Vaginally Administered Danazol: An Overlooked Option in the Treatment of Rectovaginal Endometriosis?

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Abstract

Danazol has been used in the treatment of endometriosis and heavy menstrual bleeding for more than 40 years. This medication has both central antigonadotropic actions and direct atrophic effects on endometriotic tissue. Although it demonstrates a high-efficacy profile, the associated side effects have resulted in limited usage. Vaginal administration of the drug may prove favourable specifically in rectovaginal endometriosis. This targeted mode of delivery is associated with a significant reduction in both pain symptoms and nodule size. The relative persistence of these therapeutic benefits is likely related to the direct tissue effects after absorption through the vaginal mucosa. Vaginal administration would also limit systemic propagation of danazol and thus should minimize androgenic side effects. Use of vaginal danazol also improves heavy menstrual bleeding and may even restore fertility in some patients. In this review we provide a critical analysis of the existing literature on the use of vaginal danazol.

Résumé

Le danazol est utilisé dans la prise en charge de l'endométriose et des saignements menstruels abondants depuis plus de 40 ans. Ce médicament exerce tant des effets antigonadotropes centraux que des effets atrophiques directs sur le tissu endométriotique. Bien qu'il présente un profil solide d'efficacité, les effets indésirables qui lui sont associés en ont limité l'utilisation. L'administration de ce médicament par voie vaginale pourrait s'avérer favorable, particulièrement dans les cas d'endométriose rectovaginale. Ce mode d'administration ciblée est associé à une atténuation significative des symptômes de douleur et de la taille des nodules. La persistance relative de ces avantages thérapeutiques est probablement associée aux effets tissulaires directs qui sont constatés à la suite de l'absorption au travers de la muqueuse vaginale. L'administration par voie vaginale permettrait également de limiter la propagation générale du danazol, ce qui devrait en minimiser les effets indésirables androgéniques. L'utilisation de danazol par voie vaginale entraîne également une atténuation des saignements menstruels abondants et pourrait même restaurer la fertilité chez certaines patientes. Dans le cadre de cet article, nous offrons une analyse critique de la littérature existante sur l'utilisation du danazol par voie vaginale.

Key Words: Rectovaginal endometriosis, danazol, vaginal administration, pelvic pain

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INTRODUCTION

Several medical treatments are available for the management of endometriosis. Oral danazol has been used to treat endometriosis since the 1970s.[1] Danazol is a synthetic isoxazole derivative of 17α-ethinyltestosterone with mild androgenic properties. When orally administered, it inhibits the midcycle surge of luteinizing hormone and induces a state of chronic anovulation.[2] The inhibition of ovarian steroidogenesis, the mixed progestational/antiprogestational activity, and the androgenic properties of the medication render endometriotic tissues inactive and atrophic, and they create the ideal hormonal milieu to prevent endometriosis progression. For most patients this results in a large reduction in

1. endometriosis-related pain (dysmenorrhea, pelvic pain, dyspareunia, dyschezia);
2. lesion volume and American Society for Reproductive Medicine score evaluated by laparoscopy; and
3. serum CA 125.[3,4]

Systematic reviews have found no significant differences between danazol and GnRH agonists in reducing either the severity of pain or the volume of the lesions.[5,6] However, these two forms of treatment have very different tolerability profiles. GnRH agonists are often associated with menopausal symptoms, including loss of bone mineral density. Danazol has androgenic side effects that

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may include alteration of the blood lipid profile, but it may also have potential benefits on bone mineral density.[7] Low-dose danazol therapy (200 mg daily) has shown positive results in mild-to-moderate disease.[8] However, higher oral doses of danazol (600 to 800 mg daily) may be required in more severely affected patients, and the associated virilizing side effects have resulted in this treatment option being largely ignored.

The therapeutic effects of danazol have long been attributed to its inhibitory effects on the hypothalamo–pituitary–ovarian axis. However, it has become increasingly clear that the therapeutic benefits may also derive from a direct effect on endometriotic tissues. An increased expression of aromatase in endometriotic nodules is a feature of endometriosis. This overexpression leads to a hyperestrogenic environment within the implant and may contribute to disease progression and to endometriosis-related infertility;[9] hence there is interest in developing treatment options using aromatase inhibitors.[10] Interestingly, in vitro studies have shown that danazol can inhibit aromatase activity completely in endometriosis tissue cultures.[11] High pro-inflammatory activity and an increased expression of angiogenic factors are two other potential therapeutic targets. These pro-inflammatory and angiogenic factors have been shown to be significantly reduced within endometriotic implants following danazol treatment.[12] Finally, although oral danazol induces elevation of free androgen levels, it can also directly induce androgen-dependent DNA transcription and apoptosis in exposed tissues,[2,13] which may be beneficial in cases of endometriotic implants.

The idea of danazol having a direct effect on endometriotic tissue is also supported by data showing that danazol may produce further improvement in disease after treatment with a GnRH agonist or in combination with a levonorgestrel-releasing intrauterine device.[14,15] This suggests that the two mechanisms of action of danazol (inhibition of the HPO axis and direct atrophic effects on endometriotic implants) may be synergistic.[16] In fact, there is a high recurrence of lesions and symptoms with inhibition of the HPO axis, whereas the direct effects of danazol on endometriotic implants may provide more persistent reduction in lesion volume and symptom relief.[17]

ABBREVIATIONS

DZL-IUD	danazol-loaded intrauterine device
HPO	hypothalamo–pituitary–ovarian
LNG-IUD	levonorgestrel-releasing intrauterine device

In light of this information, it is logical to consider re-integrating danazol into the medical treatment of endometriosis. Recent interest has focused on vaginal administration of the drug, which allows for direct targeting of lesions in the proximity of the vagina. Vaginal administration allows use of doses that are markedly lower than those required for oral administration, and results in higher drug concentrations in the surrounding area. In turn, it also results in significantly lower circulating levels of the drug.[13,17] Vaginal administration of danazol is possible using the commercially available capsules intended for oral intake. Vaginal danazol suppositories can also be made by compounding pharmacies. Local delivery of danazol should therefore minimize the side effects frequently associated with oral intake. Of note, vaginal administration does not inhibit ovulation,[13,17] which, in addition to confirming the low systemic propagation, suggests that it could have synergistic effects when combined with treatments that provide HPO inhibition. In this article we critically review the evidence regarding use of vaginally administered danazol in the treatment of rectovaginal endometriosis.

METHODS

We searched for relevant published articles in PubMed using the terms "rectovaginal endometriosis" and "vaginal danazol." We also identified additional published material found in the reference section of these articles. Overall, we identified 12 studies involving 334 patients treated with focused pelvic delivery of danazol for various indications.[13,14,17–26] The findings in these studies are summarized in the Table and reviewed below.

RESULTS

Efficacy

Deeply infiltrating endometriosis

An uncontrolled study by Razzi et al. showed that vaginal administration of danazol 200 mg daily for one year in women with laparoscopy-proven deep infiltrating endometriosis involving the rectovaginal septum or uterosacral ligaments (American Society for Reproductive Medicine stages III or IV) resulted in complete disappearance of moderate-to-severe pelvic pain in all 21 participants.[21] Dysmenorrhea and dyspareunia disappeared in 19 out of the 21 women and was greatly improved in the remainder, despite all previous medical treatment having been unsuccessful. These authors observed improvement in symptoms as early as the third month of treatment. Interestingly, the treatment was administered as monotherapy, and all patients continued