Int J Clin Exp Med 2016;9(10):19935-19943
www.ijcem.com /ISSN:1940-5901/IJCEM0027833

Original Article

Clinical outcome of various regimens of gonadotropin-releasing hormone analogues after conservative surgery in patients with endometriosis

Wei Liu[1*], Chao Chen[1*], Jun Shi[1], Xing-Xing Zang[2], Ai-Min Zhao[1]

[1]Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200127, China; [2]Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461, USA. [*]Equal contributors.

Received March 9, 2016; Accepted August 20, 2016; Epub October 15, 2016; Published October 30, 2016

Abstract: Objective: To assess the efficacy of three GnRHa therapies after conservative surgery for ovarian endometriosis by analyzing sex hormones, hypo-estrogenic symptoms, quality of life and bone mineral density. Methods: Thirty-six ovarian endometriosis patients with 20 to 48 years old were divided into three groups after conservative surgery according to their own wills. GnRHa conventional dosage regimen group was intramuscularly injected of triptorelin 3.75 mg every 4 weeks. Tibolone 'add-back' therapy group received the same treatment as the conventional group and orally took tibolone tablets 1.25 mg/d from the eighth week. GnRHa extended-interval dosage group received a 4-dose regimen every 6 weeks. The treatment lasted for 24 weeks. The EMs (VAS score), menopausal score, recurrence, menstruation and vaginal bleeding were assessed. The levels in sex hormones, bone metabolism indicators, lumbar spine bone mineral density, CA125 and other parameters were observed. Results: The symptoms including dysmenorrhea, dyspareunia and chronic pelvic pain were relieved in three groups. At 12th and 24th week of GnRHa treatment, the levels of serum sex hormones (FSH, LH and E2) in all groups were decreased compared with the baseline, the modified Kupperman scores in Tibolone 'add-back' group and extended-interval group were lower than those of the conventional group. At the end of the 24th week, T scores and CA125 serum in all groups were decreased compared with the baseline. Conclusions: Tibolone 'add-back' therapy and GnRHa extended-interval regimen had better effects on improving symptoms of perimenopause than GnRHa conventional regimens. Tibolone 'add-back' therapy was more effective in protection of bone density than other treatments.

Keywords: Endometriosis, conservative surgery, gonadotropin-releasing hormone analogues, 'add-back' therapy, tibolone

Introduction

Endometriosis is a common invasive disease with a high recurrence rate in reproductive-age women. Prevalence and incidence rates are reported to be between 8.1 and 3.5 per 1000 women, respectively. The highest prevalence is in women aged 35-44 years old with a rate at 12.8 per 1000 women [1]. In addition, an ENDO study shows that 11% of women have undiagnosed endometriosis at the population [2]. Although conservative surgery is currently the first line treatment of choice for women of reproductive-age with ovarian endometriosis [3], recurrence poses a formidable challenge. The reported recurrence rate is high; 38.4% of patients experienced moderate or severe pain after laparoscopy, and endometriotic lesions were observed by TV-US in 18.4% patients [4]. Adjuvant therapy to surgical treatment has been widely used in clinical settings [5]. Gonadotropin-releasing hormone analogues (GnRHa) are commonly used in the treatment of endometriosis as the primary medical adjuvant therapy to surgical treatment because it decrease recurrence [6], and improves IVF pregnancy rates [7, 8]. GnRHa are currently the most extensively used drugs for endometriosis management; however, adverse effects of treatment with gonadotropin-releasing hormone agonists, such as the loss of bone mineral density and hypoestrogenemia symptoms, have limited the long-term use of GnRHa. Therefore, a number of clinical studies investi-

Table 1. The plan of follow-up

Item	Before surgery	The end of Week 12 of GnRHa treatment	The end of Week 24 of GnRHa treatment	The end of Week 12 after GnRHa treatment	The end of Week 24 after the close of GnRHa treatment
Pain related to EMs menorrhalgia	√			★	√
Pelvic pain	√	√	√	√	√
Perimenopausal symptoms	√	√	√		
Sexual hormone	√	√	√		
CA125	√		√		
Bone metabolism indicators	√	√	√		
Lumbar spine bone mineral density	√	√	√		
Type-B ultrasonic	√	√	√	√*	√*
Menstruation	To record the duration from the GnRHa injection of the last dose to the resumption of menstruation				
Uterine bleeding	To record the information of vaginal bleeding everyday during the GnRHa treatment				

★Evaluated on resumption of menstruation. *If the ultrasound was abnormal, the CA125 was measured at the same time.

Table 2. Baseline data of the patients

Parameter	Conventional dosage regimen group (8)	Tibolone 'add-back' therapy group (10)	Extended-interval group (n=18)
*Age (y)	33.25±7.81	33.5±6.49	35.67±7.07
*Height (m)	1.59±0.04	1.60±0.06	1.57±0.07
*Weight (Kg)	54.72±12.13	56.23±16.37	53.8±15.69
*BMI (kg/m^2)	23.7±3.9	24.1±4.0	24.0±3.8
rAFS score	38±27.77	34.7±11.84	36.33±18.56
*Stage III	6	8	13
*Stage IV	2	2	5
*Half ovarian EMs	4	7	12
*Double ovarian EMs	4	3	6

Note: Values are mean ± SD. **P* values by Student's t-test comparing mean values between study groups were all not statistically significant, P>0.05.

gating hormonal 'add-back' therapy, extended-interval dosing regimens [9], and other treatments have been conducted. However, the efficacy and safety of these therapies is disputed. This study was designed to explore the more safe and effective post-operative GnRHa treatment after conservative surgery for endometriosis by means of observing the effect of three different GnRHa therapies (GnRHa conventional dosage regimen, Tibolone 'add-back' therapy and GnRHa extended-interval regimen), in order to evaluate the impact of these GnRHa therapies on sex hormones, hypoestrogenic symptoms, quality of life and bone mineral density in women with ovarian endometriosis undergoing conservative surgery.

Materials and methods

Patients

Thirty-six 20 to 48 year-old ovarian endometriosis women, who accepted conservative surgery at Department of Obstetrics and Gynecology of the Ren Ji Hospital of Shanghai Jiao Tong University School of Medicine during the period of August 2009 to March 2010, were enrolled to this study. The patients were selected using the following criteria: ① willing to participate in this study voluntarily and signed the informed consent; ② a diagnosis of ovarian endometriosis by pathology; ③ surgically confirmed as having revised American Fertility Society (AFS) stage III and IV endometriosis, ④ had not received any hormonal therapy in the three months preceding this trial; ⑤ no contraindication of Tibolone such as thrombotic disease, pregnancy, hormone-dependent tumor, severe liver disease and so on; and ⑥ no severe cardiac, liver, renal, metabolic disease, or disease of digestive system.

Clinical grouping

The participants were assigned into three groups according to their own wills. The GnRHa conventional dosage regimen group (8 patients) was treated with an injection of 3.75 mg triptorelin (Diphereline, Triptorelin acetate for injection, Beaufour Ipsen Pharmaceutical Co) intramuscularly every 4 weeks for a total of 6 doses. The GnRHa combined with Tibolone 'add-back' therapy group (10 patients) had the same triptorelin regimen as the first group, combined with oral Tibolone tablets (Livial,

Table 3. VAS score of dysmenorrhea before and after treatment

Group (number of dysmenorrhea patients)	VAS score		
	Preoperative	Resumption of menstruation	At week 24, after GnRHa treatment
Conventional dosage regimen group (4)	6.33±1.53◆	0.33±0.58*,◆	0.33±0.58*,★,◆
Tibolone 'add-back' therapy group (6)	4.17±2.64◆	0.17±0.41*,◆	0.5±1.2*,★,◆
Extended-interval group (14)	5±2.37◆	0.25±0.62*,◆	0.33±0.89*,★,◆

Note: Values are presented as mean ± SD. *Compared with the preoperative pain score, the difference has statistical significance; P<0.05. ★Compared with the pain score on resumption of menstruation, differences had no statistical significance; P>0.05. ◆Compared with the pain score over the same period of the three groups, differences had no statistical significance; P>0.05.

Table 4. VAS score of pelvic pain before and after treatment

Group (number of dysmenorrhea patients)	VAS score		
	Preoperative	End of Week 24 of GnRHa treatment	End of Week 24 after GnRHa treatment
Conventional dosage regimen group (4)	4.56±1.67◆	0.31±0.21*,◆	0.33±0.46*,★,◆
Tibolone 'add-back' therapy group (6)	6.78±2.14◆	0.28±0.33*,◆	0.83±0.31*,★,◆
Extended-interval group (14)	5.69±1.75◆	0.43±0.56*,◆	1.21±0.76*,★,◆

Note: Values are presented as mean ± SD. *Compared with the preoperative pain score, differences have statistical significance; P<0.05. ★Compared with the pain score at the end of Week 24 of GnRHa treatment, differences have no statistical significance; P>0.05. ◆Compared with the pain score over the same period for the three groups, differences had no statistical significance; P>0.05.

Tibolone Tablets, Nanjing Organon Pharmaceutical Co), 1.25 mg/d, from the eighth week to the end of week 24. The GnRHa extended-interval dosage group (18 patients) received a 4-dose regimen (3.75 mg triptorelin by intramuscular injection every 6 weeks for a total of 4 doses).

Follow-up

As shown in **Table 1**, all patients continued to follow-up for 12 months after conservative surgery.

1. Pain related to EMs: to assess the degree of pelvic pain and dysmenorrhea and dyspareunia by visual analogue scale VAS. 2. Perimenopausal symptoms were assessed by the modified Kupperman scoring method. 3. Menstruation was recorded the duration from the last GnRHa injection to the resumption of menstruation. 4. Uterine bleeding was recorded every day during the GnRHa treatment. We divided uterine bleeding into three types: no bleeding, spotting, and irregular bleeding. 5. Serum sex hormone, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), and estradiol (E2) were measured by radioimmunity methods. 6. Serum CA125 was measured by radioimmunity methods. 7. Bone metabolism indicators were obtained by determining the level of serum calcium, calcium, phosphonium and alkaline phosphatase by immunochemistry methods. 8. Lumbar spine BMD was obtained by measuring the T score of lumbar spine BMD with dual energy X-ray absorptiometry (DXA; QDR-2000, Hologic, Waltham, MA). 9. The morphology of adnexa uteri was assessed by ultrasonography. 10. Recurrence was diagnosed if the patient had two or more of the following indexes: (1) the presence of menorrhalgia and or pelvic pain in which the VAS score reached or exceeded the preoperative score; (2) the discovery of a pelvic mass and or rectal lacunae tenderness nodules by gynecologic examination; (3) ultrasound showed ovarian endometrioid cysts; and (4) serum CA125 levels raised (>35 U/ml).

Statistical analysis

We analyzed the data using the SAS8.0 package. The data showed normal distribution and homoscedasticity was analyzed by Student's t-test. Numeration data was compared using the fisher's exact test. For all analyses, P<0.05 was considered statistically significant.

Results

Preoperative baseline data of the patients

The data regarding the patient's age, height, and BMI showed no significant difference

Table 5. Modified Kupperman scores before and after treatment

Time	Conventional dosage regimen group (n=8)	Tibolone 'add-back' group (n=10)	Extended-interval group (n=18)
At the end of Week 12 of GnRHa treatment	20.62±5.63	12.70±3.68*	15.05±2.74*,★
At the end of Week 24 of GnRHa treatment	18.75±3.77◆	9.87±3.40*,◆	12.1±3.41*,★,◆

Note: Values are presented as mean ± SD. *Compared with the conventional dosage regimen group, differences had statistical significance; P<0.05. ★Compared with the Tibolone 'add-back' group, differences have no statistical significance; P>0.05. ◆Comparing the end of week 24 treatment with the end of Week 12 treatment, differences have no statistical significance; P>0.05.

Table 6. Hot flashes/sweating scores before and after treatment

Time	Conventional dosage regimen group (n=8)	Tibolone 'add-back' group (n=10)	Extended-interval group (n=18)
At the end of Week 12 of GnRHa treatment	10.50 ±2.98	6.40±2.07*	6.22±3.42*,★
At the end of Week 24 of GnRHa treatment	9.00±3.54	4.8±1.69*,◆	4.66±2.83*,★,◆

Note: Values are presented as mean ± SD. *Compared with the conventional dosage regimen group, differences had statistical significance; P<0.05. ★Compared with the Tibolone 'add-back' group, differences have no statistical significance; P>0.05. ◆Comparing the end of week 24 treatment with the end of Week 12 treatment, differences have no statistical significance; P>0.05.

among the three groups (P>0.05). The mean revised AFS score before medical therapy was 38±27.77 in the GnRHa conventional dosage regimen group, 34.7±11.84 in GnRHa conventional dosage combined with Tibolone 'add-back' therapy group, and 36.33±18.56 in the GnRHa extended-interval dosage group, also with no significant difference (P>0.05). There were no significant differences in rAFS Stages or clinical types (P>0.05) (**Table 2**).

Dysmenorrhea

During the GnRHa treatment and the follow-up, we did not find any new dysmenorrhea patients who did not have preoperative dysmenorrhea. The pain score decreased, and the reduction in the pain score was statistically significant throughout the 24-week treatment period as well as upon resumption of menstruation (P<0.05). The pain score over the same period for each of the three groups was similar (P>0.05) (**Table 3**).

Pelvic pain

In patients who had preoperative pelvic pain, the pain score decreased and the reduction in the pain score was statistically significant throughout the 24-week treatment period and also at the end of Week 24 after the end of the GnRHa treatment (P<0.05). The pain score over the same period for each of the three groups was similar (P>0.05) (**Table 4**). No patients suffered newly developed pelvic pain.

Algopareunia

There was a preoperative algopareunia patient with a VAS pain score of 3 in the GnRHa conventional dosage regimen group. And her symptoms disappeared post-treatment and did not reappear until the end of week 24 after GnRHa treatment. None of the patients had algopareunia in the GnRHa conventional dosage combined with Tibolone 'add-back' therapy group throughout the study. Two patients in the GnRHa extended-interval dosage group had preoperative algopareunia with a mean pain VAS pain score of 2.5±0.5; their algopareunia disappeared post-treatment and did not reappear until the end of week 24 after GnRHa treatment.

Perimenopausal symptoms

Climacteric complaints induced by post-operative GnRH-a injection were evaluated by KMI and hot flashes/sweating scores at 12 and 24 weeks after therapy. The modified Kupperman scores in the Tibolone 'add-back' group and extended-interval group after 12 weeks and 24 weeks of GnRHa treatment were significantly lower than conventional group (*P*<0.05). The modified Kupperman scores of the extended-interval group appeared to be higher than the scores in the Tibolone 'add-back' group

Table 7. Duration until the resumption of menstruation (d)

	Conventional dosage regimen group (n=8)	Tibolone 'add-back' group (n=10)	Extended-interval group (n=18)
Duration to resumption of menstruation (d)	81.21±18.64	78.35±20.34*	76.12±22.84*

Note: Values are presented as mean ± SD. *Compared twice conventional dosage regimen group, the difference has no statistical significance; P>0.05.

Table 8. Uterine bleeding

Group	Weeks 1 to 4		Weeks 5 to 8		Week 8 to the resumption of menstruation	
	Spotting	Irregular bleeding	Spotting	Irregular bleeding	Spotting	Irregular bleeding
Conventional dosage regimen group (n=8)	0	8	2	3	0	0
Tibolone 'add-back' group (n=10)	0	10	3	4	1	0
Extended-interval group (n=18)	0	18	5	7	1	0

Note: the data was analyzed by fisher's exact test. There had no statistically significant difference in the three treatment groups (P>0.05).

over the same period, but without significant difference (*P*>0.05). The modified Kupperman scores for each group at the end of week 12 of GnRHa treatment were lower than the scores at the end of week 24, but the differences were not statistically significant (*P*>0.05) (**Table 5**). As the most important symptom of climacteric complaints, the scores of hot flashes/sweating show the similar characteristics which like the total modified Kupperman scores (**Table 6**).

Menstruation

The mean duration from the injection of the last dose to the resumption of menstruation was similar for the three regimens without statistical significance (P>0.05) (**Table 7**).

Uterine bleeding

All patients displayed temporary irregular uterine bleeding lasting for about 5 to 14 days during the first four weeks after the injection of the first dose. Most of the patients had uterine bleeding again from the 5th week to the 8th week after injection of the first dose. From the 8th week to the resumption of menstruation, spot bleeding was observed, but irregular bleeding obviously diminished. The cases of vaginal bleeding or spotting during the observation had no statistically significant difference in the three groups (P>0.05) (**Table 8**).

Serum sex hormones

The level of serum sex hormones (FSH, LH and E2) in all groups at 12 and 24 weeks of GnRHa treatment declined significantly compared with the baseline (P<0.05). The E2 levels at 12th and 24th week of the three groups were similar (P>0.05) and were maintained below 150 pmol/L from 12 weeks till the end of the trial. The E2 levels over the same period in the conventional dosage regimen group and Tibolone 'add-back' group were similar (P>0.05). The E2 levels of the conventional dosage regimen group at 12th and 24th week of GnRHa treatment seemed to be higher than in the conventional dosage regimen group, but the difference was not statistically significant. Serum sex hormones levels (FSH, LH and E2) for the three groups after 12 weeks of GnRHa treatment showed no statistical differences compared with the levels at the end of week 24 of GnRHa treatment (P>0.05). Serum sex hormone levels (FSH, LH and E2) for the three groups were not significantly different over the same period (P>0.05) (**Table 9**).

Bone metabolism

The level of serum calcium, phosphorus and alkaline phosphatase of each group at the beginning, and after 12 and 24 weeks of GnRHa treatment had no significant difference (P> 0.05) (**Table 10**).

Lumbar spine bone mineral density

At the end of week 24, the lumbar spine bone mineral density T score in all groups decreased significantly compared with the baseline (P<0.05). We analyzed the d score, which indi-

Table 9. The level of serum sex hormones before and after treatment

Groups	Sex hormones	Pretreatment	The end of week 24 of GnRHa treatment	The end of week 24 of GnRHa treatment
Conventional dosage regimen group (n=8)	E2 (pmol/L)	236.75±111.73◆	61.37±27.69*,◆	76.00±27.72*,★,◆
	LH (IU/L)	5.49±3.13◆	1.05±0.82*,◆	1.29±0.56*,★,◆
	FSH (IU/L)	7.78±2.84◆	2.77±1.45*,◆	2.67±1.21*,★,◆
Tibolone 'add-back' group (n=10)	E2 (pmol/L)	261.50±154.27◆	66.74±29.66*,◆	69.10±28.65*,★,◆
	LH (IU/L)	5.08±2.71◆	1.18±1.04*,◆	1.74±1.04*,★,◆
	FSH (IU/L)	10.36±3.65◆	3.50±2.23*,◆	3.28±1.71*,★,◆
Extended-interval group (n=18)	E2 (pmol/L)	221.11±137.02◆	78.41±31.34*,◆	88.88±23.92*,★,◆
	LH (IU/L)	5.50±2.88◆	1.12±0.74*,◆	1.73±1.73*,★,◆
	FSH (IU/L)	9.86±3.09◆	4.90±2.23*,◆	5.14±3.02*,★,◆

Note: Values are presented as mean ± SD. *Compared with the preoperative level, differences have statistical significance; P<0.05. ★Compared with the level at the end of week 12 of GnRHa treatment, differences have no statistical significance; P>0.05. ◆Compared with levels over the same period in the three groups, differences have no statistical significance; P>0.05.

Table 10. Bone metabolism indicators before and after treatment

Groups	Time	Calcium (mmol/l)	Phosphorus (mmol/l)	Alkaline phosphatase (U/L)
Conventional dosage regimen group (n=8)	Pretreatment	2.23±0.06	1.28±0.16	63±14.93
	End of Week 12	2.22±0.05*	1.23±0.23*	64.75±12.26*
	End of Week 24	2.24±0.07*,★	1.25±0.18*,★	62.75±10.23*,★
Tibolone 'add-back' group (n=10)	Pretreatment	2.26±0.08	1.19±0.21	56.2±11.10
	End of Week 12	2.24±0.06*	1.21±0.32*	57.9±10.73*
	End of Week 24	2.26±0.06*,★	1.24±0.19*,★	62.1±10.09*,★
Extended-interval group (n=18)	Pretreatment	2.25±0.06*	1.26±0.17*	61.72±13.75*
	End of Week 12	2.24±0.06*	1.25±0.21*	61.17±12.43*
	End of Week 24	2.25±0.07*,★	1.23±0.12*,★	67±14.70*,★

Note: Values are presented as mean ± SD. *Compared with the preoperative level, differences have no statistical significance; P>0.05. ★Compared with the level at the end of week 12 of GnRHa treatment, differences have no statistical significance; P>0.05.

cated the decrease of T score; the d1 score indicated the difference between pre-treatment and the post-treatment week 12, and the d2 score showed the difference between post-treatment week 12 and post-treatment week 24. The decrease of T scores in the Tibolone 'add-back' group was significantly less than other two groups (P<0.05). Although the data showed that the loss of bone mineral density seemed to be more obvious after the end of week 12, the d1 score seemed to be less than d2, but the difference was not statistically significant (P>0.05). The decrease in T score in the Tibolone 'add-back' group were significantly less than those of the conventional group and extended-interval group during the last 12 weeks of treatment, and the d2 in the Tibolone 'add-back' group was significantly lower than that in the conventional group and extended-interval group, (P<0.05) (**Tables 11**, **12**).

CA125

The serum CA125 level of each group at the end of week 24 decreased significantly compared with baseline (P<0.05) (**Table 13**).

Recurrence

Our study continued to follow-up patients for 6 months after GnRHa treatment; only one patient, in whom a 23 mm×33 mm×34 mm echoless was found in the right adnexa by ultrasound, had a suspected relapse.

Discussion

Effect of three different GnRHa therapies after conservative surgery for ovarian endometriosis

It is recently reported that the mean interval between surgery and symptom recurrence

Table 11. The T score of all groups before and after treatment

Groups	Pretreatment	End of Week 12	End of Week 24
Conventional dosage regimen group (n=8)	0.45±0.77	0.1±0.72	-0.58±0.90*
Tibolone 'add-back' group (n=10)	-0.38±1.45	-0.53±1.43	-0.74±1.42*
Extended-interval group (n=18)	-0.22±1.10	-0.44±1.09	-0.88±1.16*

Note: Values are presented as mean ± SD. *Compared with the preoperative level, differences have statistical significance; P<0.05.

Table 12. Decrease of T score

Decrease of T score	Conventional dosage regimen group (n=8)	Tibolone 'add-back' group (n=10)	Extended-interval group (n=18)
d1= prior to treatment - end of treatment week 12	0.35±0.24	0.15±0.07	0.22±0.14
d2= end of treatment week 12- end of treatment week 24	0.68±0.45◆	0.21±0.19*,◆	0.54±0.18◆

Note: Values are presented as mean ± SD. *Compared with the extended-interval group and Conventional dosage regimen group, the difference has statistical significance; P<0.05. ◆In all groups, the difference between d2 compared with d1 had no statistical significance; P>0.05.

Table 13. Serum CA125 level before and after treatment (mIU/ml)

Groups	Cases	Preoperative	End of week 24 of treatment
Conventional dosage regimen group	8	57.39±12.98	9.34±4.88*
Tibolone 'add-back' group	6	46.28±29.79	12.45±2.14*
Extended-interval group	18	58.37±25.90	11.19±5.81*

Note: Values are presented as mean ± SD. *compared with baseline, differences have statistical significance; P<0.05.

requiring alternative therapy is significantly longer for patients who received postoperative treatment with GnRH agonists (>24 months) than for patients who received placebo (12 months) [6]. Our data revealed that endometriosis associated pain decreased significantly after post-operative GnRHa treatment in all three treatment groups, and that the pain relief could be effectively maintained up to one year postoperative. The visual analogue scale score of the three treatment groups had no significant difference. The serum CA125 level at the end of week 24 decreased significantly compared with the level before surgery. Our data also showed that Tibolone 'add-back' therapy and GnRHa extended-interval regimen did not affect the efficacy of GnRHa as the exact efficacy of pain relief was seen as for the GnRHa conventional dosage regimen. The resumption of menstruation took a mean of 70-80 days after the extended-interval dosing regimen, which is similar to previous reports. Also, there was no significant difference regarding intervals among the three treatment groups. This means that the Tibolone 'add-back' therapy and GnRHa extended-interval regimen did not affect the recovery of ovarian function. With regard to the characteristics of vaginal bleeding or spotting, there were no statistically significant differences in the treatment groups; therefore, we consider that the Tibolone 'add-back' therapy and GnRHa extended-interval regimen do not increase the risk of vaginal bleeding or spotting. A prospective study reported, at one-year follow up visits, that endometriotic lesions were observed by TV-US in 18.4% of patients who accepted the GnRHa treatment after conservative surgery [4]. However, in our study, there was only one patient with a suspected relapse, indicating that the recurrence rate is much less than previous reports. As a result of only including one-year follow up visits whether post-operative treatment with GnRHa after conservative surgery for endometriosis influences the long-term recurrence rates needs further study.

Sex hormone levels and hypoestrogenic symptoms

It is suggested that 120 to 180 pmol/L of effective E2 levels indicate a consistent and satisfactory hypoestrogenised state for endometriosis treatment [10]. Our data showed that the

hormonal profile of E2 significantly reduced during the treatment period and remained well below 150 pmol/L until the 28th week of the study, indicating that if the serum E2 level remains below 110 pmol/L during the GnRH-agonist treatment period, peri-menopausal symptoms could appear. We evaluated the quality of life and symptoms of estrogen deficiency via a modified Kupperman score and found that the modified Kupperman scores in the Tibolone 'add-back' group at 12 weeks and 24 weeks of GnRHa treatment were significantly lower than in the conventional group ($P<0.05$). This suggests that the Tibolone 'add-back' group had more of an advantage in relieving symptoms of estrogen deficiency. We found that the modified Kupperman scores of all groups at 12 and 24 weeks of GnRHa treatment had no significant difference, which was perhaps related to the tolerance of estrogen deficiency. Our study found that the E2 levels over the same period for the extended-interval group and conventional group were similar, but that the extended-interval group had more of an advantage in relieving symptoms of estrogen deficiency than the conventional group. This led to the question what further induces this advantage? We presumed that this symptom was perhaps related to the lower speed of serum E2 level decrease in the extended-interval group, because the appearance and degree of peri-menopausal symptoms are not only determined by the serum E2 level but also by the speed of serum E2 level decrease. Regarding this point, further research is urgently needed.

For a time, people worried whether sex hormone 'add-back' would impact the efficacy of GnRHa. From our data, the E2 level of the Tibolone 'add-back' group was similar to the other two groups over the same period ($P>0.05$), indicating that Tibolone 'add-back' did not increase the level of E2 and did not impact the efficacy of GnRHa. This is related to fact that the internal active modality of Tibolone was not estradiol. Tibolone is a synthetic tissue-specific steroid that shows estrogenic, progestagenic, and androgenic activity. The various effects of Tibolone are tissue-specific; it has an estrogenic effect on the vagina (releases algopareunia and improves the vaginal environment), on bones and on the thermoregulatory centers in the brain (hectic fever). Tibolone also has predominantly progestagenic and anti-estrogenic effects on the breast, and mild androgenic and progestagenic effects on the endometrium.

In view of our results and the physiological functions of Tibolone, we confirmed that although Tibolone 'add-back' therapy did not impact the effective E2 level range of GnRHa and relieved perimenopausal symptoms, it is a more reasonable therapy.

GnRHa treatment and the loss of bone mineral density

Our study data showed that, at the end of week 24, the lumbar spine bone mineral density T scores in all groups decreased significantly compared with the baseline ($P<0.05$). However, at the end of treatment week 12, the T score in all of the groups was similar to the baseline. This indicates that the loss of bone mineral density could be more obvious at the end of week 12. We analyzed the d scores, and although the data showed that d1 was not significantly different compared with d2, the d score showed an increasing tendency. The data also suggest that the loss of bone mineral density could be more obvious after the end of week 12. The decrease of bone mineral density T scores in the Tibolone 'add-back' group was significantly less than conventional group, which showed that although the Tibolone 'add-back' group could not avoid the loss of bone density fully, it had an advantage in decreasing the speed of the loss compared with the other two groups. These results are consistent with previous reports [11]. Although the d1 and d2 of the extended-interval group seemed to be lower than the conventional group, the difference was not significant. This may be caused by the smaller sample size or by the fact that the extended-interval therapy had no protection for bone density. Whether extended-interval therapy confers protection for bone density needs further investigation.

Overall, Tibolone 'add-back' therapy and GnRHa extended-interval regimens had very similar efficacies for endometriosis after conservative surgery; these two therapies did not appear to alter the efficacy of GnRHa, and had better effects with regard to improving symptoms of perimenopause than GnRHa conventional regimens. Tibolone 'add-back' therapy was more

effective for the protection of bone density than GnRHa conventional treatment and the GnRHa extended-interval regimen. The GnRHa extended-interval regimen is convenient and cheap, but whether extended-interval therapy conferred any protection for bone density needs further study.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ai-Min Zhao, Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China. Tel: +86-21-68383802; Fax: +86-21-68383802; E-mail: zamzkh0526@sina.com; Dr. Xing-Xing Zang, Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, NY 10461, USA. E-mail: xxfexf@126.com

References

[1] Abbas S, Ihle P, Köster I, Schubert I. Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. Eur J Obstet Gynecol Reprod Biol 2012; 160: 79-83.

[2] Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, Stanford J, Chen Z, Fujimoto VY, Varner MW, Trumble A, Giudice LC; ENDO Study Working Group. Incidence of endometriosis by study population and diagnostic method: the ENDO Study. Fertil Steril 2011; 96: 360-365.

[3] Giudice LC. Clinical Practice: Endometriosis. N Engl J Med 2010; 362: 2389-2398.

[4] Coccia ME, Rizzello F, Palagiano A, Scarselli G. Long-term follow-up after laparoscopic treatment for endometriosis: multivariate analysis of predictive factors for recurrence of endometriotic lesions and pain. Eur J Obstet Gynecol Reprod Biol 2011; 157: 78-83.

[5] Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, Hummelshoj L, Prentice A, Saridogan E; ESHRE Special Interest Group for Endometriosis and Endometrium Guideline Development Group. ESHRE guidelines for the diagnosis and treatment of endometriosis. Hum Reprod 2005; 20: 2698-2704.

[6] Yap C, Furness S, Farquhar C. Pre- and postoperative medical therapy for endometriosis surgery. Cochrane Database Syst Rev 2004; 3: CD003678.

[7] Vercellini P, Chapron C, De Giorgi O, Consonni D, Frontino G, Crosignani PG. Coagulation or excision of ovarian endometriomas? Am J Obstet Gynecol 2003; 188: 606-610.

[8] Rickes D, Nickel I, Kropf S, Kleinstein J. Increased pregnancy rates after ultralong postoperative therapy with gonadotropin-releasing hormone analogs in patients with endometriosis. Fertil Steril 2002; 78: 757-762.

[9] Kang JL, Wang XX, Nie ML, Huang XH. Efficacy of gonadotropin-releasing hormone agonist and an extended-interval dosing regimen in the treatment of patients with adenomyosis and endometriosis. Gynecol Obstet Invest 2010; 69: 73-77.

[10] Barbieri RL. Hormone treatment of endometriosis: the estrogen threshold hypothesis. Am J Obstet Gynecol 1992; 166: 740-745.

[11] Lindsay PC, Shaw RW, Bennink HJ, Kicovic P. The effect of add-back treatment with tibolone (Livial) on patients treated with the gonadotropin-releasing hormone agonist triptorelin (Decapeptyl). Fertil Steril 1996; 65: 342-348.