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UPDATE ON MEDICAL TREATMENT OF ENDOMETRIOSIS:
NEW DRUGS OR NEW THERAPEUTIC APPROACHES?

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ABSTRACT

Background: No conceptually new drugs for the safe and successful cure of endometriosis are likely to become available soon. Hormonal modulation of ovarian function and suppression of menstruation remain the pillars of disease control. However, existing drugs may be used following novel modalities to limit the consequences of endometriosis progression.

Objectives: To propose a pharmacological approach aimed at limiting the potential detrimental effects of the recent dramatic increase in postmenarcheal repetitive ovulatory menses and to define the type of hormones and the routes of administration that can be used to maximize safety and tolerability in the medical treatment of endometriosis.

Methods: For this narrative review, we selected the best quality evidence, prioritizing RCTs, systematic reviews, meta-analyses, network meta-analyses, and international guidelines, preferably published in the last decade.

Outcome: Medical treatment of endometriosis should be included into all aspects of prevention. Very-low-dose combined oral contraceptives can be used for years to counteract the increased risk of ovarian cancer observed in patients with endometriosis. This primary prevention measure saves lives and can effectively integrate targeted risk-reducing surgery. Secondary pharmacological prevention, based on a working diagnosis of early-onset adenomyosis-endometriosis selectively in adolescents with severe dysmenorrhea and heavy menstrual bleeding, can potentially impede the development of advanced disease forms, and reduce the need for management of complications due to a delay in diagnosis and treatment. Tertiary prevention, i.e., medical therapy of established disease, is based initially on the safest available estrogen-progestogen combinations and progestogen monotherapies. Whenever possible, ethinyl estradiol and cyproterone acetate should be avoided because of thromboembolic and meningioma risks, respectively. Estradiol can be administered transdermally. Switching to GnRH agonists and antagonists should not be delayed when first-line agents fail.

Conclusions and Outlook: Two-thirds of symptomatic endometriosis patients can be managed satisfactorily for many years using, with the right modality, the existing safe, effective, and well-tolerated medications. Despite the constant plea for new drugs, this already appears to be an excellent clinical outcome, unsurpassed in managing other human chronic inflammatory diseases. Cohort studies are needed to verify whether turning off the recurrent inflammation caused by repeated ovulation and menstruation could also affect the risk of systemic conditions associated with endometriosis.

INTRODUCTION: EX NIHILO NIHIL FIT

The years go by, but the leitmotif remains the same: hormonal medications for endometriosis are only partially effective, are associated with side effects that limit their tolerability, cannot be used in women seeking conception, and, most importantly, do not cure endometriosis, so that pain symptom recurrence is the rule when treatment is discontinued [1–8]. Gonadotropin-releasing hormone (GnRH) antagonists have recently become available, but whether this overcomes the above criticisms seems doubtful [3]. Therefore, at first glance, there appears to be nothing substantially new under the sun regarding the pharmacological management of endometriosis, and the marketing of safer and more effective therapeutics may not be around the corner [3].

Thus, an alternative conceptual approach will be adopted here, i.e., instead of describing new molecules that could potentially be developed for treating endometriosis in the future, we will try to delineate a plausible physiopathological framework in which the already available, and sometimes old, drugs are proposed according to novel pharmacological strategies based on the hypothesized etiologic roots of endometriosis. In fact, a huge archive of ideas and findings has been available for decades, although scattered in different research fields. This may have hindered a logical connection between reliable but isolated observations.

Afterwards, the medical treatment of endometriosis will be reconsidered, aligning the use of hormonal medications with the proposed main pathogenic mechanism. We will also attempt to address the most common clinical questions and doubts that health care providers encounter in their daily practice when dealing with the pharmacologic management of endometriosis and that are rarely addressed in guidelines.

This approach inevitably introduces a personal interpretation of the available data and provides a nuance of evidence-based and experience-based medicine, as nicely described by Ata and Saridogan [9]. For a detailed, factual, analytical, and unbiased overview of the effect of the currently available medications to control endometriosis, the reader can refer to several excellent reviews on the topic [10–20].

In addition, three premises are necessary. First, from a pathogenic perspective and for the reasons explained below, we will consider adenomyosis and endometriosis as different phenotypes of a single disorder [21,22], as also suggested by Brosens *et al.* [23] who proposed the definition ‘*endomyometrial dysfunction syndrome*’. Second, we addressed only hormonal treatment, but recognize that many other important interventions are included under the umbrella of ‘medical treatment’, such as pharmacological therapy for neuropathic and nociplastic pain [24–27], as well as complementary and alternative therapies [28,29]. Third, regardless of potential pathogenic backgrounds, this review refers to the European Society of Human Reproduction and Embryology (ESHRE) and the recently updated National Institute for Health and Care Excellence (NICE) guidelines on endometriosis [30,31] for all recommendations regarding diagnosis and medical management, even if reinterpreted and adapted.

For this narrative review, we selected the best quality evidence, prioritizing RCTs, systematic reviews, meta-analyses, network meta-analyses, and international guidelines. Information was identified through a PubMed search using combinations of the MESH terms ‘endometriosis’, ‘adenomyosis’, ‘epidemiology’, ‘evolution’, ‘dysmenorrhea’, ‘dyspareunia’, ‘pelvic pain’, ‘ovarian cancer’, ‘medical treatment’, ‘oral contraceptives’, ‘progestogens’, ‘dienogest’, ‘norethisterone/norethindrone acetate’, ‘drospirenone’, ‘GnRH agonists’, and ‘GnRH antagonists’. References from relevant publications were screened and further articles were identified using the “similar articles” and “cited by” functions of PubMed. The search was restricted to peer-reviewed, full-text, English-language articles, preferably published within the last decade. Selective progesterone receptor modulators and aromatase inhibitors were not considered because the former are associated with safety issues (i.e., liver toxicity and endometrial hyperplasia), and the latter can induce arthralgia and cannot be used alone, but do not appear to add much benefit when combined with standard medications.

A SCHEMATIC OUTLINE OF THE ENDOMYOMETRIAL DYSFUNCTION SYNDROME HYPOTHETICAL PHYSIOPATHOLOGICAL MILIEU

“The influence of our evolutionary past and its implications for understanding human diseases can no longer remain overlooked by medical practice; evolutionary perspectives must inform medicine” [32].

Evolutionary medicine offers several possible explanations for the onset of diseases based on the interaction of complex biological systems with diverse and changing environments. One of the explanations involves a mismatch between our biological adaptation to environments through natural selection, and modern lifestyles [32]. Classic examples of this evolutionary mismatch include obesity, diabetes, hypertension, and heart disease. Adaptive

Neanderthal alleles resulted in phenotypes that were favored in ancestral environments. However, following demographic and environmental changes, such genetic variants no longer confer the same advantages, but actually predispose to certain diseases [32]. Thus, the 'mismatch' arises because genetic traits that once favored the survival, reproduction, and transmission of selected genetic lineages, instead render those individuals susceptible to developing specific diseases when the environment and lifestyle change substantially and rapidly. Biological adaptation through natural selection is an extremely long process (tens of thousands of years). In ancestral times, environmental and lifestyle changes were also very slow, allowing for progressive genetic adaptation. In modern times, environmental and lifestyle changes have become relatively fast (hundreds of years). This has prevented an adequate genetic adaptation, resulting in 'mismatches'.

According to several evolutionary researchers, and here very simplistically synthesized, in ancestral times those females who, due to several factors including possible intrauterine exposure to low testosterone levels and higher relative effects of estrogens [33], precocious maturation of the hypothalamic-pituitary-ovarian axis, early menarche and regular ovulatory cycles, higher gonadal estrogen synthesis, and early development of an accentuated estrogenic-type phenotype, were reproductively favored [34–36]. It cannot be excluded that particularly those females who were advantaged in mating competition typically conceived after a few postmenarcheal ovulatory menses, breastfed for years after each delivery, and became pregnant again soon after ovulation resumed. Thus, they rarely menstruated, and the absence of menses constituted the physiological state [37–43]. In that environment and according to that lifestyle, genetic adaptation took place through natural selection [44].

In the post-industrial era, due to several factors including improved nutrition and living conditions and, possibly, increased exposure to endocrine disrupting chemicals, the median age at menarche decreased from 16 to 12 years [45]. At the same time, as a result of major societal changes, the median age at first conception increased from 19 to over 30 years, the median number of pregnancies dropped dramatically from 5-6 to 1-2, and the median duration of exclusive breastfeeding fell from 2-3 years to 4-6 months [37,38,43,46]. In this rapidly changing environment and modified lifestyle, recurrent ovulatory menses (ROM) over years/decades became the norm. But what does this rapid transition from prolonged amenorrhea to prolonged uninterrupted cycling implies for the female reproductive tract [37–39,47,48]?

Early menarche and nulliparity are associated with an increased risk of endometriosis [49–53]. Breastfeeding significantly reduces the risk not only of ovarian cancer [54] but also of endometriosis [55,56]. Both ovulation and menstruation are inflammatory events [57,58]. Ovulation involves the release of lytic enzymes to degrade the granulosa, theca, and overlying cortical layers, the release of blood and abundant amounts of 17- β -estradiol, and the creation of a transient inflammatory and hyperestrogenic local environment [57]. Menstruation involves ischemia, necrosis, immune cell infiltration at the endometrial-myometrial interface, release of blood, free catalytic iron, and inflammatory mediators, and tissue remodeling [59]. If this endometrial-myometrial disruption occurs repeatedly every month for years, the growth and invasion of stratum basalis cells and the establishment of endometrial implants within the inner myometrium would be facilitated. In the absence of a submucosal layer beneath the endometrium, the inner myometrium is not protected from early postmenstrual downward basalis gland infiltration. Once adenomyotic foci are established, cyclic ectopic bleeding would cause local repeated tissue injury and repair processes, chronic inflammation-induced local 17- β estradiol synthesis, and would trigger epithelial–mesenchymal transition, fibroblast-to-myofibroblast transdifferentiation, smooth muscle metaplasia, and ultimately fibrosis [3,58–61].

Adenomyosis is associated on one hand with increased menstrual bleeding [62], and on the other hand with myometrial dysperistalsis and hypercontractility, with loss of the physiologic peri-menstrual directionality of the contraction wave from the fundus to the cervix [63,64]. The combination of these two factors would substantially increase the amount of transtubal retrograde menstruation with augmented pelvic exposure to blood and endometrial cells [65]. An excessive number of pelvic erythrocytes would overwhelm the scavenging potential of local macrophages with the release of heme groups and free catalytic iron [66–70]. This would generate reactive oxygen species with consequent damage to the mesothelium, exposure of the extracellular matrix, facilitated implantation of refluxed endometrial cells, and replication of an inflammatory process similar to that occurring in the myometrial wall, ultimately leading to fibrosis, exacerbation of pain, reduced fertility, and potential loss of organ function [3,61,71–73].

According to this hypothesis, adenomyosis would occur early in the reproductive life of susceptible individuals and endometriosis could be interpreted as an epiphenomenon [74,75]. Indeed, several investigators have observed that the prevalence of adenomyosis in adolescents and young women is much higher than previously

thought, reaching 30-50% in those complaining of severe dysmenorrhea and menorrhagia [76–81]. More than a decade ago, Brosens *et al.* [23] suggested that adenomyosis and endometriosis coexist so frequently that they ‘could well represent two phenotypes of a similar endomyometrial dysfunction syndrome rather than two different diseases’.

If this theoretical evolutionary scenario is valid, those adolescents who would have been reproductively favored in ancestral times, would be those who would suffer the most from the above-mentioned genetic/environmental mismatch, and would be at the highest risk of developing adenomyosis-endometriosis. Indeed, epidemiologic studies confirm that the risk of endometriosis is associated with a high number of cycles and with regular and heavy menstrual flow [50,51,53,82–86]. Moreover, it has been hypothesized that, among non-modifiable factors, genetic predisposition may determine the amount of menstrual flow [87]. In addition, abundant abdominopelvic bleeding from hemorrhagic corpora lutea has recently been reported to be a precursor not only of ovarian endometriomas but also of deep infiltrating endometriotic (DIE) lesions [88–91].

In addition to ROM, several other factors are likely to play a role in the development of adenomyosis-endometriosis [12,14,15,17,19], but it cannot be excluded that potential contributing causes are superimposed and manifest their effect(s) in a particularly susceptible subset of individuals, i.e., women with a genetic profile that would once have ensured the highest likelihood of trait transmission [35,36], but who are now particularly disadvantaged by the transition from prolonged amenorrhea to prolonged cycling.

If these etiologic premises are correct, it follows that a physiopathology-based pharmacologic control of adenomyosis-endometriosis begins with the restoration of what were the physiologic conditions of the reproductive system in the decade following menarche up to a couple of centuries ago, that is, anovulation, amenorrhea, and the creation of a stable hormonal environment devoid of repetitive major serum and tissue 17- β -estradiol and progesterone concentration fluctuations. This should translate in eutopic and ectopic endometrial quiescence, reduction of uterine, ovarian, and pelvic bleeding and the consequent iron-related oxidative stress and tissue damage [66–70,92], shutdown of local and systemic inflammation, and prevention of lesion progression. As Brosens stated already in the last century [93], ‘*endometriosis [is] a disease because it is characterized by bleeding*’.

THE PHARMACOLOGICAL BASIS FOR HORMONAL CONTROL OF ENDOMETRIOSIS

If the theory of the transition from prolonged amenorrhea to prolonged cycling is valid, uterine bleeding should be avoided as soon as the clinical and ultrasonographic diagnosis of adenomyosis-endometriosis is made, and amenorrhea should be maintained until conception is sought, with the aim of not only relieving symptoms but also preserving the residual reproductive potential and interrupting the possible sequence of events that starts with acute pain episodes, but can lead to central sensitization and nociplastic pain through the establishment of prolonged chronic pain phases [94]. The therapeutic goal is clear: intervene early to prevent disease progression, rather than waiting and then dealing with late disease complications [95].

Within this general therapeutic framework, individualized pharmacological strategies should be defined based on pharmacological trade-offs. In addition to efficacy, also safety, tolerability, cost, and patient preferences here come into play and together shape customized care [96–98]. According to the ESHRE guideline [30], medications for endometriosis are divided into first-line therapies, i.e., estrogen-progestogen combinations and progestogen monotherapies, and second-line therapies, i.e., GnRH agonists and antagonists, which are used selectively when first-line drugs are either ineffective, intolerable, or contraindicated [98,99]. This stepwise approach is suggested by safety and cost concerns. Indeed, GnRH agonists and antagonists may be more effective than COCs and progestogens in establishing amenorrhea and relieving pain symptoms, but they are also much more expensive and, when used alone, less safe and well tolerated than first-line medications [100,101].

1. Which estrogen? Should ethinyl estradiol be abandoned for good in the treatment of endometriosis?

In a landmark opinion paper published in 2017, Casper [102] highlighted the excessive estrogen exposure of endometriosis patients using common combined oral contraceptives (COCs) containing ethinyl estradiol (EE), as 5 mg of EE is equivalent to about 1 mg of micronized estradiol or 0.625 mg of conjugated equine estrogens. A daily dose of 0.9 to 1.25 mg of oral conjugated estrogen is required to approximately mimic the physiologic mean serum estradiol levels during the reproductive years [103]. Therefore, women using COCs containing 20 to 30 mg of EE would be exposed to 2 to 3 times the physiological effect of 17- β -estradiol. This relative estrogen dominance, despite the combination with a progestogen, would result in stimulation of endometriotic lesions and reduced efficacy. Moreover, EE has a marked pro-inflammatory activity [104], which could counteract the anti-inflammatory properties of the combined progestogen [105–107].

In addition, the risk of thromboembolic events is determined not only by the type of progestogen used (the more androgenic the progestogen, the lower the thromboembolic risk, due to antagonization of the estrogen-induced hepatic synthesis of prothrombotic factors), but also by the type and dose of estrogen contained in COCs [108–111]. In this regard, COCs containing 20 mg of EE are associated with a lower thromboembolic risk compared to COCs containing 30–35 mg of EE [112,113]. In addition, the use of COCs containing estradiol instead of EE has been shown to be associated with a similar thromboembolic risk as COCs containing EE and levonorgestrel [109,114]. Unfortunately, levonorgestrel is associated with androgen-like side effects and with spotting and breakthrough bleeding when COCs are used continuously, which should be the standard modality of use in endometriosis patients [115–117].

Interestingly, Meaidi *et al.* [118] have recently categorized hormonal contraceptives into high-risk, medium-risk, and low/no-risk based on literature evidence. The high-risk hormonal contraceptive category includes combined estrogen-progestogen patches, vaginal rings, and COCs containing 50 µg EE, or the progestogens desogestrel, gestodene, drospirenone, or the anti-androgen cyproterone acetate. The medium-risk category includes all other COCs and depot medroxyprogesterone acetate (DMPA). The low/no-risk category includes progestogen-only pills (POPs), implants, and levonorgestrel-releasing intrauterine devices (LNG-IUDs). This classification appears to be clinically very useful and is adopted in this review. We recognize that the thrombogenic risk of COCs is determined by the combination of a specific type of estrogen and a specific type of progestogen [110,111]. The main venous thromboembolism (VTE) determinant of COCs is the type and dose of estrogen used. In this regard, EE is thrombogenic and shows a dose-response gradient [112,113]. The progestogens combined with EE have limited prothrombotic effects *per se* [119]. Their contribution to the overall VTE risk is mainly due to the androgenic/anti-estrogenic profile of the progestogen [109,120]. For example, drospirenone alone has no major prothrombotic effect. The combination of drospirenone, which has no androgenic activity, with EE defines the COC as high risk, but the combination with a natural estrogen such as estetrol, defines the COC as medium risk [110,111,118,121]. This raises the question of whether it would be better to use COCs containing a natural estrogen in combination with a better tolerated (i.e., less androgenic) progestogen rather than COCs containing a less tolerated progestogen with androgenic activity chosen to antagonize the prothrombotic effect of EE [110,111,120]. As several alternative combinations containing micronized estradiol, estradiol valerate, and estetrol are now available [122–127], it appears reasonable to discontinue EE at any dose whenever possible to limit the risk of VTE [110,111]. This seems even more important given the synergistic thrombogenic effect of COCs and NSAIDs [118], as both types of drugs are often used concomitantly in symptomatic endometriosis patients.

Moreover, estradiol can be used transdermally [128–130] in combination with an oral progestogen. For example, oral dienogest, 2 mg/day or oral drospirenone, 4 mg/day, can be combined with transdermal estradiol, 1 mg/day. This low-dose, natural estrogen dual therapy may decrease EE-associated side effects, including mastodynia, headache, and nausea, and at the same time may help limit spotting and breakthrough bleeding, estrogen deprivation effects, and the bone loss associated with long-term oral progestogen monotherapies, without substantially increasing the VTE risk as EE does [120,128–132]. Oral combinations containing estradiol valerate 1 mg (equivalent to estradiol 0.76 mg) and dienogest 2 mg are available in Europe.

2. Which progestogen monotherapy?

Few progestogens are popular/approved for the treatment of endometriosis, i.e., norethisterone/norethindrone acetate (NETA), dienogest, medroxyprogesterone acetate, and levonorgestrel released by intrauterine devices (LNG-IUD) [2]. Drospirenone is being increasingly used especially in adolescents and young women [133–135]. Data on dydrogesterone are limited [107].

Medroxyprogesterone acetate has been studied primarily in subcutaneous and intramuscular depot formulations (DMPA). Disadvantages of DMPA include frequent breakthrough bleeding episodes that are sometimes difficult to manage, a reduction in bone mineral density, an increase in the risk of VTE (medium-risk category) [118,136], and unpredictable resumption of ovarian activity that may take several months after the last injection. Its main advantage is its very low cost [137,138].

Until a few years ago, NETA was considered a good choice due to its strong inhibitory effect on the endometrium, satisfactory efficacy on pain associated even with deep infiltrating lesions [2,139], relatively good tolerability, especially when used at the oral 2.5 mg/day dose instead of the FDA-approved 5 mg dose, appreciable bone-sparing properties, lack of estrogen-deprivation side effects as NETA is partially converted to EE (NETA 2.5 mg equals 5 µg EE) [140–142], and negligible cost. For these reasons, NETA was also among the preferred add-back therapies to be combined with GnRH agonists [143]. However, typical androgenic side effects,

such as seborrhea, acne, and weight gain, are common. Moreover, oral NETA is associated with a dose dependent risk of VTE [136], and some cases of mild liver toxicity have been reported [144]. Therefore, patients using oral NETA should be prescribed the lowest effective dose (i.e., 2.5 mg/day), and undergo regular liver function monitoring even if asymptomatic.

Dienogest at the oral dose of 2 mg/day consistently inhibits ovulation [145], is as effective as NETA for pain symptoms, is associated with a similar frequency of spotting and breakthrough bleeding events, is better tolerated [146], and can be safely prescribed for several years [147,148]. Long-term use of dienogest is associated with mild and generally stable degrees of osteopenia [148–150]. In the past, the main obstacle to its systematic use was economic affordability [146], but with availability of off-patent generic dienogest, the cost has dropped dramatically. As a result, dienogest can now be considered the oral progestogen monotherapy of choice, being supported by the largest and best evidence in this drug class [147]. Irregular bleeding, i.e., the most common side effect [151], and bone loss can be counteracted by combining dienogest with transdermal estradiol, 1 mg/day. Drospirenone, 4 mg/day, has been used continuously (without placebo pills) in 61 adolescent and young women with surgically confirmed endometriosis [133]. After a median follow-up of almost 6 months, about half of the patients reported amenorrhea and two-thirds experienced reduction of pain symptoms, whereas one-fourth discontinued the progestin, mostly due to breakthrough bleeding. The same regimen has been used to suppress menstruation in 116 adolescents with severe dysmenorrhea or chronic pelvic pain [134]. After a median follow-up of approximately 12 months, dysmenorrhea and pelvic pain were relieved in, respectively, 85% and 78% of those reporting the symptom. However, 26/116 participants (22%) discontinued the treatment, mostly because of breakthrough bleeding (11/26; 42%).

Several RCTs and systematic reviews support the role of the 52-mg LNG-IUD for the long-term treatment of endometriosis, as no substantial differences in the effect on pain have been demonstrated when this system was compared with COCs, progestogens, and even GnRH agonists [2,152–154]. However, the 52-mg LNG-IUD does not consistently suppress ovulation except during the first few months of use. This limits the protective effect against postoperative endometrioma recurrence [155], as ovarian endometriotic cysts originate from ovulation and hemorrhagic corpora lutea formation [91]. Indeed, LNG-IUDs have been proposed as the method of choice for adolescents with severe dysmenorrhea precisely because of their efficacy in reducing cyclical bleeding without affecting ovarian function. On the one hand, menstrual flow would be limited or suppressed, and on the other hand, bone loss would not occur [156–158]. Therefore, LNG-IUDs could be considered among the first-line options for adolescents after their sexual debut. In addition, the 52-mg LNG-IUD is an excellent treatment for adenomyosis, as high concentrations of a potent progestogen are delivered directly into uterine cavity, allowing for a more pronounced endometrial atrophy effect than is possible with standard dose oral progestogen regimens [159].

However, the impact of levonorgestrel released by medicated IUDs is not only local, and absorption through the subendometrial venous network may lead to systemic untoward effects. In particular, the adolescent population seems to be vulnerable to psychiatric adverse effects associated with hormonal contraception and LNG-IUDs are no exception [160,161]. In a French nationwide matched cohort study [160], use of the 52-mg LNG-IUD vs a 19.5-mg levonorgestrel intrauterine system was associated with a slightly higher, but statistically significant, use of an antidepressant within 2 years of insertion (4.0% in the 52-mg group vs 3.6% in the 19.5-mg group). Moreover, females < 25 years of age with a 52-mg LNG-IUD had a significantly increased risk of hypnotics use compared to those with a 19.5-mg LNG-IUD (3.2% vs 2.2%). In a Danish nationwide prospective cohort study, nulliparous first-time LNG-IUD users aged 15–34 years with no medical history of depression or major psychiatric illness, were assessed for their risk of depression associated with different doses contained in the devices [161]. First use of antidepressants was registered in 5% of the 52 mg, 2% of the 19.5 mg, and 3% of the 13.5 mg LNG-IUD.

Therefore, the use of the 52-mg LNG-IUD may be recommended in women >25 years of age who have been diagnosed with adenomyosis or endometriosis. The 19.5-mg LNG-IUD seems to be preferable in younger females with dysmenorrhea and menorrhagia, especially when a presumptive diagnosis of endometriosis has been made in the absence of overt clinical and US evidence of lesions [30].

Subdermal progestogen implants have also demonstrated efficacy and overall safety in the treatment of endometriosis and are not inferior to the 52-mg LNG-IUD, although the associated frequent bleeding is not always easy to manage [162,163] and the risk of VTE may be slightly increased [112].

3. Estrogen-progestogen combinations or progestogen monotherapies?

For the reasons outlined above, Casper believes that progestogens are a better choice for the treatment of endometriosis [102]. Although his argument is plausible and convincing, the results of comparative studies, including RCTs, have not shown major differences in pain relief based on the presence or absence of estrogens combined with progestogens [122,125,154,164,165]. Moreover, the problem of excessive estrogen exposure, which is real when 20–30 mg EE COCs are used, should be largely mitigated by the use of COCs containing low doses of natural estrogens [122–127]. Provided that EE is abandoned, whether a very-low-dose COC (VLD-COC) used continuously, or a progestogen monotherapy is better, may be a question of limited relevance today, and it is plausible that ensuring amenorrhea and avoiding irregular bleeding is more important than the modality chosen to achieve these goals. In this context, the transdermal patch and the vaginal ring containing EE are associated with an increased VTE risk compared to standard COCs [166], and are categorized as high-risk combinations according to the Meaidi *et al.* classification [118]. In addition, these systems have been associated with frequent irregular bleeding and limited adherence when used continuously [167] and may not constitute the best choice for endometriosis management. In general, VLD-COCs seem to be more clinically effective and cost-effective than rings and patches for controlling endometriosis-related pain [5,168].

Progestogen monotherapies, instead of COCs, are indicated as first-line options especially in patients with advanced DIE forms, such as rectovaginal plaques, bladder and bowel lesions, and parametrial nodules near the ureters. Moreover, women experiencing deep dyspareunia may benefit from the temporary absence of any estrogenic effect on lesions infiltrating the Douglas pouch, the uterosacral ligaments, and the posterior vaginal fornix [137,138,169].

When deciding on a first-line medication, attention should be paid to the choice of the progestogen type, also in light of the recently reported increased risk of meningioma with some compounds in this hormonal class [170]. In 2022 Hoisnard *et al.* [171] published the results of a French nationwide population-based case-control study on the association between exposure to cyproterone acetate (CPA, ≥ 25 mg/day), norgestrel acetate (NOMAC, 3.75–5 mg/day), and chlormadinone acetate (CMA, 2–10 mg/day) and surgically treated intracranial meningiomas. A robust association was observed for prolonged use of CPA (OR, 22.7; 95% CI 19.5–26.4), NOMAC (OR, 6.5; 95% CI 5.8–7.2), and CMA (OR, 4.7; 95% CI 4.5–5.3). The findings of a similar study were recently published by Roland *et al.* [172], this time focusing on the risk associated with the use of progesterone, hydroxyprogesterone, dydrogesterone, medrogestone, DMPA, promegestone, dienogest, and LNG-IUD. An excess risk of meningioma was observed, particularly for use >1 year, for medrogestone (OR, 3.49; 95% CI, 2.38–5.10), DMPA (OR, 5.55; 95% CI, 2.27–13.56), and promegestone (OR, 2.39; 95% CI, 1.85 to 3.09). No excess risk was observed for progesterone, dydrogesterone, and LNG-IUD. Small numbers precluded conclusions for dienogest and hydroxyprogesterone.

The risk of meningioma is determined by the cumulative progestogen dose, i.e., the daily dose per exposure time [170]. Furthermore, age is by far the most important risk factor [173]. Discontinuation of CPA, NOMAC, and CMA is generally followed by meningioma regression [172,173]. However, if surgery is required, complication rates are not negligible, as these tumors are usually located in the anterior and middle skull base [170,173]. Endometriosis patients are generally young but necessitate prolonged treatment, so the above findings are relevant. In particular, NOMAC is a potent, well tolerated progestogen with a long half-life and excellent bleeding control that has been used successfully in combination with estradiol (NOMAC 2.5 mg/estradiol hemihydrate 1.5 mg) in the management of symptomatic endometriosis [114,122,125,127,174,175].

Thus, the use of CPA should be avoided whenever possible due to both an increased risk of VTE [119] and a markedly increased risk of meningioma [171,172]. Positions regarding the use of NOMAC in COCs are mixed, with some authoritative investigators recommending no substantial changes in clinical practice in the absence of an evocative medical history and neurologic symptoms [176]. Regardless of the relative estimates, the absolute risk percentage in women younger than 35 years of age is very small. For example, almost 4,000 women aged 20–34 years would have to be treated continuously with NOMAC 2.5 mg/day for five years to cause one additional meningioma compared with non-users [177]. The EMA's Pharmacovigilance Risk Assessment Committee reviewed the available data, including post-marketing safety data, and concluded that “*the benefits of medicines containing norgestrel or chlormadinone outweigh the risks, provided new measures are taken to minimize the risk of meningioma*” and the European Commission (EMA/H/A-31/1510) finally stated that “*no new safety concern regarding a risk of meningioma associated with the use of [...] low dose (2.5 mg) norgestrel acetate containing contraceptives could be identified*”. (<https://www.ema.europa.eu/en/medicines/human/referrals/norgestrel-chlormadinone>).

4. Which GnRH analogs, agonists or antagonists?

The class of GnRH analogs includes agonists (GnRHa; buserelin; goserelin; leuprorelin; nafarelin; triptorelin) and antagonists (GnRHant; elagolix; linzagolix; relugolix). Both GnRHa and GnRHant suppress ovarian function, induce a profound and stable hypoestrogenic milieu, and are currently the most effective drugs for relieving symptoms associated with endometriosis [178–180]. No difference has been shown between GnRHa and GnRHant when the latter are used in doses sufficient to induce amenorrhea [181,182]. For analytical descriptions of efficacy, safety, and tolerability issues, readers are referred to the various available reviews and meta-analyses [30,178–180,182–184]. Of relevance, GnRHant are contraindicated in patients with severe hepatic impairment [185], and can be implicated in some drug-drug interactions [186,187]. We will focus here exclusively on the alleged advantages of GnRHant over GnRHa.

GnRHa are peptides, cannot be taken orally, and are usually administered by monthly- or three-monthly depot injections. Elagolix, linzagolix, and relugolix are small-molecule, non-peptide, and orally active GnRH antagonists [180,188–190]. A daily oral regimen may be more acceptable and associated with better adherence compared with depot formulations. However, opinions differ on this aspect, with Cooper *et al.* [165] suggesting that ‘*continuation rates and adherence to treatment might be improved by use of long acting progestogens (LAPs) as there is no need to take drugs on a daily basis*’. The ability to immediately discontinue the medication in case of severe adverse effects is an undeniable advantage of daily oral intake, although such events have been infrequently reported with depot GnRHa [95,138].

In contrast to GnRHant, which have a rapid onset of action, GnRHa induce an initial so-called ‘flare-up phase’ at the beginning of treatment. This transient gonadal hyperstimulation, which results in increased peripheral and local estradiol concentrations, may promote endometriotic lesion progression, worsen pain symptoms, and delay onset of action. However, this can be prevented by injecting the first dose of GnRHa during the mid-luteal phase or while taking an oral progestogen for approximately 10 days [95].

GnRHant can be used at low doses with the goal of only partially suppressing ovarian function and estradiol synthesis, thus avoiding the need for add-back therapies. However, lower doses are associated with erratic bleeding, reduced pain relief, and unpredictable ovulation [191]. Serial pregnancy tests would be required when using low-dose regimens, as it would not be possible to promptly differentiate between pregnancy and drug-induced amenorrhea. Likely, full-dose regimens will be chosen more frequently.

The oral route allows the combination of a GnRHant with an add-back therapy, thus avoiding the need for two separate tablets. However, this makes it difficult to tailor the type of add-back based on patient preference and potential metabolic benefits. The most physiologic and safe add-back would be to combine a GnRHa with transdermal estradiol (1 mg/day) and transvaginal micronized progesterone (200 mg/day) [129,192], although data are needed to demonstrate the bone-sparing effect of this combination. Lastly, when add-back therapy is taken separately from the analog, it can be temporarily discontinued in the event of unexpected bleeding, which is not possible when the drugs are combined in the same tablet.

Finally, there is no substantial difference in the monthly cost of treatment between GnRHa and GnRHant. However, a large body of data supports the possibility of injecting the 3.75 mg depot formulation of triptorelin every six weeks instead of every four weeks, and the 11.25 mg formulation of triptorelin every 16 weeks instead of every 12 weeks, without resumption of ovarian function and loss of efficacy [193]. This represents saving a quarter to a third of the cost of this specific GnRHa, a relevant aspect for individual families and public health services when GnRHa or GnRHant are needed for years [180,188,190,194].

In conclusion, GnRHa and GnRHant achieve a similar metabolic result, i.e., suppression of ovarian function, hypoestrogenism, and amenorrhea, although via different mechanisms of action. Both types of drugs are highly and equally effective in alleviating endometriosis-associated symptoms [181,182] and can represent a real pharmacological rescue when COCs and progestogens fail, especially because of uncontrollable and painful bleeding. The combination with add-back therapy allows a safe extension of the treatment period [184]. However, whether the potential advantages associated with GnRHant use represent a major progress in endometriosis management to the point of improving clinical outcomes is debatable [3,182].

SECONDARY PREVENTION OF EARLY-ONSET ADENOMYOSIS-ENDOMETRIOSIS

‘Secondary prevention aims to reduce the impact of a disease or injury that has already occurred. This is done by detecting and treating disease or injury as soon as possible to halt or slow its progress’ [195].

The ambitious goal here is to intercept adenomyosis and endometriosis as early as possible, hopefully at the onset, and promptly suppress ROM by establishing a mildly estrogenic but stable hormonal milieu until

conception is sought. If this goal is achieved, many patients would no longer be faced with advanced disease with known and potentially dramatic sequelae. This appears to be the new frontier of the hormonal control of adenomyosis-endometriosis, probably one of the most important interventions in this field, presumably the only medical approach that has the potential to change the natural endometriosis trajectory [95].

It is now clear that a large proportion of adolescents and young women with dysmenorrhea, heavy menstrual bleeding, and non-cyclic pain symptoms have early-onset adenomyosis-endometriosis [76–80,196–199]. If the diseases go unrecognized and diagnosis is delayed, lesion progression is possible [53,200–202], pain may worsen, and reproductive potential may be compromised. Several investigators believe that the riskiest period for lesion formation is from early adolescence to approximately 25 years of age, after which most lesions stabilize [43,95,203,204].

Adenomyosis must be searched for at US examination. In adolescents who are not yet sexually active, a transrectal probe may be used or a pelvic MRI may be ordered. Endometriosis must be clinically suspected and diagnosed in a timely manner also using reliable predictive questionnaires [205,206]. A non-surgical presumptive diagnosis is sufficient to initiate empiric medical treatment aimed at immediately interrupting the pathogenic sequence of events that could lead to advanced, complicated disease [11,30], or the onset of central sensitization [94].

Prolonged amenorrhea is the goal here. This should be achieved by taking into account individual patient and parental preferences, bone metabolism, and the feasibility of IUD insertion [207]. In adolescents who are already having sexual intercourse, the 19.5-mg LNG-IUD may be one of the preferred options, because it usually reduces or eliminates menstrual flows without suppressing ovulation, while limiting side effects [156–158]. Alternatively, a VLD-COC containing a natural estrogen can be used continuously [124]. If possible, prolonged oral or subcutaneous/intramuscular progestogen monotherapies should be considered with caution at this young age to avoid interfering with the achievement of the peak bone mineral accrual [95]. However, if this option is chosen [133], transdermal estradiol, 1 mg/day may be added. The use of vitamin D3 (cholecalciferol), 1200 IU/day, is inexpensive and may be beneficial [208].

GnRHa and GnRHant should be used only when COCs and progestogens fail and for the shortest possible time [133,209,210].

TERTIARY PREVENTION OF COMPLICATED ENDOMETRIOSIS

'Tertiary prevention aims to soften the impact of an ongoing illness or injury that has lasting effects' [195].

Tertiary prevention of endometriosis is the role of therapy, i.e., reducing the impact of established disease by limiting suffering and improving health-related quality of life. One of the differences with secondary prevention is that here more advanced, complicated disease should be managed, and medical treatment is an alternative to surgery except for some conditions such as obstructive uropathy, bowel endometriosis associated with subocclusive symptoms, ovarian cysts with doubtful US appearance, endometriomas >5 cm especially in patients >40 years of age, women seeking conception, and those who refuse hormonal therapies [138].

In addition to safety [98], efficacy, tolerability, and cost, at least two additional aspects should be considered when choosing medical treatment: the main type of symptom reported by the patient and the most severe type of lesion present, with DIE considered more severe than ovarian endometriomas.

According to a symptom-based approach, relief of dysmenorrhea is fairly simple as long as menses are suppressed, and VLD-COCs, or progestogens monotherapies plus transdermal estradiol add-back, or the 52-mg LNG-IUD, are all good first-line alternative options.

Treatment of deep dyspareunia is less straightforward as it can be difficult to achieve complete relief of this symptom with hormones alone. Several additional factors may be involved, and psychological status, quality of interpersonal relationships, pelvic floor muscle dysfunction, and nociplastic pain, may confound the efficacy of medications for nociceptive pain. If pain is clearly evoked on palpation of specific DIE lesions in the posterior compartment during the rectovaginal visit, a trial of a progestogen monotherapy can be proposed, with the woman being informed that the effect is generally slow but progressive over time and that a substantial result may not be perceived for several months [138,169]. The goal is to induce lesion regression and reduce intra- and peri-lesional inflammation, although nerve entrapment within established fibrosis may not resolve completely. If progestogens fail, GnRH analogs can be tried, but surgery should also be suggested.

Hormonal treatment should be approached in a context of warm, direct, and practical communication without fear or embarrassment on the part of the physician. Psychological, sexological, and physiotherapeutic support

may be indicated, based on identified needs and according to a stepped care order. The importance of self-management, adaptation of sexual modalities, use of the Ohnut [211], or temporary non-penetrative sex should be emphasized in most severe cases while waiting for the effect of hormonal medications to manifest. Non-cyclic pelvic pain is often caused by general intra-abdominal inflammation and may benefit from oral progestogen monotherapies, rather than LNG-IUDs which do not suppress ovulation. Estrogens should be avoided, at least initially. When progestogens fail, GnRH analogs are usually effective [137,138]. Nutritional advice should be given to reduce bowel inflammation, and patients should be encouraged to gradually resume aerobic physical exercise. Opioid analgesics should not be used because of the known risk of addiction. In general, hormonal treatments should not be lesion-oriented. However, it is reasonable to assume that VLD-COCs are adequate to suppress superficial peritoneal endometriosis and ovarian endometriomas (low- and intermediate-risk lesions, respectively), whereas progestogens and GnRH analogs are indicated for DIE lesions (high-risk lesions) to minimize estrogen stimulation and limit the probability of lesion progression [138,169,212]. There is now a wealth of evidence demonstrating the efficacy of COCs and progestogens in reducing the diameter of ovarian endometriomas [213,214] and the dimension of DIE lesion [149,212,215]. If DIE lesions are very close to the ureters or have already caused bowel stenosis <40-50% of the lumen diameter, and medical therapy is chosen instead of surgery, long-term progestogen monotherapies or GnRHa or GnRHant plus add-back should be preferred and COCs avoided [138,169].

Prevention of postoperative lesions and symptom recurrence has been one of the major advances in endometriosis management over the past two decades and is now a mainstay of treatment. The turning point was the realization that only long-term treatment until pregnancy seeking was meaningful and effective. Unfortunately, for many years, post-operative medical treatment was conceived similarly to adjuvant chemotherapy after debulking surgery for ovarian cancer. Therefore, the classic six-month treatment was indicated, often with GnRH agonists, in the belief that the deeper the induced hypoestrogenism, the greater the likelihood of eliminating residual endometriotic foci that had escaped lesion eradication. However, hormonal treatments are not cytoreductive and can only inhibit, but not destroy, residual ectopic endometrial cells. Moreover, surgery allows the elimination of existing lesions but, regardless of radicality, does not influence the individual predisposition to the development of new lesions in the future. Once these concepts were accepted by the scientific community, there was a proliferation of RCTs and meta-analyses demonstrating that prolonged ovulation suppression dramatically reduced the risk of postoperative lesion recurrence, particularly for ovarian endometriomas [216].

As early as 2009, Guo [217] indicated the probability of endometriosis recurrence at approximately 10% per year for the first postoperative quinquennium. This was confirmed by a recent meta-analysis [218] which showed that more than a quarter (27%) of patients who underwent surgery without postoperative ovarian suppression developed a recurrent endometriotic cyst within two years of follow-up. On the other hand, long-term ovulation suppression is associated with an approximately 50% reduction in symptom severity, and a 60% reduction in endometrioma recurrence compared with expectant management [219]. With the use of dienogest, the incidence rate of endometriosis recurrence in patients was 2% over a mean follow-up of 29 months compared to 29% managed expectantly over a mean follow-up of 36 months [220]. In the more recent meta-analysis by Muzii *et al.* [221], the use of dienogest reduced the risk of postoperative ovarian recurrence by > 80% over 24 to 60 months of follow-up compared with no postoperative treatment (pooled OR, 0.14; 95% CI, 0.07 to 0.26).

Cooper *et al.* [165] recently reported the results of a multicenter pragmatic RCT of postoperative use of long-acting progestogens (150 mg DMPA intramuscularly every three months or 52-mg LNG-IUD) vs COCs (30 µg +150 µg levonorgestrel, used cyclically, or continuously, or in a three-cycle regimen) that recruited over 400 endometriosis patients. At the 3-year follow-up, mean pain scores improved by approximately 40% compared to preoperative levels with no statistically significant differences between the groups.

Finally, long-term VLD-COCs and progestogens appear to reduce the risk of undergoing further surgery [222,223]. In light of all the above data, quantitative information should be provided to patients undergoing surgery for endometriosis and who do not wish to seek a pregnancy immediately [224,225].

PRIMARY PREVENTION OF ENDOMETRIOSIS-ASSOCIATED OVARIAN CANCER

'Primary prevention aims to prevent disease or injury before it ever occurs' [195].

Endometriosis increases the risk of ovarian cancer. In a landmark systematic review, Pearce *et al.* [226] reported a pooled OR = 1.46 (95% CI, 1.31-1.63), demonstrating an association with all type I cancers, i.e., not only clear cell

and endometrioid, but also low-grade serous tumors. A more recent meta-analysis by Kvaskoff *et al.* [227] slightly increased the estimate (summary relative risk, 1.93; 95% CI, 1.68–2.22). Recently, Barnard *et al.* [228] reported a fourfold increased risk of ovarian cancer in a large population-based cohort study (adjusted hazard ratio, 4.20; 95% CI, 3.59–4.91). The risk was particularly high in patients with deep infiltrating endometriosis and/or ovarian endometriomas (adjusted hazard ratio, 9.66; 95% CI, 7.77–12.00). The reasons for this progressive increase in risk estimates in recent years are not clear. However, systematic screening and risk-reducing surgery are being considered [226,229,230].

Of note, i) ovarian cancer risk is associated with lifetime number of ovulations [231]; ii) long-term use of COCs dramatically reduces ovarian cancer risk with a clear exposure time-response gradient [232]. In the first decade of COC use, the risk of ovarian cancer decreases by approximately 5% per year. The protective effect of COCs gradually declines with time after COC discontinuation but persists for more than a decade [233–237]; iii) COC use for > 10 years reduces the risk substantially in endometriosis patients to below the estimate for the general population of non-users (OR, 0.21; 95% CI, 0.08–0.58) [238]. In this context, the last sentence of a Lancet editorial [239] is instructive: *‘We strongly endorse more widespread over-the-counter access to a preventive agent that can not only prevent cancers but also demonstrably save the lives of tens of thousands of women’*. In the same vein, Wojtyla *et al.* [240] concluded that *‘favourable trends in ovarian cancer mortality are expected to persist in Europe and can be mainly attributed to the increased use of oral contraceptives in subsequent generations of European women’*.

Therefore, a reasonable measure to abate the increased risk of ovarian cancer in endometriosis patients would be to suggest prolonged use of COCs as primary prevention [234,238]. Pragmatic trials would be needed to evaluate the clinical effectiveness and cost-effectiveness of such an approach combined with targeted rather than systematic screening and risk-reducing surgery in patients with ovarian and deep endometriotic lesions.

In addition, the risk of endometrial cancer also seems to be increased in women with endometriosis [241,242]. If this is confirmed, the similar and well-known protective effect of COCs would be extended to this type of cancer.

It can be argued that the use of COCs is associated with an increased risk of breast cancer. In a Swedish national cohort study, the use of the 52-mg LNG-IUD was also associated with a 13% increased risk of breast cancer (adjusted HR, 1.13; 95% CI, 1.10–1.17) [243]. However, this increase is small and disappears a few years after discontinuation of the COCs and, presumably, also after removal of the LNG-IUD, thus before the peak incidence of this type of cancer [244,245]. Therefore, the overall oncological balance of prolonged COC use, including the protective effect on colorectal cancer, appears to be favorable [244], and patients should be specifically informed about this aspect, which is one of the main determinants of hormonal contraceptive hesitancy. Whether the same protective effects also apply to progestogen monotherapies is currently undefined but biologically highly plausible.

MANAGING DIFFICULT CASES

1. How do you manage heavy, or prolonged, or recurrent bleeding when using continuous VLD-COCs and oral progestogen monotherapies?

Maintaining amenorrhea is one of the most important therapeutic goals in endometriosis patients who choose medical treatment. Unexpected bleeding is associated with pain, psychological distress, decreased treatment adherence, and thus reduced clinical effectiveness [246]. Therefore, candidates for pharmacologic management should be adequately informed of the likelihood of prolonged and/or repetitive bleeding, so that anxious reactions are limited because the event is expected. Unfortunately, irregular bleeding is by far the main drawback of all first-line medications, and it is not easily corrected even by adding estrogens when subcutaneous, subdermal, or intramuscular progestogen formulations are used [247]. When using continuous VLD-COCs or oral progestogen monotherapies, the simplest intervention is tailored cycling, which implies stopping the medication for 5–7 days if uterine bleeding is abundant or persists more than five days [138,248]. When this approach fails, a cautious increase in the dose of estrogen in COCs or the addition of estradiol, preferably transdermally [120,130–132], to progestogens may be attempted.

Kitawaki *et al.* [249] reported that dienogest-associated erratic bleeding was less frequent when a single GnRHa depot injection preceded progestogen use. The same measure (i.e., interval, single depot GnRHa injection) can be used also during oral progestogen therapy. In this case, the progestogen should be continued for 7–10 days after the GnRHa injection to prevent a flare-up phase and then discontinued for the remaining duration of the GnRHa effect.

If this approach fails, and bleeding-associated pain persists, switching to GnRH analogs is recommended [30]. In particular, GnRH agonists appear to be advantageous in these circumstances, as the decision as to when and how to start add-back therapy is made together with the patient, taking into account how much and how long she has been distressed by irregular bleeding, and whether she would prefer to minimize the risk of further unexpected bleeding for a limited period of time, even at the cost of temporarily experiencing hypoestrogenic symptoms.

2. Depression and worsened sexual functioning during VLD-COCs and progestogens use: what to do?

The onset of depression or substantial decrease in libido is relatively common in users of COCs and progestogen [250]. These two symptoms are often combined, although they may also occur as isolated side effect [251].

Findings on the development of de-novo depression in first-time COC users are controversial [252,253]. In general, the risk is concentrated in a subgroup of predisposed users with a history of depression and antidepressant prescriptions [253–255]. The risk appears to be higher in adolescents and young adult women [250,255–258]. Moreover, endometriosis patients seem to be particularly vulnerable to this adverse effect [251], and a common genetic pattern linking depression and endometriosis has been observed [259]. Careful history taking is recommended to identify pre-existing traits or predisposition to mood disorders [255,257]. In the case of positive personality traits and symptoms suggestive of past or present depression, patients must be informed that depression may recur or worsen during COC use [250]. In these circumstances, psychiatric consultation seems advisable before prescribing COCs or progestogens, especially in depot formulations. Whether the use of GnRH analogs plus add-back therapy is associated with the same degree of risk is currently unclear.

A detrimental effect of COCs and progestogen on sexual functioning, particularly libido, has been the subject of recent debate, but findings are inconsistent [260–264]. According to the European Society of Sexual Medicine [265], *'a minority of women experience a change in sexual functioning with regard to general sexual response, desire, lubrication, orgasm, and relationship satisfaction'*. However, *'There is not enough evidence to draw a clear algorithm for the management of hormonal contraception-induced sexual dysfunction'*. In other words, no clear associations have been observed between COCs containing specific estrogen doses or progestogen types, and there is no evidence that one COC is less harmful than another [266,267]. Therefore, switching to a more estrogenic combination or a COC containing a progestogen with androgenic activity is not necessarily beneficial [266,268]. Changing COCs until a combination is found that does not greatly affect sexual functioning is sometimes successful, regardless of COC type [262,265,266].

3. Non-response to first-line medications after a presumptive diagnosis of endometriosis: the GnRH agonist *ex juvantibus* test

When patients do not respond to empirical first-line medications prescribed on the basis of a presumptive diagnosis of endometriosis, doubts may arise as to whether the reported abdominopelvic pain symptoms are really due to localized lesions not identified on US or MRI, or whether other causes and pathogenic mechanisms are at play. In these circumstances, *ex juvantibus* diagnosis using one or two three-monthly depot injections of a GnRH agonist may be attempted before scheduling a laparoscopy [95,269,270]. Although the post-test probability of endometriosis is higher after a favorable response to GnRH_a use, a positive test result is not synonymous with endometriosis presence, as other conditions may be improved by profound hypoestrogenism. More importantly, the likelihood that superficial peritoneal endometriosis is the origin of pain symptoms after a negative test result (non-response to GnRH_a) is greatly reduced, so other causes should be sought with a multidisciplinary approach. Caution should be exercised before suggesting a diagnostic laparoscopy in patients who may be suffering from nociplastic pain and chronic overlapping pain conditions and may not benefit from surgical abdominal exploration [271].

CONCLUSION: TOO MUCH DATA, NOT ENOUGH INSIGHT?

The production of data on endometriosis management has become immense and it is becoming difficult to keep up with all the publications on the subject. Furthermore, even the reports of RCTs, the best quality evidence, originate from strictly controlled conditions where participants are highly selected according to definite inclusion and exclusion criteria, are assisted by dedicated and trained professionals, and have immediate access to care and support for any need. Real life is different, patients may not have the same demographic characteristics, medical history, comorbidities, symptom type and severity, lesion type and extent, and level of motivation to use the suggested medications. Moreover, their access to care may be less convenient, and the time available for medical encounters may be pre-scheduled and difficult to extend. Finally, the drugs used, and tests performed in an RCT

are free of charge, which is generally not the case outside research settings. For many people, affordability can make a difference in their choice of treatment.

According to Pollack and Dal Pra, '*Evidence-based medicine is the intersection of three main factors: The use of current best available evidence, physician clinical experience, and patients or family values, all of which should contribute to trade-off considerations [...]. These are key components in shared decisions [...]*' [272].

We have attempted to describe the pharmacological armamentarium for endometriosis from a pragmatic therapeutic perspective and the main overall conclusions are summarized in Tables 1 and 2. Some limitations of this narrative review must be acknowledged. We have not recapitulated the results of RCTs and meta-analyses and have not tried to quantitatively compare the efficacy, adverse effects, and safety of available hormonal treatments for endometriosis. There are many excellent recent reviews on this topic [10–20], and we wondered whether another similar one would have added value. Instead, we have here attempted to describe the problems that health care providers encounter in their daily practice, and the situations that they face in their outpatient clinics in real-world circumstances, that is, in an environment very different from that of research.

In addition, we propose to draw pieces of evidence from multiple disciplines, including evolutionary biology and psychology, epidemiology, neuroendocrinology, imaging, histopathology, and oncology, combine them along a plausible sequence of pathogenic events, and adapt medical interventions for endometriosis within a general therapeutic scenario that goes well beyond the usual contingent need for temporary pain relief, but instead encompasses a life-cycle trajectory. At the same time, we acknowledge that the material presented is not definitively proven as an integrated theoretical construct. Furthermore, because we may have prioritized those publications that support our hypothesis, the reader must be aware that a confirmation bias (cherry-picking fallacy) is likely. Nevertheless, such a perspective is also intended to stimulate debate among investigators with different beliefs, but whose efforts are focused on a common goal, i.e., improving the health-related quality of life of women with endometriosis [273].

The exclusive focus on pain symptom management constitutes another limitation of this review. Indeed, it should be emphasized that some hormonal medications used as pre-cycle treatments have a favorable impact on IVF/ICSI outcomes in patients with endometriosis. In particular, an ultra-long protocol with GnRH agonists appears to improve cycle outcomes in patients with advanced endometriosis, whereas GnRH antagonists are generally not recommended for ovarian suppression in these conditions. In addition, dienogest has been associated with better outcomes in fresh embryo transfer cycles. For a detailed analysis of the available data on this specific application of medical therapies in the field of endometriosis-associated infertility, readers are referred to the recent comprehensive and critical review by Naem *et al.* [274].

As a general concluding remark, and as Meaidi [275] eloquently pointed out, it must be emphasized that hormone combinations are pharmaceuticals, and physicians should be fully aware of the advantages and disadvantages of different formulations when prescribing them. Hormone therapy for endometriosis may be associated with several adverse events, including but not limited to thromboembolism, hypertension, meningioma, depression, sexual dysfunction, osteopenia, and climacteric symptoms. Hormones are not used here for contraception [97] but for the treatment of a serious disease. However, medications may be required for many years, and we need to ensure that each patient is prescribed the safest hormone compound, delivered by the safest route of administration for her. Most patients are young and have no apparent contraindications to the medications used to treat endometriosis [98,99], so the individual absolute risks are small. However, given the very large number of people suffering from endometriosis, it is time to adopt a more balanced approach, focusing equally on safety and efficacy.

Finally, it is now accepted that endometriosis also induces systemic inflammation and is associated with several comorbidities [15,276,277]. Cohort studies are needed to verify whether turning off ovulation- and menstruation-associated inflammation in endometriosis patients when conception is not desired could influence the risk of future systemic diseases.

CONFLICT OF INTEREST STATEMENT

P.Ve. is a member of the Editorial Board of Human Reproduction Open, the Journal of Obstetrics and Gynaecology Canada, and the International Editorial Board of Acta Obstetrica et Gynecologica Scandinavica; has received royalties from Wolters Kluwer for chapters on endometriosis management in the clinical decision support resource UpToDate; and maintains both a public and private gynecologic practice. P.Vi. is Co-Editor-in-Chief of the Journal of Endometriosis and Uterine Disorders. E.S. is Editor-in-Chief of Human Reproduction Open, discloses payments from Ferring for research grants and honoraria from IBSA and Gedeon-Richter for lectures; and maintains both a public and private gynaecological practice. C.B. declares she has no conflicts of interest.

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AUTHOR CONTRIBUTIONS

P.Ve. conceived the text and drafted the original version of the manuscript. C.B., P.V., and E.S. participated in conceiving and drafting part of the manuscript and critically revising it. All authors approved the final version of the manuscript.

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TABLE 1. TEN KEY ISSUES TO BE CONSIDERED IN THE PHARMACOLOGIC
MANAGEMENT OF ENDOMETRIOSIS

1. A pharmacologic approach based on the neo-evolutionary pathogenic theory aims at restoring prolonged periods of amenorrhea when a conception is not desired to prevent the onset of complicated forms of endometriosis, rather than treating them after they have developed.

2. Inhibiting ovulation prevents the formation of ovarian endometriomas, while abolishing menstruation controls adenomyosis, halts transtubal retrograde flow, decreases the likelihood of superficial peritoneal endometriosis development, counteracts progression of deep lesions, reduces pelvic inflammation and iron-associated oxidative stress. This should result in an improvement in pain symptoms and health-related quality of life.

3. The two main pillars of successful medical treatment of endometriosis are the avoidance of uterine bleeding associated with the use of hormonal medication and the identification of the compound associated with the best possible individual tolerability. These factors appear to determine treatment adherence.

4. In the management of endometriosis, COCs are not prescribed for contraception, but rather for the treatment of a debilitating and potentially disabling chronic disorder associated with systemic inflammatory implications. Therefore, the usual balance of benefits and harms considered in women seeking contraception may not apply exactly here and may

TABLE 2. PROPOSAL FOR A PRACTICAL STEPWISE MEDICAL MANAGEMENT OF PATIENTS WITH SYMPTOMATIC ENDOMETRIOSIS AND NO ABSOLUTE SURGICAL INDICATIONS OR CURRENT PREGNANCY DESIRE*

Drug class	Indications	Contraindications	Pros	Cons	Tips & tricks	Comment
<u>Estrogen-progestogen combinations</u>	Superficial peritoneal endometriosis (low-risk lesions) and ovarian endometriomas (intermediate-risk lesions). Dysmenorrhea as the most disabling symptom.	Categories 3 (“theoretic or proven risks usually outweigh advantages of contraceptive methods”) and 4 (“unacceptable health risk if contraceptive method used”) of the WHO's medical eligibility criteria for contraceptive use [99].	Popular, generally well-accepted, and tolerated medications. Breakthrough bleeding easy to manage. Inexpensive. Substantial reduction in postoperative endometrioma recurrence risk. Long-lasting reduction in ovarian cancer risk.	Several but usually minor side effects. Risk of VTE associated with estrogen type and dose. Limited and temporary increase in breast-cancer risk.	Suggest a continuous flexible regimen, with 4 to 7-day hormone-free intervals triggered by breakthrough bleeding or prolonged spotting of ≥ 5 days, and followed by resumption of continuous oral contraceptive use until the next bleeding episode	Choose oral preparations containing “natural” estrogens (estradiol or estetrol) combined with progestogens such as DNG, DRSP, and NOMAC. Avoid combinations containing EE.
<u>Progestogens</u>	Deep infiltrating endometriosis (high-risk lesions). Deep dyspareunia as the most distressing symptom.	No absolute contraindications except breast cancer. Rare relative contraindications, including severe hypertension, history of VTE, ischemic heart disease, or stroke, SLE, complicated diabetes, and severe liver disorders [99].	Safe and generally well-tolerated. Can be used in most patients with contraindications to combined oral contraceptives (DNG, DRSP, LNG-IUD). Inexpensive.	Progestogens can be associated with depression, reduction in sexual functioning, and bone mineral density. Frequent breakthrough bleeding, which are more difficult to manage if subdermal implants are used. LNG-IUD do not suppress ovulation. CPA strongly associated with meningioma risk	Avoid DMPA and CPA for safety reasons. Do not use NETA >2.5 mg/day to limit VTE risk. Inform patients how to manage bleeding episodes (tailored cycling). Shift to DRSP if weight gain, depression, or reduced libido with DNG. Shift to DNG if excessive bleeding with DRSP. Favor the 19.5 mg dose when the LNG-IUD is chosen in sexually active adolescents.	To limit low estrogen symptoms and bone resorption, oral progestogens can be combined with transdermal estradiol, 1 mg/day. Cholecalciferol (vitamin D3), 1200 IU/day can be beneficial (limited data).
GnRH agonists	Non-response, intolerance, or contraindications to estrogen-progestogen combinations and progestogen monotherapies.	Extremely rare.	Timing, type, dose, and delivery route of add-back therapy can be customized. Depot GnRH formulations can be combined with transdermal estradiol, 1 mg/day, plus vaginal progesterone, 200 mg/day; or with a weekly transdermal patch releasing estradiol, 50 μ g	Estrogen deprivation symptoms. Substantial reduction in bone mineral density during prolonged use without add-back therapy. Financial toxicity.	Do not hesitate to step up when first-line medications are ineffective or not tolerated, especially because of intractable breakthrough bleeding. GnRH agonists can also be used <i>ex juvantibus</i> to discern whether endometriosis is the	GnRH analogues are highly effective and can control pain symptoms when first-line medications fail, especially due to repetitive bleeding episodes. To avoid flare-up,

			and levonorgestrel, 7 µg/24 hours; or with oral tibolone, 2.5 mg/day. A separate add-back therapy allows its temporary discontinuation in case of breakthrough bleeding.		main source of pain. To reduce costs, triptorelin 3.75 and 11.25 can be injected, respectively, every six instead of four weeks, and every 16 instead of 12 weeks.	administer the first depot injection at midluteal phase or during a 10-day oral progestogen course.
GnRH antagonists	Non-response, intolerance, or contraindications to estrogen-progestogen combinations and progestogen monotherapies.	Rare. Elagolix: severe hepatic impairment and co-administered strong organic anion transporting polypeptide 1B1 inhibitors (e.g., cyclosporine and gemfibrozil). Drug-drug interactions with strong cytochrome P450 inhibitors (e.g., ketoconazole, rifampin). Potential interactions with midazolam, rosuvastatin, and digoxin.	Some patients prefer the oral rather than the parenteral route. The medication can be immediately discontinued if adverse effects ensue. The GnRH antagonists can be combined with add-back therapies in a single tablet.	Low-dose GnRH antagonists suppress estradiol synthesis only partially and add-back therapies can be avoided. However, low-dose GnRH antagonists are associated with more frequent erratic bleeding, and suboptimal pain relief.	Low-dose GnRH antagonists do not consistently suppress ovulation. When using low-dose regimens, serial pregnancy tests would be required to promptly differentiate between pregnancy and drug-induced amenorrhea. Full-dose regimens combined with add-back therapy appear more practical.	GnRH antagonists are as expensive as GnRH agonists. This can limit access to therapy, reduce treatment adherence, and result in healthcare disparities.

*Largely based on recommendations included in the ESHRE [30] and the updated NICE [31] guidelines on the diagnosis and management of endometriosis. CPA, cyproterone acetate; DMPA, depot-medroxyprogesterone acetate; DNG, dienogest; DRSP, drospirenone; EE, ethinyl estradiol; GnRH, gonadotropin-releasing hormone; LNG-IUD, levonorgestrel-releasing intra-uterine device; NETA, norethisterone acetate; NOMAC, nomegestrol acetate; SLE, systemic lupus erythematosus; VTE, venous thromboembolism; WHO, World Health Organization.