regarding both anatomic abnormalities and symptom severity. Moreover, these two variables are not necessarily positively correlated. This entails difficulties when trying to schematize treatment options, because many subgroup populations exist with very different clinical conditions (7).

Although alternate intriguing hypotheses have been suggested (8, 9), a vast body of evidence supports the notion that endometriosis originates from retrograde menstruation during reproductive years. If this is true, important practical implications follow. Surgery would eliminate lesions present at the moment of direct pelvic visualization, but, because it would not affect the pathogenic mechanisms of endometriosis, it would not "cure" the disease. In this regard, the high incidence of postoperative recurrence of symptoms and lesions (10–13) indirectly supports the hypothesis that, at least in a large proportion of patients, lesions may re-form even after radical excision. Whether this is due to persistent ovulation and (retrograde) menstruation or to persistence of microscopic endometriotic foci not detected at surgery and that would undergo postoperative growth constitutes a debate without a definitive answer.

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If ovulation and menstruation play a major role in endometriosis development, then the therapeutic possibility of controlling the disease and its associated symptoms seems to be readily available: suppression of ovulation and menstruation by means of hormonal treatments. However, pharmacologic therapies have major limitations. They impede conception during use and do not increase the likelihood of conception after their use in case of infertility. Therefore, medical treatment has no role in women seeking pregnancy. Moreover, hormonal compounds used for endometriosis are not cytoreductive. Therefore, lesions can be controlled, but not eliminated, by hormones, and although ectopic endometrial foci generally regress during therapy, they usually resume their metabolic activity at drug discontinuation. As a consequence, symptoms also frequently recur. Therefore, when medications are chosen for endometriosis-associated pain, long treatment periods should be anticipated, even for years or until pregnancy desire ensues. According to the available evidence (14–18) and to the guidelines issued by major gynecologic societies (19–22), there are no major differences in terms of efficacy between various hormonal regimens. As a consequence, the issues of safety, tolerability, and costs are decisive, and in this regard a consensus exists on the indication of estrogen-progestins and progestins as the first-line medical treatment option (19–22).

Unfortunately, despite the above facts, the available evidence seems to leave many important clinical issues still open. In fact, most studies were not designed to adequately answer the questions that matter to patients and their physicians, such as whether progestins are superior to estrogen-progestins in particular clinical conditions, or whether one progestin is more effective, safer, or better tolerated than the existing alternatives (17). Most of the controlled data are derived from industry-supported trials conducted for registration purposes. This frequently implies selection of outcomes that may favor the experimental drug, choice of a scarcely tolerated comparator, short periods of treatments, no follow-up after treatment, and reporting of only part of the findings (16, 23–26). When the results of primary research are of limited usefulness owing to poor design (e.g., uncontrolled studies) or because, though derived from formally correct trials, they may not satisfactorily inform decision making, then secondary research (systematic reviews and meta-analyses) can not always disentangle clinical uncertainties.

Many narrative and systematic reviews that condense data from individual studies on estrogen-progestins and progestins for endometriosis have been published (14–16, 18, 27–40), and the reader may refer to those publications for detailed information. The objective of the present narrative review is to offer, based on the best current evidence, an outline of the types of estrogen-progestins and progestins that can be used for symptomatic endometriosis, a description of the effects of these compounds in patients with the symptoms most frequently associated with endometriosis (i.e., dysmenorrhea and deep dyspareunia) in those with the most severe forms (deep lesions) and in those in whom a preventive intervention appears advisable. The recommendations of major scientific societies regarding the use of estrogen-progestins and progestins for endometriosis are summarized and compared, and a commonsense approach to medical treatment is proposed.

COMPOUND TYPES AND ROUTE OF ADMINISTRATION

Endometriosis-associated chronic pelvic inflammation results in lesion progression, adhesion formation, tissue fibrosis, neurotropism, pain symptom development, and infertility (6, 41). Estradiol has proinflammatory and antiapototic effects on endometrial cells, especially when ectopically located. Conversely, progestins inhibit inflammatory pathways and responses, and induce apoptosis in endometriotic cells (41).

Current monophasic estrogen-progestins used for contraceptive purposes generally contain limited amounts of ethinyl-estradiol, compared with those used in the past, and have a prevalent progestin effect. Moreover, both estrogen-progestins and progestins reduce the amount of uterine bleeding or abolish it, thus potentially greatly limiting the number of erythrocytes regurgitated in the pelvis. This should result in a reduction of the pelvic oxidative stress burden derived by an excess of free peritoneal iron and heme secondary to erythrophagocytosis and lysis by pelvic macrophages (3). In fact, a vast amount of data points to excessive oxidative stress originating from retrograde menstruation as the source of inflammation that triggers macrophage activation, with associated antiapoptotic and neurotropic effects (3, 42).

Notwithstanding the strong rationale supporting the use of estrogen-progestins and progestins in the management of symptomatic endometriosis, between one-fourth and one-third of patients treated with these compounds do not respond to therapy (14–18). Progesterone resistance has been adduced to explain this unexpected outcome (43, 44). In endometriosis, local estrogens are overproduced, and the expression of progesterone receptors may be altered or their activity diminished. This can result in attenuated or dysregulated progesterone response and secondary silencing of progesterone-responsive genes (43, 44).

Despite the above epigenetic mechanism that mediates progesterone resistance, at least two-thirds of women with symptomatic endometriosis still respond to estrogen-progestin and progestin therapy. The availability of such a safe, well tolerated, and relatively inexpensive therapeutic modality enabling long-term disease control would be considered a substantial success for any other human chronic inflammatory disorder. However, safety is particularly important here because patients may need long periods of treatments even during advanced reproductive years. The main issue is the risk of venous and arterial thrombosis associated with estrogen-progestin and progestin use, because several population-based and case-control studies demonstrated an increased risk of both complications.

The number of venous thrombotic events in nonusers of estrogen-progestins is ~4–5 per 10,000 woman-years. The