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Review

Add-Back and Combined Regulation in GnRH-a Treatment of Endometriosis

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Abstract

Objective: The purpose of this review is to summarize drug selection for peri-menopausal symptoms caused by gonadotropin releasing-hormone agonist (GnRH-a) in the treatment of endometriosis. **Mechanism**: GnRH-a treatment often leads to low estrogen levels, resulting in peri-menopausal symptoms and osteoporosis. Add-back therapy relieves clinical symptoms by supplementing low-dose estrogen. The idea of "combined regulation" is to improve symptoms by adding plant preparations or proprietary Chinese medicines. Studies have shown that they may play a role by regulating serotonin activity. **Findings in Brief**: For patients treated with GnRH-a for less than 3 months, the combined-regulation regimen can be considered, whereas for patients who have had more than 3 courses of GnRH-a, add-back therapy with sex hormones must be used because the patients will have begun to have obvious bone-mass loss and even bone pain; this bone-mass loss is often irreversible. **Conclusions**: In the early treatment of endometriosis with GnRH-a, non-hormone combined-regulation therapy is a relatively safe and feasible choice, but hormone add-back therapy should be selected for patients who have had more than 3 courses of GnRH-a.

Keywords: add-back therapy; combined regulation; endometriosis; GnRH-a; sex hormone

1. Introduction

Endometriosis (EMS) seriously affects the quality of life of female patients, and is one of the most difficult problems for gynecologists. Conservative surgical treatment of EMS has many limitations, and the postoperative reoccurrence rate is high. Therefore, gonadotropin releasing-hormone agonist (GnRH-a) and other drugs are often needed to reduce or delay postoperative reoccurrence of EMS [1]. However, GnRH-a treatment can cause severe low-estrogen status, which not only affects the quality of life of patients, but can also lead to irreversible osteoporosis [2]. Although add-back therapy, based on "estrogen-window-dose theory", can solve the problems of peri-menopausal symptoms and bone-mass loss caused by GnRH-a treatment, the application of sex hormones may increase a number of risks. Not all patients are willing to accept this kind of sex-hormone therapy. In addition to sex-hormone-based add-back therapy, some plant medicinals (such as black cohosh isopropanol extract) or proprietary Chinese medicines (*Kuntai* capsule, *Xiangshao* granules, etc.) can play a significant role in relieving peri-menopausal symptoms caused by GnRH-a treatment. This is only for the relief of symptoms during the use of GnRH-a within 3 months; this short-term application of non-hormone add-back therapy is referred to as "combined regulation". Clinically, the GnRH-a treatment for EMS should be based on clinical needs, and a reasonable individual choice, regarding the add-back of sex hormones or a non-hormone combined-regulation program.

1.1 The Necessity of GnRH-a Treatment for EMS

1.1.1 Limitations of Conservative Surgical Treatment of EMS

EMS can appear as a wide range of lesions, in diverse forms, with malignant biological behavior of infiltration, metastasis, and reoccurrence. For a long time, this kind of benign disease has been perplexing clinicians. Although there are many methods to diagnose and treat EMS, the results are not always satisfactory. No matter what treatment is applied, the reoccurrence rate within 5 years is more than 40% [3].

The current consensus is that the purpose of EMS treatment is to eliminate lesions, relieve pain, solve infertility, and prevent or reduce reoccurrence. EMS is known to be a sex-hormone-dependent disease that mostly occurs in women of childbearing age. The development of EMS and

its postoperative reoccurrence cannot be ignored. The biological basis of EMS reoccurrence is the survival of ectopic endometrial cells and the continuous maintenance of hormones [4,5]. Surgical resection of diseased endometrium is the key to improving the symptoms and preventing reoccurrence. At present, laparoscopic surgery is considered to be the best surgical method for the treatment of EMS, and inhibition of ovarian function is the best drug therapy to prevent postoperative reoccurrence; laparoscopic surgery plus drug therapy is the best combination therapy. There are obvious limitations to surgical treatment alone. Patients with EMS who undergo a conservative surgery to preserve reproductive function, which naturally could not ensure the complete removal of the lesion, have residual ectopic endometrial cells, which always have the potential of regrowth with metabolic activity. Therefore, it is necessary to use drugs to cause "drug-induced ovariectomy" after the operation in order to make the residual lesions atrophy and become necrotic, so as to reduce reoccurrence.

1.1.2 Patients with EMS Need GnRH-a and Other Drugs after Surgery

A number of guidelines for diagnosis and treatment of EMS [6–8] suggest that there is still a high proportion of patients with ectopic reoccurrence of EMS, and a return of pain symptoms, after a conservative operation. Gonadotropin-releasing hormone agonist (GnRH-a) can effectively prevent the reoccurrence of EMS after surgical removal. GnRH-a is currently recognized as the most effective drug for the treatment of EMS. GnRH-a is a synthetic decapeptide that has the same effect as natural GnRH. It can promote the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) from anterior pituitary cells; its activity is 10× or even 100× that of natural GnRH. If GnRH-a is used continuously for a long time, the anterior pituitary GnRH-receptor activity is significantly reduced. This leads to pituitary-gonadotropin desensitization (receptor desensitization and down-regulation), resulting in a loss of response to both GnRH-a and natural GnRH. Ultimately, this results in a significant decrease of LH and FSH secreted by the anterior pituitary, and a disturbance of follicular development in the ovary and temporary amenorrhea. This long-term use of GnRH-a leads to what is called "drug-induced ovariectomy". In view of these consequences [9], the number of EMS surgeries should be kept as low as possible. The concept of "only one operation in a lifetime for EMS" has gradually taken root in gynecological practice. Studies [10,11] have confirmed that the use of GnRH-a can significantly reduce the reoccurrence rate of EMS, and the effect of 6 courses of GnRH-a is better than that of 3. In view of the importance of reducing the reoccurrence of EMS, it is necessary and significant to use GnRH-a in patients with EMS after surgery. It is also important to note that GnRH-a can also be used in young patients over the age of 16. However, because it can cause bone loss, the use of this drug has a particularly bad effect on bone deposition in adolescent patients, who have not yet reached the peak bone-mineral density, so it is suggested that for those patients, continuous or periodic oral contraceptive is selected as the drug therapy of first choice.

2. Problems with GnRH-a Treatment of EMS

2.1 GnRH-a Treatment of EMS can Cause Severe Hypoestrogenic Status

Reoccurrence of EMS is very likely after surgery, so GnRH-a plays a very important role in postoperative drug therapy. However, GnRH-a treatment can have serious side effects. Adverse reactions mainly include peri-menopausal symptoms and osteoporosis caused by low estrogen. After GnRH-a treatment, the symptoms of low estrogen are obvious, resulting in serious peri-menopausal symptoms such as hot flashes, vaginal dryness, lack of libido, emotional instability, and sleep disorders. Long-term use (more than 6 months) can lead to a decrease in bone-mineral density. Because of low estrogen levels, the average bone-mass loss can reach 4–6% [12]. One study [13,14] found that there were obvious complaints of hot flashes, fatigue, and insomnia after one month of treatment with GnRH-a alone. After using GnRH-a, the bone mass of patients decreased at a rate of 1%/month, and about 20% of patients had obvious bone pain after 3 months of treatment. Related study [15] has confirmed that GnRH-a treatment generally does not cause significant bone loss within 3 months, and has little effect on the long-term quality of life of patients. However, the bone-mineral density of patients treated for more than 3 months significantly decreased, and after one year of treatment, the bone-mineral density of patients cannot be completely restored to pre-treatment levels.

2.2 Add-Back Therapy may Effectively Solve the Problems Caused by GnRH-a Treatment

Many studies [16,17] have indicated that GnRH-a treatment may have a lasting and far-reaching effect on bone metabolism in patients. However, in many cases, in order to improve the curative effect and reduce reoccurrence of EMS, when GnRH-a is used for 6 months longer, the treatment regimen is often supplemented with low-dose estrogen and progesterone after the 3rd month (i.e., "add-back therapy"). Exogenous estradiol can control ectopic lesions without the concurrent changes in the level of bone metabolism.

3. The Theoretical Basis and Strategy of Add-Back Therapy

The theoretical basis of add-back therapy is the "estrogen-window-dose theory" [18]. Estrogen is very important for maintaining the function of many tissues and organs in the body, and the sensitivity to estrogen (the concentration of estrogen to maintain tissue or organ function) of various tissues and organs differs. For example, if the blood

estradiol level is lower than 30 pg/mL, peri-menopausal symptoms such as hot flashes and sweating occur; when the blood estradiol level is lower than 20 pg/mL, significant bone loss occurs [19]. Among estrogen-related pathologies, different diseases have different sensitivities to estrogen. For example, breast cancer is the most sensitive to estrogen; if the level of estradiol in blood rises to 20 pg/mL, the growth of breast cancer cells can be stimulated; uterine leiomyoma is also sensitive to estrogen, and when the level of estradiol in blood rises to about 30 pg/mL, the growth of the leiomyoma can be stimulated [20]. However, when the level of estradiol in blood exceeds ~40–50 pg/mL, the growth of endometriosis can result. Therefore, keeping the level of estradiol between ~40–50 pg/mL during treatment for endometriosis can reduce or eliminate stimulation of the growth of ectopic foci, and also avoiding peri-menopausal symptoms and bone loss. This is the so-called "window-dose theory of the estrogen effect". This window does not affect the therapeutic effect, but can effectively reduce side effects [18].

4. Main Strategies for Add-Back Therapy after GnRH-a Treatment

4.1 Regimens

According to the guidelines for diagnosis and treatment of EMS of the Endometriosis Cooperative Group of the Obstetrics and Gynecology Branch of the Chinese Medical Association [21], add-back (sometimes deferred to as reverse addition) there are several main strategies:

The first strategy is the administration of estrogen + progesterone. A combination of estrogen and progesterone (either estradiol valerate 0.5–1.5 mg/d; conjugated estrogen 0.3–0.45 mg/d; estradiol patch with daily release of 25–50 μg; or estradiol gel 1.25 g/d smeared percutaneously) and progesterone (5 mg/d) or medroxyprogesterone acetate (2–4 mg/d) is administered continuously. Alternatively, a compound preparation of estrogen spirosterone tablets can be administered (1/day).

A second strategy is the administration of norethisterone acetate (1.25–2.5 mg/d), which is a synthetic progesterone that also binds to estrogen receptors.

The third strategy is to administer a continuous regimen of tibolone (1.25–2.5 mg/d), which is a synthetic progesterone that metabolizes into compounds that have both progestogenic and estrogenic properties.

The dose of add-back treatment should be individualized, and the level of estrogen should be monitored if possible.

4.2 Start-Up Time for Add-Back Therapy

It is not clear when add-back therapy for GnRH-a therapy should begin. There are mainly three viewpoints: (1) when GnRH-a starts. Barbieri [22] proposed that low-dose estrogen be used to prevent damage to other systems, and to improve patients' compliance. In addition, progesterone, plays a role in preventing estrogen from promoting intimal overgrowth. In view of the fact that the side effects of GnRH-a may affect patients from the beginning of treatment, some scholars think that the treatment can be added from the beginning of the use of GnRH-a [23,24]. (2) Add-back therapy can begin in the second month (second injection) of GnRH-a treatment (within 1–2 weeks after the use of GnRH-a). Because of the "ignition effect" of GnRH-a, the level of estrogen increases temporarily then drops and remains stable at a low level (close to menopausal levels) after 2 weeks. Accordingly, menopausal symptoms are generally more obvious from the second month and can be alleviated by add-back treatment. (3) Add-back therapy should begin after 3 courses of GnRH-a treatment. Related studies have found that obvious complaints of hot flashes, fatigue, and insomnia can occur after one month of treatment with GnRH-a alone, and about 20% of the patients will have obvious bone pain after 3 months of treatment [13,14]. Bone mass is lost at a rate of 1% per month after the use of GnRH-a. Therefore, low-dose estrogen and progesterone should be supplemented after 3 months because the patients will have obvious bone-mass loss and even bone pain after 3 months, and this bone-mass loss is often irreversible [25]. By adding estrogen, estradiol can be maintained at a level that can control ectopic endometrial lesions without affecting bone metabolism.

Although the start-up time for add-back therapy is still inconclusive, individual choices can be made according to the clinical conditions of patients. However, the prevalent point of view is that add-back therapy must be started after 3 courses of GnRH-a.

5. The Construction of the Concept of "Combined Regulation"

5.1 The Background of the Concept of Combined Regulation

As mentioned earlier, although sex-hormone-based add-back therapy solves most of the problems of peri-menopausal symptoms and bone-mass loss caused by GnRH-a treatment, sex hormone use may increase the risk of hormone-dependent tumors such as endometrial cancer and breast cancer [24,26]. For patients with sex-hormone-dependent tumors, there must be caveats for the use of sex-hormone-based add-back therapy, so this scheme cannot always be adopted. As a second point, clinically, not all patients are willing to accept this kind of sex-hormone therapy. Third, gynecologists and obstetricians of non-endocrinological gynecology are often not familiar with the add-back therapy using sex hormones. The above three cases can be summarized as unable to use, unwilling to use, and will not use this kind of sex-hormone-based add-back therapy.

Clinically, in addition to sex-hormone-based add-back therapy for peri-menopausal symptoms caused by GnRH-a treatment, some plant preparations (such as black cohosh

isopropanol extract) or proprietary Chinese medicine (*Kuntai* capsule, *Xiangshao* granules, etc.) can play a significant role in relieving peri-menopausal symptoms caused by GnRH-a therapy [15,27,28], but only for the relief of symptoms. The short-term application of non-hormonal therapy for GnRH-a within 3 months is called "combined regulation".

5.2 Possible Drug Regimens for Combined Regulation

Studies have confirmed [29,30] that postoperative use of GnRH-a in EMS patients leads to peri-menopausal symptoms, seriously affecting the quality of life of patients and compliance to continue treatment. Black cohosh preparation or proprietary Chinese medicine (such as *Kuntai* capsule or *Xiangshao* granules) can effectively improve the symptoms of the natural peri-menopausal period, as do sex hormones, but have limited effect on liver and kidney function and blood-lipid metabolism, and have no obvious estrogen-like effects. These plant-based preparations may be a safe and effective choice for patients who require careful use or prohibition of estrogen.

Black cohosh is a plant of the genus *Ranunculaceae* (*Actaea racemose* or *Cimicifuga racemose*), growing in eastern North America, that can effectively relieve the symptoms of peri-menopausal women. The extract of black cohosh has no estrogen or progesterone activity, and it does not belong to the phytoestrogen class of plant substances [31]. The mechanism of action is not clear. It may be a neurotransmitter regulator that acts directly on 5-hydroxytryptamine(5-HT) receptors, or through direct action on μ-opioid receptors in the brains of postmenopausal women, but has no significant effect on serum FSH, LH, estradiol (E2), or prolactin (PRL) [32]. Therefore, black cohosh preparation is also effective on non-physiological peri-menopausal symptoms caused by drugs, and does not antagonize the inhibitory effect of GnRH-a on pituitary gonadotropin secretion. This indicates that black cohosh may be an effective preparation when combined with GnRH-a in the treatment of EMS.

The *Kuntai* capsule, a proprietary Chinese medical preparation, contains six kinds of Traditional Chinese Medicine ingredients, such as *Radix Rehmanniae*, *Coptis chinensis*, *Radix Paeoniae Alba*, *Ejiao*, *Scutellaria baicalensis,* and *Poria cocos*, which are thought to nourish yin and reduce fire, calm nerves and relieve annoyance, regulate yin and yang, and cure both symptoms and root causes. *Kuntai* capsule treatment appears to improve various peri-menopausal symptoms and improve the quality of life of patients [33,34]. However, whether the *Kuntai* capsule is as effective and as safe as tibolone in relieving peri-menopausal symptoms caused by GnRH-a is not clear, and needs to be confirmed by further study.

The *Xiangshao* granule is a compound preparation composed of 10 kinds of traditional Chinese medicine [35]. The study [35] has confirmed that *Xiangshao* granules can relieve the symptoms of peri-menopausal women. However, at present, the relevant studies [36,37] with *Xiangshao* granules have been based on the treatment of healthy, natural menopausal and peri-menopausal women. Study has confirmed that [38] *Xiangshao* granules have no effect on serum hormone levels, and that *Xiangshao* granules have no estrogenic effect on the uterus and vagina. In addition, clinical trials conducted by Wu *et al.* [39]. showed that treatment with *Xiangshao* granules improved the symptoms of the peri-menopausal period, but did not show any estrogenic effect. Therefore, *Xiangshao* granules apparently have no estrogen or progesterone activity, and does not belong to the phytoestrogen class. The main characteristic of Traditional Chinese Medicine prescriptions is the integrated regulation of multi-components, multiple targets, and multiple links. At present, the mechanism of action of the *Xiangshao* granule is considered to be as follows [40]: (1) it regulates γ-aminobutyric acid nerve-conduction pathways. This contributes to sedation, hypnosis, and anti-anxiety; (2) it can regulate the activity of serotonin and has the effects of anti-anxiety, anti-depression, and improving sleep quality; and (3) it inhibits the expression of μ-opioid receptors in the hypothalamus and hippocampus. Treatment with *Xiangshao* granules can relieve the peri-menopausal symptoms of autonomic nervous dysfunction such as hot flashes, night sweats, and anxiety. However, some scholars have speculated that the occurrence of hot flashes in the peri-menopausal period is due to the change of neurotransmitters, which leads to the imbalance of the thermoregulation center. Central monoamine receptors include serotonin receptors (5-HTR), adrenergic receptors (AR), and dopamine receptors (DR). Recent data have suggested that *Xiangshao* granules may act on neurotransmitter pathways to relieve peri-menopausal hot flashes [38]. Both *Xiangshao* granules and estradiol can effectively relieve the symptoms of peri-menopausal period, but whether they play a role through neurotransmitters such as 5-HT needs to be confirmed by further research.

In the past few years, serious attention has been paid to the long-term safety of estrogen and progesterone therapy, especially regarding the impact on breast tissue. A series of clinical and observational studies has shown that such treatments increase the risk of breast cancer [41–43]. Some studies have shown that treatment with *Xiangshao* granules will not lead to adverse effects on breast tissue, yet is still effective for climacteric symptoms [44,45].

6. Summary and Prospect

EMS is an estrogen-dependent disease that is likely to reoccur after surgery. Postoperative use of GnRH-a, a substance that inhibits estrogen synthesis, can effectively inhibit gonadotropin secretion by the anterior pituitary, lead to a significant decrease in ovarian hormone levels, and promote ectopic endometrial atrophy, thereby decreasing the chances of postoperative reoccurrence. Long-term use of

GnRH-a can lead to a secondary peri-menopausal reaction, which is the main reason for patients giving up treatment. Although the symptoms of peri-menopause can be solved by add-back therapy, long-term use of sex hormones may lead to liver-function damage, venous embolism, vascular disease, and an increased risk of endometrial cancer, ovarian cancer, or breast cancer. Therefore, there is a search for effective and safe anti-additive drugs and preparations. Studies have shown that [26,46] black cohosh preparation, *Kuntai* capsule, and *Xiangshao* granules can all relieve the symptoms of natural menopause and the peri-menopausal period, so we can infer that they can also antagonize the peri-menopausal symptoms of EMS patients treated with GnRH-a after surgery. The efficacy, safety, and mechanism of these drugs in antagonizing peri-menopausal symptoms caused by GnRH-a, are not clear, and are worthy of further discussion and study.

7. Conclusions

In treatments using more than 3 courses of GnRH-a, sex-hormone add-back therapy must be used, because the patients will have obvious bone-mass loss, and even bone pain, and this bone-mass loss is often irreversible. Add-back therapy using sex hormones can effectively protect bone, but the effect of a combined-regulation scheme on bone protection is limited, and the mechanism is not clear. Therefore, the current consistent point of view is: GnRH-a treatment within 3 months can be accompanied by the use of a combined-regulation regimen, whereas GnRH-a treatment of more than 3 months requires sex-hormone-based add-back therapy.

Author Contributions

JMC and BRX designed the research study. HMT, QCJ and ZYD wrote and revised manuscripts, proposed methodology and conceptualization. YC, YHW and WLS conducted data collection and analysis. MM, TWX and WWW did formal analysis and investigation. BT, RXS and HZ did clinical medication experience guidance. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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