"PER VAGINAM"

TOPYCAL USE OF HORMONAL DRUGS IN WOMEN WITH SYMPTOMATIC DEEP ENDOMETRIOSIS: A NARRATIVE LITERATURE REVIEW

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ABSTRACT

Purpose: We aim to provide a comprehensive overview of the role of the vagina as a route for drug delivery and absorption, with a particular focus on the use of vaginal hormonal compounds for the treatment of deep infiltrating symptomatic endometriosis.

Methods: A MEDLINE search through PubMed was performed to identify all published studies in English language on vaginal hormonal treatments for symptomatic endometriosis.

Results: Main advantages of the vaginal route include avoidance of the hepatic-first pass metabolic effect, the possibility of using lower therapeutic dosages, and the reduction of side effects compared with the oral administration. Studies on endometriosis treatment mainly focused on the use of vaginal danazol (*n*=6) and the contraceptive vaginal ring (*n*=2). One pilot study evaluated the efficacy of vaginal anastrozole in women with rectovaginal endometriosis. Most investigations evaluated the vaginal use of hormonal agents in women with deep infiltrating endometriosis/rectovaginal endometriosis. Overall, a substantial amelioration of pelvic pain symptoms associated with endometriosis was observed, particularly of dysmenorrhea. A significant reduction in rectovaginal endometriotic nodule dimensions measured at ultrasound examination was detected by some but not all authors.

Conclusions: The vaginal route represents a scarcely explored modality for drug administration. High local hormonal concentrations might achieve a greater effect on endometriotic lesions compared with alternative routes. Future studies should focus on the use of the vagina for delivering target therapies particularly in patients with deeply infiltrating rectovaginal lesions.

KEYWORDS: Intravaginal administration; vaginal ring; endometriosis; aromatase inhibitors; danazol; contraceptive vaginal ring

INTRODUCTION

In the last decades, technological innovations in drug delivery have led to a wider range of sites for drug administration. Historically, the oral route represents the most frequently adopted one. However, another scarcely explored way of drug delivery is the vaginal route; although a large body of evidence proves the ability of this organ to absorb a wide variety of medication [1].

The first published reports of drugs administered intravaginally are dated 1918, when Macht reported the absorption of morphine, potassium iodide and atropine [2]. Since then the vaginal route has been adopted for numerous, chemically different, compounds, such as misoprostol, bromocriptine, indomethacin, antimicrobials, and various steroidal hormones including estrogens, progestogens and androgens [1, 3].

An important field of application for intravaginal therapies could be endometriosis; in fact, in the past years, some authors have evaluated the efficacy of various vaginal hormonal compounds for the treatment of rectovaginal endometriosis with promising results [4-6].

Endometriosis is an estrogen-dependent chronic inflammatory disorder that requires a life-long management plan. Some authors suggest that women with endometriosis should no longer be evaluated as a single and unique population [4]. In this optic, each woman should have a tailored approach based on her main disabling symptom and the type of lesion [4]. In particular, deep infiltrating endometriosis (DIE) represents the truly severe endometriotic disease [7]. DIE is a form of endometriosis characteristically related to marked proliferation of smooth muscle cells and fibrosis [8]. Deep lesions could infiltrate the muscular layer of different hollow organs, such as vagina, bowel, and bladder. Patients with DIE are usually the ones complaining most for pain and with the greatest alteration on the quality of life (QoL).

Long-term adherence to treatment is pivotal to ensure an effective clinical management [4,9]. The rationale of the pharmacological therapy for symptomatic endometriosis is the

establishment of a hypo-estrogenic milieu, generally achievable through the use of hormonal therapies such as, for instance, estrogen-progestins and progestins [4]. These compounds could be administered orally, vaginally, intra-uterine, subcutaneously or intramuscularly [4].

In this narrative review, we aimed to provide a broad overview on the role of the vagina as a route for drug delivery and absorption, with a specific focus on the use of vaginal hormonal compounds for the treatment of deep infiltrating symptomatic endometriosis.

MATERIALS AND METHODS

For this review, the best quality evidence was selected with preference given to the most recent and definitive original articles and reviews. Information was identified by searches of Pubmed/MEDLINE and references from relevant articles, using combinations of MESH terms "intravaginal administration", "pharmacodynamics", "endometriosis", "deep infiltrating endometriosis", "vaginal danazol", "contraceptive vaginal ring", "vaginal ring", and "aromatase inhibitors". The search was limited to peer-reviewed, full-text articles in the English language. For most issues, papers published between March 1990 and December 2016 were considered. No attempt was made to find unpublished studies. Since only published data were considered, the current research project was exempt from Institutional Review Board approval.

RESULTS

- *Role of the vagina as a route for drug delivery and absorption*

The vagina is a collapsed organ, in which the surface absorption area is augmented by the presence of numerous rugae and could reach a maximum of 95 cm^2 in standard conditions [10].

One of the peculiar aspects of the vagina is represented by its vascular supply that comprises a complex network of veins. In particular, the different portions of the vagina are drained by various venous systems influencing drug absorption depending on the level at which the compound has

been introduced [10]. The uterine and ovarian plexus are linked to the venous return of the superior part of the vagina, and they drain directly into the internal iliac vein, by-passing the hepatic portal system. In particular, a pharmacological compound administered in the superior part of the vagina has a specific affinity for the uterine tissues, especially for the endometrium, due to the extensive vascular connections between these two organs. This phenomenon, given its similarity with the hepatic-first pass metabolism secondary to the oral administration, has been termed "uterine first-pass effect" [11]. Instead, the inferior part of the vagina is connected to the hemorrhoidal and pudenda internal plexus, which leads to the portal system and is subject to the metabolizing action of the liver [3].

In general, drug absorption is a passive process regulated by different factors such as molecular weight, liposolubility, constancy of diffusion, time, and surface of diffusion [10]. In addition, vaginal drug absorption is also influenced by some physiological factors, including age, pregnancy, hormone status, and pH changes. The modifications of this latter element are secondary to numerous variables such as bacterial colonization, semen, menstruation, and estrogen status. Vaginal absorption of a drug could be impacted by the presence of a larger volume of vaginal fluids that can favor a more rapid and efficient dissolution of compounds characterized by low hydrosolubility but, at the same time, can raise the possibilities of a drug to be ejected due to gravity. Moreover, the presence of cervical mucus with high viscosity could represent an obstacle to drug absorption [12].

Another factor to keep in mind when prescribing intravaginal therapies is the age of the patient; in fact, in post-menopausal women, the thickness of the vaginal walls is reduced, and the absorption of steroids is higher than in fertile women [13]. In addition, changes in hormone levels, especially estrogen, during the menstrual cycle, cause alterations in the thickness of the epithelial cell layer, width of intercellular channels, pH, and secretions, with subsequent variations in vaginal drug absorption [10,14]. Estrogenization of the vaginal mucosa improves absorption of hormones

119 through the vaginal wall [10,15]. Finally, the formulation and the carrier also influence the
120 absorption rate. For example, creams' absorption is higher compared to rings and tablets [10].

121 One of the most studied vaginal pharmacological compounds is represented by the vaginal
122 contraceptive ring (CVR) (ethinyl estradiol (EE) 15 μg + etonogestrel (ENG) 120 μg). Numerous
123 studies have compared the pharmacokinetics of the steroids released by the CVR with those
124 discharged by various combined oral contraceptive (COC) [16-18]. Timmer and Mulders [17]
125 performed a randomized crossover study on 16 healthy women demonstrating that maximal serum
126 concentration (C_{max}) of ENG and EE obtained with the vaginal contraceptive ring were 40% and
127 30% inferior of those gained with a COC containing 150 μg of desogestrel (DSG) and 30 μg of EE.
128 In the same study group, absolute bioavailability was comparable for EE but higher for ENG with
129 the CVR compared with the COC (103% vs 79%) [17].

130 A randomized open-label study [18], performed on 24 women, compared different serum EE
131 levels subsequent to the use of the CVR, of the transdermal patch or of a COC (EE 30 μg +
132 levonorgestrel (LNG) 150 μg). C_{max} of EE for the ring, the patch, and the COC were 37.1 pg/ml,
133 105 pg/ml, and 168 pg/ml, respectively. In addition, analysis of area under the EE concentration-
134 versus-time curve (AUC) during 21 days of treatment showed that exposure to EE in the CVR
135 group was 3.4 times lower than in the patch group and 2.1 times lower than in the COC group.
136 These findings suggest that suppression of ovulation with the CVR is comparable to that reached
137 with COCs but with lower circulating levels of EE.

138 Moreover, Roumen *et al.* [19] compared the uterine concentrations of EE and ENG after use
139 of CVR and a COC (EE 20 μg + DSG 150 μg). In both groups, concentration of ENG and EE were
140 comparable in uterine samples of the myometrium and cervical region. However, unexpectedly, in
141 women treated with the CVR concentration of both ENG and EE were significantly lower in tissue
142 samples from the endometrium. Finally, Dogterom *et al.* [20] performed a pharmacokinetic study in
143 order to assess the potential interaction of a concomitant treatment with oral antibiotics (amoxicillin

and doxycycline). No differences in ENG or EE serum concentrations were identified between women using vaginal contraceptive ring alone versus those receiving the ring plus either of the antibiotics. Conversely, co-administration of vaginal anti-mycotic resulted in a slight rise in systemic exposure of both ENG and EE, in particular with suppositories antifungal formulations [21].

Pharmacokinetic studies on progestogen only CVR demonstrated a good correlation between *in vitro* and *in vivo* release rates of LNG [22]. Serum levels reached the peak concentration 2 hours after the insertion of the ring, after which levels diminished at a rate of 0.2%/day during 90 days of continuous use. Other pharmacokinetic studies on various progestogen-releasing vaginal ring have been conducted. As an example, Landgren *et al*. [23, 24] evaluated two types of vaginal ring releasing norethisterone (NET) at a rate of 50 μg/daily and 200 μg /daily. The ring containing the lower dose of NET did not inhibit ovulation with consequent high pregnancy rate, whereas those releasing the higher dose of NET displayed a strong ovulation-inhibiting effect but showed a high frequency of unscheduled bleeding.

- *Vaginal therapies for the treatment of symptomatic deep infiltrating endometriosis*

The intravaginal route has been underused for the treatment of endometriosis (Table 1). The majority of the evidence regarding the vaginal route for the management of endometriosis are derived from the use of danazol.

Danazol is a synthetic derivative of 17α-ethyniltestosterone with mild androgenic activity. Oral danazol has been widely adopted in the treatment of endometriosis at the daily dosage of 400-800 mg, resulting in high serum concentration of the compound, which may elicit androgenic adverse effects, such as acne, hirsutism, weight gain, deepening of voice pitch, and alteration of the blood lipid profile [32,33]. Oral danazol acts on endometriotic lesions at two levels: firstly, danazol shows inhibitory effect on the hypothalamic-pituitary-ovarian axis; secondly, danazol can work

directly on endometriotic tissues through the inhibition of aromatase activity, reducing inflammation and the production of angiogenic factors, making endometriotic lesions inactive and atrophic [34]. However, danazol used orally for an extended period is not advisable, due to the important androgenic side effects, and for this reason different study groups have assessed its vaginal use (Table 1).

First, Igarashi *et al.* [25,26] evaluated the efficacy of a danazol-loaded vaginal ring in women with endometriosis. In the first study [25], the vaginal ring (releasing 95 mg of danazol per day) was used in 35 infertile women with endometriosis. Authors found a substantial amelioration in both dysmenorrhea and a decrease in the extent of pelvic endometriosis. In addition, as vaginal danazol did not inhibit ovulation, 13 patients conceived while using the vaginal ring. This point is particular concerning due to the potential teratogenic effects of this drug [35]. In fact, as reported in a previous retrospective review [35] on 129 women exposed to danazol during pregnancy, only 37 delivered a normal male and 24 a non-virilized female, whereas, 23 women gave birth to a virilized female. All the abnormalities have been reported in those patients who continued danazol administration after the 8^{th} week of gestation. In this view, danazol should remain contraindicated in pregnancy and a careful contraceptive advice to patients under danazol therapy should be given.

In the second study [26], danazol was administered using a vaginal ring drug delivery system containing 1500 mg of danazol. Igarashi *et al.* [26] enrolled 56 infertile women with endometriosis, 42 with DIE, and 14 with ovarian endometriomas. All the enrolled patients showed normal menstruation pattern and basal body temperature curves; in addition, 39 of them conceived during the study period, and none of the female infants born presented signs of masculinization. Serum levels of danazol remained undetectable. The effectiveness on pain symptoms differed in the two groups, in fact, dysmenorrhea disappeared in 76% (32/42) of the patients with DIE, but only in 50% (7/14) in the group with ovarian endometriomas. In addition, also at transvaginal ultrasound the size of the ovarian cysts, conversely to endometriotic deep nodules, remained unchanged in

almost 80% of cases (11/14). Moreover, one woman out of four (2/8) conceived in the ovarian endometriotic cyst group, compared to one out of two (17/31) in the DIE group. A plausible explanation for this different outcome in the two study groups could be attributed to the proximity of deep endometriotic lesions to the site of action of the vaginal ring. In this way, the drug released from the vaginal ring should ideally reach higher concentrations in the vaginal endometriotic lesion.

Razzi *et al*. [27] treated 21 symptomatic patients with DIE with low dose vaginal danazol (200 mg/d) for 12 months. Dysmenorrhea and dyspareunia were relieved in 19 out of the 21 women and were improved in the remainders. Relief from dyschezia was also observed. At ultrasound examination, a reduction of the volume of the rectovaginal nodule was demonstrated (from 3.1±1.2 mL to 1.2±0.8 mL). Moreover, the vaginal use did not alter metabolic or thrombophilic parameters, and the main reported side effect was a vaginal irritation during the first month of treatment in only four cases. These promising results were similar to those obtained by Bhattacharya *et al.* [29], who adopted in 21 patients with severe endometriosis (stage IV), for a total treatment period of six months, the same vaginal dosage of danazol.

In 2011, Ferrero *et al*. [30], evaluated the effectiveness of therapy with very low-dose of vaginal danazol (100 mg/d) in patients with rectovaginal endometriosis and persistent pain symptoms refractory to the use of a levonorgestrel-releasing intrauterine device (LNG-IUD). 15 women were enrolled for the study, and the daily administration of danazol lasted six months. At the end of the study period, the satisfaction rate associated with the treatment was 80%. In addition, the volume of the rectovaginal plaque decreased during treatment (from 2.3±0.9 cm^3 to 1.7±0.8 cm^3). Side effects were minimal and well-tolerated, the most frequently reported was acne (n = 4).

The above-mentioned studies confirm the potential beneficial role of vaginal danazol in the treatment of women with endometriosis, in particular in those with deep infiltrating and vaginal localizations. Contrarily to oral administration, vaginally administered danazol showed limited androgenic side effects, and its serum levels remained low or undetectable. These results are

consistent with those of Mizutani *et al.* [36], who demonstrated that danazol concentration in the ovary and uterus after daily vaginal administration of 100 mg of danazol were analogous to those reached after oral administration of 400 mg, and, at the same time, serum level after daily intravaginal danazol use was less than 1/20 of that after oral administration.

Another vaginally administered drug that has been evaluated for the treatment of endometriosis is an estrogen-progestogen contraceptive ring [5,31] (Table 1). In 2010, Vercellini *et al*. [5], performed a patient preference trial on 207 women with recurrent moderate or severe pelvic pain after conservative surgery for symptomatic endometriosis, comparing the CVR (EE 15 μg + ENG 120 μg) and a transdermal patch (EE 20 μg + norelgestromin 150 μg). A total of 123 (59%) women preferred the CVR, whereas 84 (41%) chose the patch. Both treatments were administered continuously for 12 months. Fifty-nine (28%) patients with rectovaginal endometriosis were included in the study group. The rate of withdrawal was high in both group, 36% in the CVR group and 61% in the transdermal patch group. Bleeding control was suboptimal with both delivery systems, in fact, by the end of the study period 46% of the patients who chose the ring and 42% of those who preferred the patch changed from continuous to cyclic use. Pelvic pain symptoms were reduced in both groups. In particular, the CVR performed better than the patch regarding dysmenorrhea relief in patients with rectovaginal endometriotic lesions. A considerable amelioration of deep dyspareunia was also obtained. No significant major adverse event was recorded. At the end of study, 71% of the patients who have chosen the CVR declared to be satisfied with the treatment, whereas the percentage of satisfied women dropped to 48% in the patch group. In the sub-group of women with rectovaginal lesions, the percentage of satisfied women was higher in both groups: 79% in the CVR group and 57% in patients treated with the patch.

A second patient preference trial [31] compared the CVR, administered cyclically, to the desogestrel-only contraceptive pill (75 μg/d) for the treatment of symptomatic patients with rectovaginal endometriosis. The duration of the treatment was 12 months; 60 women chose the

243 progestin-only pill and 83 the CVR. At the end of the study, the rate of satisfied women was higher
244 in the group treated with desogestrel-only pill (61.7% vs. 36.1%). The discontinuation rate and the
245 reduction in volume of rectovaginal nodules were similar in the two study groups. Gastrointestinal
246 symptoms, chronic pelvic pain and deep dyspareunia were improved more in the progestin-only pill
247 than in CVR group.

248 The potential beneficial role of vaginally administered aromatase inhibitors has been
249 evaluated in a pilot study [6] on ten symptomatic patients with histologically confirmed
250 rectovaginal endometriosis. Women received 0.25 mg/d of vaginal anastrozole for 6 months. The
251 preliminary results were encouraging and patients reported an improvement of dysmenorrhea and
252 QoL. However, chronic pelvic pain, dyspareunia as well as rectovaginal lesion size remained
253 unchanged. The dual energy absorptiometry (DEXA) scans, performed before the initiation of the
254 study and within one month after the end of the treatment, show no change in bone mineral density.
255 Serum hormonal levels were repeatedly measured during the study period and within one month
256 after the completion of the treatment. No statistically significant differences were observed in
257 values for gonadotropins FSH and LH or for P and E_2. In women with endometriosis the inhibition
258 of the hypothalamic-pituitary-ovarian axis is of fundamental importance. Therefore, as suggested by
259 Hefler *et al*. [6], a combined therapy with a hormonal drug capable of inhibit ovulation should be
260 proposed.

261 Recently, a vaginal ring containing a combination of anastrozole (ATZ) and the progestin
262 LNG has been developed for the treatment of endometriosis and tested in healthy cycling female
263 cynomolgus monkeys [37]. The intravaginal system was effective in causing a reduction of
264 systemic E_2 by about 30% in the proliferative phase without stimulating the development of ovarian
265 cysts or the increase of FSH. In fact, one of the major limitation of aromatase inhibitors use in
266 premenopausal women is the possible stimulation of follicular development, secondary to the rising
267 of gonadotropin levels, which can lead to the formation of ovarian cysts [38]. To prevent this

phenomenon, a combination of aromatase inhibitors and a combined oral contraceptive (OC) or progestin could be advisable.

A multicenter Phase I, randomized controlled trial [39], was conducted to evaluate the pharmacokinetics, pharmacodynamics, safety and tolerability of intravaginal ring containing three different dose combinations of AZT and LNG (Treatment A: 1 ring, 500 μg/d ATZ and 20 μg/d LNG; Treatment B: 1 ring, 1000 μg/d ATZ and 30 μg/d LNG; Treatment C: 2 ring, 1500 μg/d ATZ and 40 μg/d LNG. The trial was performed on 60 healthy premenopausal women and the treatment period consisted of 56 days (two cycles of 28 days without ring-free interval). During the study period the mean size of the largest follicle-like structures was higher in all three treatment arms than during the pre-treatment cycle; however, changes in the mean size of the cysts were comparable to those described for low-dose progestin-only OC and generally resolved during the 2-month treatment period. Serum E2 levels were below 20 pg/ml in both cycles only in the mid- and high-dose groups. All the three combinations of AZT and LNG were well tolerated. To achieve a LNG systemic exposure similar to that obtained after daily oral administration, the optimal intravaginal ring LNG delivery rate was 40 pg/ml. The doses selected for AZT to be investigated in Phase 2 studies on patients with endometriosis were 300, 600 and 1050 μg/d.

DISCUSSION

The main potential advantages of the vaginal administration of therapeutics are the reduction of daily dosages and the continuity of drug release. Moreover, the possibility of extending the interval between doses represents a favorable option for the patient that can enhance her adherence to the drug regimen [3].

Another advantage of the vaginal route compared to oral administration is the by-passing of gastrointestinal absorption and thus of the hepatic first-pass effect. Unpredictable factors, like vomiting or reduced absorbent capacity of the bowel, could interfere with the gastrointestinal absorption. In addition, both the liver and the gastrointestinal system are accountable for the

293 elimination of numerous compounds [40]. For this reason, avoidance of the hepatic first-pass effect
294 is especially useful for drugs subject to an intense hepatic metabolism. As an example, natural
295 estrogens, when given orally, are metabolized by the liver for the 95%. Consequently, the
296 possibility of vaginal drug delivery permits the prescription of lower doses with reduced incidence
297 of side effects and, at the same time, is able to reach the same pharmacodynamic effect [41]. In fact,
298 the avoidance of hepatic first pass metabolism with vaginal delivery of estradiol permits the use of a
299 10- to 20-fold lower dose to obtain the same systemic levels compared with oral administration
300 [41].

301 An additional advantage of the intravaginal route is its reversibility and easiness of use,
302 which makes the woman in control of its application. However, at the same time, this represents one
303 of the major obstacles to overcome. In fact, a large part of the female population perceives the idea
304 of inserting a drug (ring, tablet or gel) in the vagina as a "foreign body" that can interfere with
305 personal hygiene or can cause adverse effects on coitus [42]. In addition, as demonstrated by an
306 online survey in 2004, entitled the International Vagina Dialogue Survey, more than half of the
307 interviewed didn't know the correct anatomy of the vagina and only 35% were aware of the
308 possibility of using the vaginal route for drug administration. In this view, the role of gynecologists,
309 in counseling their patients regarding popular misconceptions about the vagina and the applicability
310 of this route for drug administration is of primary importance [42].

311 The disadvantages associated with the intravaginal route include the risk of spontaneous
312 expulsion of vaginal rings, that occasionally goes unnoticed, the possibility of increased local
313 adverse effects, such as vaginal infection, increased leucorrhea, vaginal discomfort and local
314 lesions. In a large observational study on the use of the CVR [43] the most commonly reported side
315 effects were headache (6%), vaginitis (6%) and leucorrhea (5%). Vaginal discomfort and ring-
316 related local events were described in 2% and 4% of the enrolled patients [43]. The withdrawal rate
317 due to vaginitis and leucorrhea was low (1.3%) [43]. Another clinical trial [44] compared the CVR

with a COC (EE 30 μg + LNG 150 μg), with a follow-up of 12 months. A high percentage of women enrolled in the CVR group reported vaginitis and leucorrhea during the study period (11%), however, only 1% discontinued the CVR for this reason. Fine *et al.* [45] evaluated the safety and efficacy of the CVR in 81 women who had undertaken a surgical abortion. The CVR was inserted a week after the surgical procedure. After one month, 4% of the patients had experienced a bacterial vaginosis and 2% a Candida infections. Finally, the increased risk of bacterial vaginosis was supposed also by Archer *et al.* [46], who reported an improved Nugent score in 40% of vaginal contraceptive rings users.

Another field of concern regarding CVR is the fear of feeling the ring during coitus and during everyday activity. Two large studies [47-48] showed reassuring results, in fact, more than 85% of the participants reported that they did not perceive the ring during sexual intercourses.

The rationale behind the use of local treatments for vaginal endometriosis includes the above-mentioned advantages of the vaginal route, comprising the avoiding of the hepatic first-pass effect, the possibility of adopting lower doses than those required for oral administration, the reduction of side effects. Moreover, a local administration in close proximity to the endometriotic nodules and plaques could result in higher concentrations of the drug in the surrounding area, with the potential result of a "target lesion" therapy. Overall, a substantial amelioration of pelvic pain symptoms associated with endometriosis was observed, particularly of dysmenorrhea.

Several studies have demonstrated that vaginal administration of danazol allows the use of significantly lower doses than those adopted for the oral route, with serum concentration being lower than after oral assumption [34, 36]. In fact, low-dose vaginal danazol has been adopted with positive results in mild-to-moderate endometriosis at a daily dose of 100 mg and 200 mg [27,29,30] (Table 1), whereas, in most studies, higher oral daily doses (400 to 800 mg) are needed to achieve positive outcomes on pain symptoms [49-62]. In addition, vaginal danazol has been proven to be effective for endometriosis-related pain with limited side effects [25-30,34].

In addition, an increased expression of aromatase activity has been demonstrated in endometriosis lesions. This overexpression provokes a hyperestrogenic milieu within the implant that could favor the progression of the disease [34]. Furthermore, aromatase activity is absent in normal human endometrium and is increased in endometriosis lesions [63]. Almost all the available evidence concerning the use of aromatase inhibitors in patients with endometriosis refer to oral drugs [64-74]. Only a pilot study [6] has evaluated the potential role of vaginal anastrozole on women with symptomatic rectovaginal endometriosis, with encouraging preliminary results. Given this background, the use of vaginal drugs with inhibitory activity on this enzyme, like danazol or aromatase inhibitors, could have a role specifically in the treatment of vaginal endometriosis.

CONCLUSIONS

Future studies should focus on implementation of the use of the vagina as a drug delivery modality, in particular in those patients with deep infiltrating and vaginal lesions. In fact, as demonstrated in previous studies [5,26], vaginal treatments appeared efficacious mostly in women with rectovaginal lesions, probably due to the higher local concentration of drug obtainable from direct contact between the drug itself and the lesions located in the posterior fornix.

Women should be carefully instructed about the correct modality for positioning drugs intravaginally. In fact, the compounds should be placed at bedtime, deeply into the cranial portion of the vaginal canal to prevent drug dispersion with subsequent variability of serum levels. Moreover, the correct placement of vaginal drugs appears crucial particularly in women with DIE, in order to obtain a high drug concentration near the endometriotic vaginal lesions and avoid absorption of the compound into the hemorrhoidal and internal pudendal vascular plexuses.

Ideally, in endometriosis patients' hormonal drugs should inhibit ovulation. Therefore, in case aromatase inhibitors are used vaginally, they should be combined with progestins at doses sufficient to inhibit the hypothalamic-pituitary-ovarian axis.

The vaginal route represents a partially unexplored route for drug administration, especially in women with vaginal endometriosis. Transvaginal drug delivery offers several biochemical and metabolic advantages, beyond its simplicity and reversibility of use. There is a great need for further research in this promising field of application of hormonal drugs for the treatment of the most demanding forms of endometriosis.

CONTRIBUTION TO AUTHORSHIP

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