Partial suppression of estradiol: a new strategy in endometriosis management?

Endometriosis is a chronic inflammatory disease responsible for pelvic pain and infertility (1) and characterized by frequent recurrence of symptoms and lesions, even after surgery (2). There is a lack of data from randomized clinical trials on the optimal management of endometriosis (medical versus surgical) in terms of pain relief and recurrence (2). Surgery is indicated unquestionably in cases of endometriomas more than 3 to 4 cm, as well as deep nodular endometriosis, particularly when associated with infertility. However, recurrence is common and everything must be done to prevent it.

WHAT WE KNOW SO FAR

Ovulation, menstruation, and estrogens play a major role in endometriosis development. For this reason, suppression of ovulation and menstruation, and reduction of estradiol to postmenopausal levels through hormone modulating therapies, are therapeutic means of controlling the disease and its associated symptoms in women not seeking pregnancy. Two very recent articles (2, 3) have discussed the medical approach, types of compounds used, and routes of administration.

According to the Practice Committee of the American Society for Reproductive Medicine (ASRM), endometriosis requires a life-long management plan, with the goal of maximizing use of medical therapy and avoiding repeated surgical procedures.

In a recent review, Vercellini et al. (2) clearly established that the value of treatment is a balance between potential benefits, possible harm, and cost of care. They concluded that estroprogestins should be used as first-line treatment in low- and intermediate-risk cases, with progestin-only therapy reserved for high-risk women (those with deep endometriosis), or those with contraindications or intolerance to estroprogestins. Among available progestins, norethisterone acetate (NETA) is considered to be the first choice given its extremely favorable cost-effectiveness profile, with the possibility of switching to dienogest (where available) in case of poor response to NETA (2), in settings where that medication is available.

However, in a paper published in this issue, Casper (3) strongly asserts that progestin-only pills constitute a better first-line approach than estroprogestins, considering that the dose of ethinylestradiol in a low-dose oral contraceptive pill is equivalent to 4 to 6 times the physiological dose of estrogen, which may promote attachment of endometrial cells deposited in the pelvis. Casper cites several studies that suggest an adverse effect of oral contraceptives on the incidence of endometriosis (3).

WHY DO WE NEED NEW OPTIONS?

New options are needed because of concerns about estroprogestins and progestin-only drugs:

- Two-thirds of symptomatic women find pain relief and improvement in their general condition thanks to estroprogestins and progestin-only medication, but one-third are non-responders due to progesterone resistance (2, 3).
- There is an increased risk of venous or arterial embolism (2).
- The side effects of estroprogestins are essentially related to the type of progestin used (2).

THE OPTIMAL GOAL OF MEDICAL THERAPY

An improvement in symptoms, mainly pain resulting from inflammatory endometriotic lesions, should be the main goal of long-term treatment. By inducing amenorrhea and halting menstrual bleeding (and reflux), or even simply lessening its severity, the number of regurgitated erythrocytes in the pelvis can be significantly reduced. This serves to diminish pelvic oxidative stress, which is the main source of inflammation, caused by an excess of free iron and heme in the peritoneal cavity (1).

Of course, as suggested by Barbieri (4), the ideal solution would be to lower estradiol enough to induce amenorrhea and treat symptoms, while maintaining sufficient levels to mitigate severe side effects, such as vasomotor symptoms and bone mineral density loss. Partial suppression of estradiol within the 20-60 μg/ml range could be the optimal compromise between efficacy, tolerance and safety.

HOW DO WE ACHIEVE PARTIAL ESTRADIOL SUPPRESSION?

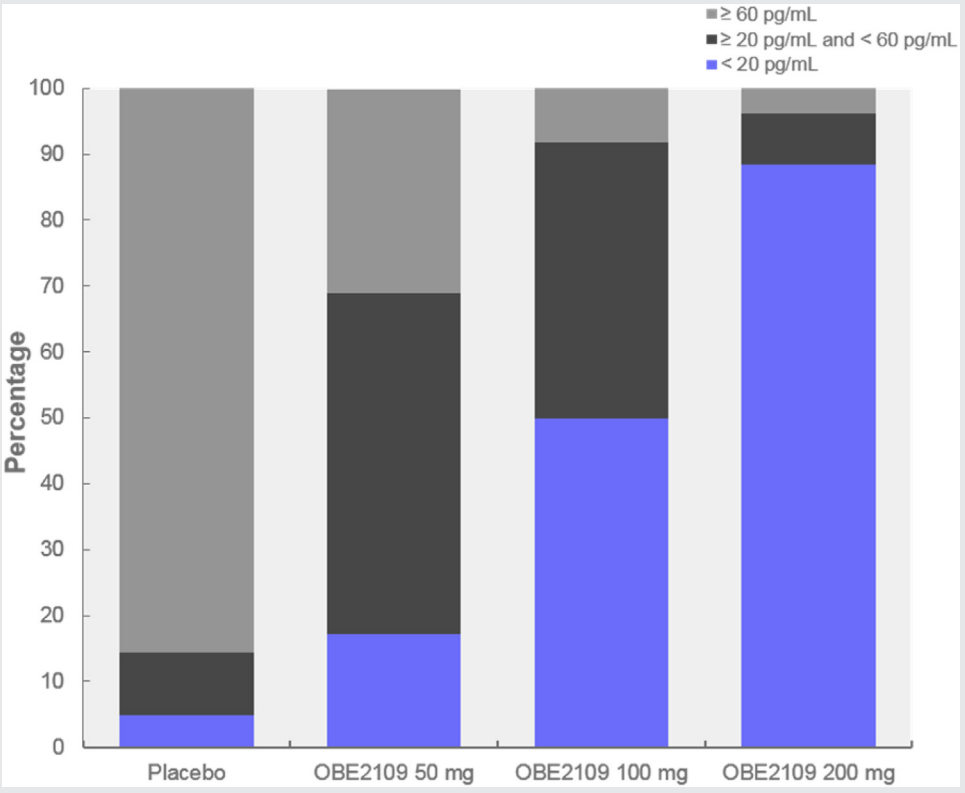
To date, the only option to restore sufficient estradiol levels to avoid menopausal symptoms and bone mineral density loss has been coadministration of a gonadotropin-releasing hormone (GnRH) agonist (depot injection) and estrogens/progestins (add-back therapy). However, according to Casper (3), administration of estrogens could have deleterious effects on disease progression. Moreover, considering most women treated for endometriosis-associated pain are middle-aged, thromboembolic risks should also be taken into account.

While GnRH agonists may be effective at treating the symptoms of endometriosis, due to their mechanism of action as agonists, they are associated with a number of drawbacks and limitations, including: delayed therapeutic impact because of the 'flare-up' effect at the start of treatment which may cause initial worsening of symptoms possibly lasting several weeks; excessive suppression of estradiol to postmenopausal levels of less than 20 pg/ml, with related unfavorable side effects; inability to titrate estradiol levels; and variable and unpredictable reversibility of treatment when injectable depot forms of GnRH agonists are used.

A NEW WAY OF ACHIEVING PARTIAL ESTRADIOL SUPPRESSION

A new class of drug particularly capable of partial estradiol suppression is orally active GnRH antagonist, which includes Elagolix (AbbVie), OBE2109 (ObsEva SA), Relugolix (Myovant), and ASP1707 (Astellas), all currently in phase 2 or 3 of clinical development in the United States and/or

FIGURE 1



Percentage of patients showing different estradiol levels in the OBE2109 trial at 12 weeks.

Donnez. Inklings. Fertil Steril 2017.

Europe. These drugs act by competitively preventing endogenous GnRH from binding and activating its pituitary receptor, and thus induce neither downregulation nor desensitization of the receptors. Importantly, levels of suppression of luteinizing hormone and estradiol are related to the dose of antagonist administered (5), allowing partial estradiol suppression.

Elagolix 150 mg (once daily) and 200 mg (twice daily) both met the coprimary endpoints of reducing scores of nonmenstrual pelvic pain and menstrual pain in the phase 3 trial (5). Responder rates for menstrual and nonmenstrual pain at 6 months were highest (75.3% and 62.1%, respectively) with elagolix 200 mg twice daily, but bone mineral density was found to have decreased by 2.64% in this 6-month period, which was subsequently confirmed by a second phase 3 trial. This loss was reduced to 0.12% in another trial evaluating Elagolix 300 mg twice daily, associated with estradiol/NETA as add-back therapy (5).

Relugolix is currently in development as a fixed-dose combination with hormonal add-back therapy (http://www.nasdaq.com/markets/ipos/filing.ashx?filingid=11120757).

OBE2109 is being investigated for use in multiple doses with or without add-back therapy. Indeed, OBE2109 has a consistent pharmacokinetic profile and low variability thanks to its high bioavailability and low volume of distribution, enabling personalized dosing that can be 'tailored' according to individual estradiol values and symptoms. (http://www.nasdaq.com/markets/ipos/filing.ashx?filingid=11243095).

In a placebo-controlled trial comparing 3 doses of OBE2109, and two further phase 2 studies in endometriosis patients (8), estradiol levels (Fig. 1) were found to be increasingly suppressed in a dose-dependent manner. Doses of 50 mg and 100 mg were shown to result in serum estradiol levels in the target range of 20 pg/ml to 60 pg/ml in a significant proportion of patients, while a dose of 200 mg was able to reduce estradiol levels to below 20 pg/ml in most patients. There is hope that by tailoring the dose of GnRH antagonist, add-back therapy may not be required in a considerable number of patients, thereby avoiding the associated side effects and allowing patients with contraindications to add-back therapy to be treated.

In addition to this unique capacity of orally active GnRH antagonists to modulate estradiol suppression, they also have several other advantages over GnRH agonist depot preparations, including: no flare-up effect, hence avoiding initially worsening symptoms; daily oral administration; and rapid reversibility.

Therefore, for the first time, we have a tool that can either partially suppress estradiol without having to administer add-back therapy, or fully suppress estradiol when combined with

add-back therapy. The real question now is whether a short-acting, nonpeptide, oral GnRH antagonist, which causes dose-dependent inhibition of pituitary and ovarian hormones, is able to deliver partial estradiol suppression and thus offer a new approach to the management of endometriosis.

In conclusion, phase 2 and 3 trials investigating GnRH antagonists have confirmed a reduction in endometriosis-associated pain, but larger clinical studies are essential to conduct comparative analyses with other endometriosis treatments. By offering the possibility of personalized dosing without the need for add-back therapy, GnRH antagonists could well show potential advantages over other therapies, but this needs to be confirmed by further investigations.

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REFERENCES

1. Donnez J, Binda MM, Donnez O, Dolmans MM. Oxidative stress in the pelvic cavity and its role in the pathogenesis of endometriosis. Fertil Steril 2016;106:1011–7.
2. Vercellini P, Buggio L, Berlanda N, Barbara G, Somigliana E, Bosari S. Estrogen-progestins and progestins for the management of endometriosis. Fertil Steril 2016;106:1552–71.
3. Casper RF. Progestin only pills may be better first-line treatment for endometriosis than combined estrogen-progestin contraceptive pills. Fertil Steril 2017;107:533–6.
4. Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol 1992;166:740–5.
5. Taylor HS, Giudice LC, Lessey BA, Abrao M, Kotarski J, Williams LA, et al. Elagolix, an oral gonadotropin-releasing hormone antagonist for the management of endometriosis-associated pain: safety and efficacy results from two double-bind randomized, placebo-controlled studies. Fertil Steril 2016;106(Suppl):e271.