Best Practice & Research Clinical Obstetrics and Gynaecology xxx (2018) 1–24

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

7

Medical treatment of endometriosis-related pain

Paolo Vercellini, MD [a, b, *], Laura Buggio, MD [a, b], Maria Pina Frattaruolo, MD [a, b], Alessandra Borghi, MD [a, b], Dhouha Dridi, MD [a, b], Edgardo Somigliana, MD [a, b]

[a] Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Italy
[b] Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122, Milan, Italy

Keywords:
Endometriosis
Pelvic pain
Oral contraceptives
Progestogens
GnRH agonists
GnRH antagonists

A B S T R A C T

Available medical treatments for symptomatic endometriosis act by inhibiting ovulation, reducing serum oestradiol levels, and suppressing uterine blood flows. For this, several drugs can be used with a similar magnitude of effect, in terms of pain relief, independently of the mechanism of action. Conversely, safety, tolerability, and cost differ. Medications for endometriosis can be categorized into low-cost drugs including oral contraceptives (OCs) and most progestogens, and high-cost drugs including dienogest and GnRH agonists. As the individual response to different drugs is variable, a stepwise approach is suggested, starting with OCs or low-cost progestogens, and stepping up to high-cost drugs only in case of inefficacy or intolerance. OCs may be used in women with dysmenorrhea as their main complaint, and when only superficial peritoneal implants or ovarian endometriomas <5 cm are present, while progestogens should be preferred in women with severe deep dyspareunia and when infiltrating lesions are identified.

* Corresponding author. Department of Clinical Sciences and Community Health, Università degli Studi di Milano and Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Ca' Granda Ospedale Maggiore Policlinico, Via Commenda, 12, 20122, Milan, Italy.

E-mail addresses: paolo.vercellini@unimi.it (P. Vercellini), buggiolaura@gmail.com (L. Buggio), mp.frattaruolo@gmail.com (M.P. Frattaruolo), alessandra.borghi.92@gmail.com (A. Borghi), dh.dridi2@gmail.com (D. Dridi), dadosomigliana@yahoo.it (E. Somigliana).

https://doi.org/10.1016/j.bpobgyn.2018.01.015
1521-6934/

Introduction: "Gimme some truth"*

*Lennon J. In: Imagine. U.K., Apple Records, 1971.

Numerous useful literature reviews on medical treatment for endometriosis have been published during recent years. Several of them are systematic and some include meta-analyses [1–4]. In most reviews, not only available drugs are evaluated, but also novel compounds under investigation [5–8]. Therefore, in this article, we have tried to address the issue from another perspective, that is, defining the conceptual framework underpinning hormonal therapy for endometriosis; suggesting theoretical and practical instruments for selecting, interpreting, and implementing data on the medications most frequently used to treat endometriosis; and describing the general health-care scenario in which physicians have to act together with their patients. In addition, the position of scientific institutions and authoritative experts in the field on specific controversial issues has been addressed.

Concerning the first point, the common final mechanism of action of hormonal drugs and the reasonable expectations regarding their use should be highlighted once more. With few exceptions, different drugs, through diverse endocrine pathways, achieve a similar end-result, i.e., interference with pituitary–gonadal stimulation, anovulation, induction of a steady hormonal milieu, and reduction or suppression of menstrual flow. If the ectopic endometrium derives from the mucosa lining the uterine cavity, the response to gonadal hormones' variations may not be substantially different from that of the original epithelium, despite purported peculiar endocrine metabolism within extrauterine implants (progesterone resistance; increased local oestrogen synthesis). Indeed, compounds have been developed to suppress the growth and the activity of the ectopic mucosa, precisely based on the principle that the ectopic endometrium responds to variations in circulating ovarian steroids similarly to the intrauterine one [9].

Nevertheless, the hypo- or atrophic glandular state induced by hormonal drugs is temporary by definition, as no definitive cytoreductive action can be expected by simply altering ovarian steroid levels. If adequately stimulated, the atrophic endometrium of a postmenopausal woman may resume its proliferative potential even after years of profound hypo-estrogenism. Therefore, until hormonal compounds will be used in women with endometriosis, disease *control* is a sensible goal, whereas disease *cure* is not. Given their mechanism of action, current medications for endometriosis work *during* treatment, whereas there seems to exist no rationale to hypothesize an enduring effect *after* treatment discontinuation.

However, some authoritative experts in the field of endometriosis have a different opinion and maintain "*there is evidence to suggest that in many women who do not respond to therapy, symptoms return after cessation of treatment, even after short follow-up periods*" and "*there remains an unmet clinical need among women with endometriosis for a specific disease-modifying therapy to provide long-term symptom relief that persists after the treatment period*" [4]. Women afflicted by endometriosis-related pain are eagerly waiting the advent of such intelligent drugs able to discriminate between the eutopic and the ectopic endometrium and to destroy selectively the latter one. In fact, only this type of drug would allow treatment for a limited period of time, achieving a long-lasting cure of pelvic endometriosis, but at the same time without causing uterine sterility due to disappearance of the intrauterine endometrium. How this differential effect could be obtained remains an unanswered question. In this regard, information from ongoing or completed trials on novel drugs for endometriosis is currently discouraging [9–11].

Comparing endometriosis with another frequent chronic disorder outside the gynecologic field may help clarify the issue further. Authoritative gastroenterologists do not maintain that proton pump inhibitors (PPIs) are inadequate for the treatment of severe erosive gastroesophageal reflux disease (GERD) because not all patients respond satisfactorily to medical treatment, or some of them report side effects, or almost all of them experience quick and severe symptom recurrence at drug discontinuation [12,13]. In fact, in general, no medical therapy is effective on all patients with a chronic condition; effective drugs with no side effects just do not exist; and medications for chronic disorders are, by definition, symptomatic. Moreover, also in this case rapid symptom recurrence at drug discontinuation is expected and constitutes no surprise. Indeed, the development of PPIs has been beneficial for about two thirds of patients suffering from GERD whose symptoms were not sufficiently relieved by previously available therapies. The only reasonable alternative to PPIs is, here, a complex

Please cite this article in press as: Vercellini P, et al., Medical treatment of endometriosis-related pain, Best Practice & Research Clinical Obstetrics and Gynaecology (2018), https://doi.org/10.1016/j.bpobgyn.2018.01.015