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

to have regular menstrual cycles throughout the study period, with no significant systemic side effects. In this study, vaginal danazol resulted in a reduction in the volume of rectovaginal lesions from 3.1 (± 1.2) mL at the beginning of the study to 1.9 (± 1.2) mL after six months of treatment ($P < 0.01$). These results are consistent with those of Bhattacharya et al., who reported an 86% improvement in reported pain in 21 patients with severe endometriosis treated with vaginal danazol 200 mg daily for six months.[20]

Ferrero et al. investigated the effects of treatment with vaginal danazol (100 mg daily for six months) in 15 women with rectovaginal endometriosis and pain persisting after the insertion of an LNG-IUD.[14] The investigators evaluated the intensity of pain as well as the volume of the rectovaginal endometriotic nodules. Fourteen women completed the study, and they showed a significant improvement in endometriosis-associated pain (on a visual analogue scale) as early as the third month of treatment. At the six-month follow-up, there were average total improvements in dysmenorrhea, non-menstrual pelvic pain, deep dyspareunia, and dyschezia of 63%, 62%, 43%, and 51%, respectively. The multidimensional rating scale also revealed a quasi-disappearance of previously severely impairing symptoms. These investigators also found a modest but significant reduction in the size of rectovaginal nodules (2.3 ± 0.9 mL to 1.7 ± 0.8 mL; $P < 0.001$). The treatment was well tolerated with very few adverse effects. Patient satisfaction reached 80%, and the average consumption of naproxen tablets reduced by 60% in these previously refractory patients. This study suggests that even at small doses (100 mg daily), the addition of vaginally administered danazol to the use of an LNG-IUD could provide significant symptom relief in women with rectovaginal endometriosis.

Two studies assessed the efficacy of a danazol-loaded vaginal ring in women with endometriosis.[13,17] In the first, 35 women with infertility for a mean of six years were fitted with a danazol ring releasing 95 mg per day.[17] After a mean treatment duration of 70.2 ± 30.9 days, endometriosis was undetectable by bimanual pelvic examination and transvaginal ultrasound in 12 women, and another 12 women had a significant reduction in the size of lesions. Thirteen women conceived while using the vaginal danazol ring. Among those who did become pregnant and stopped treatment, eight observed a reduction in lesion size while the remaining five conceived before any reduction in size was detectable. There was a similar effect on dysmenorrhea: 21 women had a complete loss of dysmenorrhea after an average of 73.6 ± 43.2 days, six had persistent dysmenorrhea, and a further eight conceived before there was a complete loss of dysmenorrhea. In the second study, Igarashi et al. investigated the effect of a vaginal ring containing 1500 mg of danazol in 42 infertile women with suspected but untreated deeply infiltrating endometriosis and 14 women with endometriotic ovarian cysts not adhering to the cul-de-sac.[13] They found levels of safety and efficacy that were similar to previous studies. Danazol remained undetectable in the serum following vaginal administration. However, these authors reported variable effectiveness depending on the location of the lesion. In women with deeply infiltrating endometriosis, transvaginal ultrasound showed the endometriotic mass disappearing in 36 women and reducing in size in the remaining six. However, the size of the mass was reduced in only three of 14 women with ovarian endometriotic cysts and was unchanged in the remainder. Dysmenorrhea disappeared in 32 women with deeply infiltrating endometriosis and was significantly reduced in another nine, leaving only one of 42 women without significant improvement in dysmenorrhea. Importantly, these improvements, together with reduced nodularity and tenderness in the cul-de-sac, were observed within three months of beginning treatment. In contrast, pain disappeared in only 5 of 10 women with ovarian cysts and dysmenorrhea; it was reduced in three, and unchanged in the remaining two. This differing effectiveness between the two types of lesions is most likely due to the tissue distribution of danazol after transvaginal absorption rather than to inherent differences between the pathophysiology of ovarian endometriomas and deeply infiltrating nodules. Indeed, Igarashi et al. reported that direct absorption of danazol into the vaginal mucosa and subsequent transportation into the adjacent cul de sac nodules results in these tissues being exposed to high danazol concentrations,[13] although increased levels have also been noted in ovarian lesions after vaginal absorption.[23] This idea is also supported by the findings of Takeda and Adachi, who reported complete disappearance of pain symptoms in 18 women with ovarian endometriomas that were punctured, flushed, and injected with a solution containing 50 mg of danazol.[24]

Two studies have investigated the effects of an intrauterine device loaded with 300 to 400 mg of danazol for the treatment of adenomyosis or endometriosis. In the study reported by Cobellis et al., the DZL-IUD was inserted in 18 women with recurrent pain six months after laparoscopic surgery for ovarian cysts (n = 12) or unexplained fertility (n = 6), during which endometriosis was histologically confirmed.[25] Average scores for dysmenorrhea, dyspareunia, and pelvic pain were all significantly reduced within the first month of treatment and were reduced by

Side effects reported in available studies

Study	Indication	Treatment	N	Side effects
Mais et al.[18]	Abnormal uterine bleeding	200 mg vaginal danazol daily	20	Vaginal dryness (n = 1) Weight gain (n = 3) Spotting (n = 2) Bloating (n = 1)
Luisi et al.[19]	Menorrhagia	200 mg vaginal danazol daily for 6 months	55	Vaginal irritation (n = 2)
Bhattacharya et al.[20]	Endometriosis	200 mg vaginal danazol daily for 6 months	19	none
Ferrero et al.[14]	Endometriosis	100 mg vaginal danazol daily for 6 months	15	Seborrhea, oily skin, acne (n = 4) Headache (n = 3) Weight gain (n = 2) Vaginal irritation (n = 2)
Razzi et al.[21]	Endometriosis	200 mg vaginal danazol daily for 12 months	21	Vaginal irritation (n = 4)
Igarashi et al.[13]	Endometriosis	1500 mg vaginal danazol ring monthly	56	Colpitis (n = ?)
Igarashi et al.[22]	Adenomyosis	400 mg danazol IUD	14	Spotting (n = ?) IUD expulsion (n = 2)
Mizutani et al.[23]	Pre-hysterectomy	100 mg vaginal danazol daily for 2 to 6 months	8	Acne (n = 1)
Takeda and Adachi[24]	Endometriosis	Endometrioma cyst puncture with 50 mg danazol solution injection	17	None
Igarashi[17]	Endometriosis/ adenomyosis	2 to 3.5 g danazol vaginal ring releasing 95 mg per day or 175 mg danazol IUD for 4 months	39	Weight gain (n = 1)
Okamura et al.[26]	Endometriosis	Danazol suppository, 3 months to 1+ year, dose N/A	52	None
Cobellis et al.[25]	Endometriosis	300 mg to 400 mg danazol IUD for 6 months	18	Spotting (n = 2) IUD expulsion (n = 1)

52%, 45%, and 53%, respectively, six months after DZL-IUD insertion. In the second study, Igarashi et al. reported positive clinical results in 14 women with adenomyosis.[22] These authors described complete remission of dysmenorrhea in nine women, a significant reduction in four, and no improvement in one. Myometrial thickness was reduced in nine of 14 patients. Among nine women with elevated serum CA 125, the treatment resulted in a decrease in the level within three months for seven. These improvements were accompanied by complete remission of hypermenorrhea in 12 of 14 women.

Bleeding

Endometriosis is often associated with heavy menstrual bleeding,[27] and oral danazol remains one of the most effective treatments for such heavy bleeding.[28] Two studies have investigated the efficacy of vaginal danazol in the treatment of menorrhagia.[18,19] In the first, 20 women with endometrial polyps or hyperplasia all had a reduction in the severity of blood loss after three months of vaginal danazol and had improved hemoglobin concentration, red blood cell count, and hematocrit.[18] Endometrial hyperplasia in 13 women regressed in all cases, and none of the women with endometrial polyps showed sonographic signs of recurrence after polypectomy. In the second study, 55 women were treated with vaginal danazol (200 mg daily), and had a greater than 60% reduction in vaginal bleeding after six months; the reported satisfaction rate was 96%.[19]

Fertility

Resolution of infertility is an important goal of endometriosis management.[29] Unlike the higher-dose oral administration, vaginally administered danazol has consistently been shown to permit regular ovulation, as evidenced by biphasic basal body temperature patterns and luteinizing hormone surges observed in multiple studies.[13,17,23] Few studies have investigated the effect of vaginal danazol treatment on fertility in women with endometriosis-related infertility, but some impressive results have been noted. Igarashi reported 13 pregnancies in 35 women with a history of infertility averaging 6.3 years during the course of their one-year study.[17] All the babies appeared normal and there were no cases of fetal virilization. The same group found similar results when 17 pregnancies occurred in a group of 31 infertile women treated with vaginal danazol.[13] All the newborns were reported to appear normal, including genital development in the 11 females. Although there is insufficient evidence to recommend using danazol for the

treatment of endometriosis-related infertility, these results suggest that vaginally administered danazol could potentially re-establish fertility in some women with deeply infiltrating endometriosis and a prolonged history of infertility.

Oral danazol administration during pregnancy has been linked to masculinization of the female fetus. This pseudohermaphroditism is characterized by clitoromegaly, labial fusion, and a urogenital sinus opening at the base of the clitoris.[30] A retrospective study reported a 24.5% rate of fetal virilization associated with oral danazol.[31] Interestingly, this teratogenic effect was frequent (28%) in fetuses exposed to an 800 mg daily dose; it was also observed, although less frequently (18%), in fetuses exposed to 200 mg daily.[32] Although it would be possible for danazol to be absorbed vaginally and cause virilization of a female fetus, it is surprising to note that there were no such reports in the studies investigating vaginal administration. However, it has been argued that these effects may be averted when danazol use is discontinued before eight completed weeks of gestation,[13] when genital differentiation occurs; this hypothesis has been corroborated in studies examining oral administration of danazol.[32] Despite what appear to be beneficial effects of vaginal danazol on fertility at low doses, and possibly even lower risks with this mode of administration, its use remains contraindicated during pregnancy. Therefore, in order to minimize these risks, it is important to provide adequate contraception counselling and to implement a protocol for early detection of pregnancy in women who wish to conceive while on treatment. For women not intending to conceive, we recommend either use of a barrier method of contraception or use of vaginal danazol as an adjuvant to other treatments with contraceptive actions (oral contraception, LNG-IUD, progestin, or GnRH agonist therapy). In addition to limiting risks to the fetus, this strategy offers the added benefit of potential therapeutic synergies.

Tolerability

We identified 334 patients treated with vaginal or intrauterine danazol for various indications in 12 reported studies.[13,14,17–26] All of these studies report few or no androgenic side effects such as weight gain, seborrhea or acne (Table). However, the specific incidence of side effects is not clearly reported for most of these studies. This seems to indicate that vaginally administered danazol has limited androgenic activity. We did not identify any objective or validated evaluation of these adverse events following vaginal danazol, and subjects most often reported these side effects on the strength of subjective impressions. Nonetheless, the incidence of such adverse events appears to be comparable to what is normally observed with treatment with progestins or oral contraceptives.[33] In fact, three Japanese studies have shown that danazol was undetectable in serum when released locally in the uterine cavity or vaginally.[13,17,22] Another study found that administration of vaginal danazol 100 mg daily results in serum levels that are less than 5% of what is observed with oral danazol 400 mg daily.[23] It is therefore not surprising to find that this treatment seems to have been very well tolerated among the 334 patients we identified. The side effect reported most frequently in these studies was vaginal irritation. In addition to vaginal discomfort, it appears that the most important factor limiting patient compliance is the psychological barrier of vaginal self-administration.[18]

CONCLUSION

Oral danazol has been widely used orally for the treatment of endometriosis and its safety and tolerability profiles in non-pregnant women are well established. The available evidence shows that vaginally administered danazol is very effective in the treatment of rectovaginal endometriosis. Doses of 100 to 200 mg daily lead to symptom relief, reduction in heavy menstrual bleeding, and reduction in the volume of lesions, as well as possible improvement in fertility. Such treatment seems to be very well tolerated. However, its use is contraindicated in pregnancy, even in smaller doses. Therefore, adequate contraception counselling and/or implementation of a protocol for early detection of pregnancy and discussion of teratogenic risks should be provided. There have been few large, well-designed, randomized trials investigating the safety and efficacy of vaginally administered danazol. Nonetheless, we believe that the dramatically positive results in several studies by different research groups provide convincing evidence to support using and investigating this alternative treatment in patients refractory to, or intolerant of, existing treatments. It can be offered as an adjuvant to conventional medical treatments, avoiding contraception issues that may arise with this treatment. It can also be an alternative to performing difficult surgery in patients with deep infiltrating endometriosis of the rectovaginal septum.

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