ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 8, Issue 2, 2015

ISSN - 0974-2441

Research Article

EFFICACY OF GOSERELIN FOR POST-OPERATIVE TREATMENT IN CHINESE PATIENTS WITH MODERATE TO SEVERE ENDOMETRIOSIS: AN OBSERVATIONAL, MULTICENTRE, OPEN-LABEL, NON-INTERVENTIONAL STUDY

JINGHE LANG[1]*, YINGFANG ZHOU[2], JINHUA LENG[1], JIANHUA ZHENG[3], ZHENG GUAN[4], XIAOLING FANG[5], JUN LIN[6], AI ZHENG[7], DUANDUAN LA[8], SHULAN ZHANG[9], LIGUO MA[10], MEIQING XIE[11], WEN DI[12], HENG CUI[13], BIN LING[14], XIAOYAN XIN[15]

[1]Department of Obstetrics and Gynaecology, Peking Union Medical College Hospital, Beijing, P.R. China. [2]Department of Obstetrics and Gynaecology, Peking University First Hospital, Beijing, P.R. China. [3]Department of Obstetrics and Gynaecology, Harbin Hospital, Harbin Medical University Harbin, P.R. China. [4]Department of Obstetrics and Gynaecology, Chinese PLA General Hospital, Beijing, P.R. China. [5]Department of Obstetrics and Gynaecology, The Second Xiangya Hospital of Central South University, Changsha, P.R. China. [6]Department of Obstetrics and Gynaecology, Women's Hospital School of Medicine, Zhejiang University, Hangzhou, P.R. China. [7]Department of Obstetrics and Gynaecology, West China Second University Hospital, Chengdu, P.R. China. [8]Department of Obstetrics and Gynaecology, Ruijin Hospital, Shanghai Jiaotong University, Shanghai, P.R. China. [9]Department of Obstetrics and Gynaecology, Shengjing Hospital of China Medical University, Shenyang, P.R. China. [10]Department of Obstetrics and Gynaecology, Shenzhen People's Hospital, Shenzhen, P.R. China. [11]Department of Obstetrics and Gynaecology, Sun Yet-Sen Memorial Hospital, Guangzhou, P.R. China. [12]Department of Obstetrics and Gynaecology, Renji hospital, Shanghai Jiaotong University, Shanghai, P.R. China. [13]Department of Obstetrics and Gynaecology, Peking University People's Hospital, Beijing, P.R. China. [14]Department of Obstetrics and Gynaecology, Anhui Provincial Hospital, Hefei, P.R. China. [15]Department of Obstetrics and Gynaecology, Xijing Hospital, Xi'an, P.R. China.
Email: drjinghelang@gmail.com

Received: 11 January 2015, Revised and Accepted: 31 January 2015

ABSTRACT

Objective: The aim was to assess the efficacy of post-operative adjuvant treatment with goserelin acetate for reducing the recurrence of pelvic symptoms and total recurrence rates in Chinese patients with moderate to severe endometriosis.

Methods: This largest non-interventional, observational study enrolled 426 Chinese patients with moderate to severe endometriosis across 15 centers in China. Goserelin acetate depot (3.6 mg) was prescribed as adjuvant post-operative treatment, subcutaneously every 4 weeks till 18 months. The primary efficacy end-point was improvement of pelvic symptom recurrence rate and total recurrence rates (including pelvic symptom and physical findings) up to 18 months post-surgery. Secondary endpoints were pregnancy rate among infertile subjects receiving post-operative goserelin treatment 18 months following the operation; and information on goserelin administration.

Results: The total recurrence rate (8.2%; 95% confidence interval [CI], 5.8-11.3%) and symptom recurrence rate (5.6%; 95% CI, 3.6-8.2%) in Chinese patients with moderate to severe endometriosis was comparatively lower than the previously reported studies. Less than 28% of the patients required add-back therapy to offset the effects of gonadotropin-releasing hormone (GnRH), and indicated that the GnRH agonist was efficacious in the majority of the patients. No serious adverse events were reported during the study.

Conclusion: Goserelin acetate was effective in reducing symptom and total recurrence rate when used post-operatively in Chinese patients with mild to severe endometriosis. The authors therefore offered goserelin acetate as a viable treatment for Chinese patients with moderate to severe endometriosis.

Keywords: Endometriosis, Gonadotropin-releasing hormone, Goserelin acetate, Pelvic symptom recurrence rate, Infertility, Pregnancy rate.

INTRODUCTION

Endometriosis is a frequently encountered gynecological condition typically seen during the reproductive years and is associated with symptoms such as dysmenorrhea, chronic pelvic pain, and infertility. It occurs in 7-10% of the general female population, including premenopausal (50%), infertile (38%) women, and those exhibiting chronic pelvic pain (71-87%). This disorder is scored as minimal, mild, moderate and severe based on appearance and size, by the revised scoring system (1985) of the American Fertility Society (r-AFS) [1].

Treatment of endometriosis-associated symptoms includes both medical and surgical options, with conservative laparoscopic surgery being the treatment of choice for advanced symptomatic endometriosis [2,3]. Currently, the accepted medical therapies for endometriosis include the weak androgen danazol, gonadotropin-releasing hormone analogues (GnRHa), and oral contraceptives, which significantly delay pelvic symptom recurrence and recurrence rate [4,5].

The overall familial recurrence rate is directly related to the stage of the disease, with a 25% and 61.5% recurrence rate in mild and severe forms, respectively, over a 3 years period [6]. Following operations to remove visible deposits, the high recurrence and low pregnancy rates associated with post-surgical treatment of moderate/severe endometriosis are the key concerns of gynecologists.

Though it is estimated that about 30-50% of the patients with endometriosis have some degree of infertility, the relationship between endometriosis and causally related infertility is tenuous at best [7].

Goserelin acetate is a GnRH agonist currently marketed for the treatment of endometriosis in China. Earlier international multicenter studies and global registration trials have demonstrated the efficacy

and safety of goserelin acetate in the treatment of endometriosis [8-11], however; no real life efficacy data in Chinese patients is currently available. This study assessed the efficacy of goserelin acetate as an adjuvant treatment for reducing the recurrence of pelvic symptoms and total recurrence rates when used for up to 18 months post-operatively in Chinese patients.

METHODS

Study design

This was a multicenter, open-label, non-interventional, observational study investigating the efficacy of post-operative treatment with goserelin acetate (Zoladex, AstraZeneca) in patients with moderate to severe endometriosis. The study enrolled 426 subjects across 15 centers in China. Patients who fulfilled all the selection criteria at the first visit were enrolled. The first subject was enrolled on July 1, 2009 and the study were conducted from mid July 2009 to February 2012. The patients' symptom score and pregnancy were recorded consecutively at visit 1, visit 2 (3 months post-operatively), visit 3 (6 months post-operatively), visit 4 (12 months post-operatively), and visit 5 (18 months post-operatively). The definition of last visit was either 18 months post-operation or the time with confirmed disease relapse or pregnancy. During visit 1 through 5, symptom scores were collected and recorded in out-patient medical records. No drug was supplied free of charge from AstraZeneca for this non-interventional study. Any drug that was clinically indicated could be selected and prescribed by the investigator. The duration of treatment ranged from 1 to 6 months depending on the number of vials of goserelin acetate that each patient had been administered, as goserelin acetate was administered every 4 weeks (Fig. 1).

Given the difficulty to measure disease relapse by invasive examination in routine practice, we selected the symptom rating scale to document the presence of relevant symptoms. All patients provided written informed consent. The independent ethics committees at each institution approved the study. The study was done in accordance with the Declaration of Helsinki, the International Conference on Harmonization/Good Clinical Practice, applicable regulatory requirements and AstraZeneca's policy on bioethics.

Study population and setting

Patients were selected based on the following inclusion criteria: Advanced endometriosis confirmed histologically (r-AFS score III-IV) with conservative laparoscopy or laparotomy; indication for goserelin use, and had been prescribed goserelin, irrespective of the inclusion in the study; goserelin prescription within 1 month after operation and provision of written informed consent prior to any study specific procedures. Exclusion criteria included: Hormone treatment within 3 months before recruitment, involvement in the planning and conduct of the study (applies to both AstraZeneca staff and staff at the study site), and previous enrolment in the present study. According to the protocol, patients could discontinue from the study treatment and assessments at any time by their own will or physician's judgment. Patients were prescribed with 3.6 mg depot of goserelin acetate as adjuvant post-operative treatment within 1 month after operation, which was determined according to physician's judgment, irrespective of the inclusion in the study.

Efficacy assessments

The primary efficacy end-point was improvement of pelvic symptom recurrence rate and total recurrence rates (including pelvic symptom and physical findings) up to 18 months post-surgery. Total recurrence was defined as the occurrence of one or more of the following: (i) Recurrence of pelvic pain with severity equal to or greater than self-reported pain before surgery; (ii) diagnosis of endometriosis (cyst diameter no <3 cm after two ultrasound examinations ≥4 weeks apart); (iii) clinical findings suggestive of recurrence (pelvic masses, pelvic tenderness, or nodulations at pelvic examination).

Secondary endpoints included: Pregnancy rate among infertile subjects receiving post-operative goserelin treatment 18 months following operation; and information on goserelin administration.

Sample size calculation

Results were presented as symptom rates and their 95% confidence interval (CI). Assuming that recurrence rates would be approximately 15%, 320 evaluable subjects would be required and hence that the one-sided width of the 95% CI would be ≤3.9%. The one-sided boundary was calculated by the formula $1.96\times\sqrt{\frac{\Pi(1-\Pi)}{n}}=3.9\%$. The total enrolled patients would need to be 400 assuming a 20% dropout rate. If the recurrence rate were lower than 15%, the required sample size would be even smaller to achieve the same accuracy.

Statistical analyses

The primary and secondary endpoint rates and associated 2-sided 95% CI were summarized for both the full analysis set (FAS) and per protocol set (PPS) patients. No test was performed and efficacy variables presented with the number and percentage of patients who had a confirmed recurrence of symptoms. The administration of goserelin acetate and the information of add-back therapy were summarized descriptively.

RESULTS

Population, disposition, and baseline characteristics

The study enrolled 426 patients (FAS, n=414; PPS, n=410). The demographics and baseline characteristics of patients in FAS are shown in Table 1.

With regard to endometriosis severity score, 213 patients (51.4%) were r-AFS III and 201 patients (48.6%) were r-AFS IV, and were all in the category of moderate to severe endometriosis. The mean of baseline visual analog scale (VAS) score was 4.8 (range 0-10). Most of the FAS subjects suffered from the obvious pain at the start of the study.

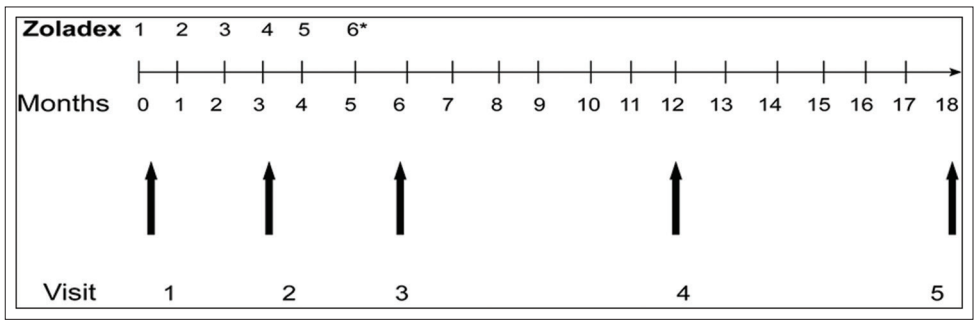

Fig. 1: Duration of goserelin acetate depot (Zoladex) treatment, *Goserelin acetate depot (Zoladex) 3.6 mg, administered subcutaneously every 4 weeks for 3-6 months

Primary and secondary efficacy outcomes

The primary endpoints, the symptom recurrence rate, and the total recurrence rate at the last visit are summarized for both FAS and PPS patients in Table 2.

Following 18 months post-surgery, 34 cases of endometriosis recurrence were reported (8.2%) among FAS patients. Among these patients, 23 patients (5.6%) had confirmed pelvic pain symptoms. Similar rates were reported between PPS and FAS subjects. Changes in VAS from baseline for each visit are summarized in Table 3.

Increasing numbers of discontinued patients during the study corresponded with an increasing number of missing VAS scores. The "last visit" referred to visit 5 or the last visit at which the patient discontinued, and, therefore, there were no missing VAS scores on the last visit. In terms of secondary endpoints, pregnancy rates classified by infertility history and desire for pregnancy are summarized in Table 4.

Table 1: Demographics and baseline characteristics (FAS)

Characteristics	N=414
Age (years)	
Mean (SD)	32.5 (6.27)
Median	32.0
Range	19~53
Weight (kg)	
Mean (SD)	55.8 (8.34)
Range	39~93
Height (cm)	
Mean (SD)	161.7 (4.60)
Range	149~175
BMI (kg/m^2)	
Mean (SD)	21.35 (3.014)
Range	14.7~36.5
Heart rate (beats/min)	
Mean (SD)	77.4 (7.79)
Range	60~115
Pregnancy desire (%)	
No	248 (59.9)
Yes	166 (40.1)
Total	414 (100.0)
Assisted reproductive technology planned	
No	409 (98.8)
Yes	5 (1.2)
Total	414 (100.0)
r-AFS score of endometriosis (n [%] of subjects)	
III	213 (51.4)
IV	201 (48.6)
Infertility history (n [%] of subjects)	
No	351 (84.8)
Yes	63 (15.2)
VAS score	
Mean (SD)	4.8 (3.00)
Min~Max	0~10

FAS: Full analysis set, BMI: Body mass index, r-AFS: Revised-American Fertility Society, VAS: Visual analogue scale, SD: Standard deviation

Table 2: Symptom recurrence rate and total recurrence rate at the last visit (FAS/PPS)

Condition	FAS (N=414)		PPS (N=410)	
	n (%)	95%CI	n (%)	95%CI
Pelvic symptom recurrence rate (n [%] of subjects)	23 (5.6)	3.6, 8.2	23 (5.6)	3.6, 8.3
Total recurrence rate (n [%] of subjects)	34 (8.2)	5.8, 11.3	34 (8.3)	5.8, 11.4

Percentages are calculated with number of non-missing cases being the denominator. All the 414 patients in FAS and 410 patients in PPS have their pelvic symptom recurrence and endometriosis recurrence evaluated. FAS: Full analysis set, PPS: Per protocol set, CI: Confidence interval

Patients were categorized into four subgroups based on their infertility history and desire for pregnancy in the case record form. The highest pregnancy rate of 33.3% was observed in the subgroup consisting of patients with both a history of infertility and desire for pregnancy. Several aspects of goserelin acetate administration were reported. The administration of goserelin acetate in association with the menstrual cycle and the total dose used are both presented descriptively in Table 5.

The number of patients was slightly higher when administered goserelin acetate based on their menstrual cycle than those who were not. Most of the patients (96.9% of FAS) were administered no <3 vials

Table 3: Summary of VAS scores by visit (FAS/PPS)

Visit	Data set			
	FAS (N=414)		PPS (N=410)	
	Value	Change from baseline	Value	Change from baseline
Baseline				
N (Nmiss)	414 (0)		410 (0)	
Mean (SD)	4.8 (3.00)		4.8 (3.00)	
Range	0, 10		0, 10	
Visit 2				
N (Nmiss)	413 (1)	413 (1)	409 (1)	409 (1)
Mean (SD)	0.7 (1.38)	−4.1 (2.94)	0.7 (1.39)	−4.1 (2.94)
Range	0, 7	−10, 1	0, 7	−10, 1
Visit 3				
N (Nmiss)	404 (10)	404 (10)	402 (8)	402 (8)
Mean (SD)	0.7 (1.38)	−4.1 (2.84)	0.7 (1.38)	−4.1 (2.85)
Range	0, 8	−10, 2	0, 8	−10, 2
Visit 4				
N (Nmiss)	375 (39)	375 (39)	373 (37)	373 (37)
Mean (SD)	0.8 (1.58)	−4.0 (2.86)	0.8 (1.58)	−3.9 (2.85)
Range	0, 10	−10, 4	0, 10	−10, 4
Visit 5				
N (Nmiss)	343 (71)	343 (71)	339 (71)	339 (71)
Mean (SD)	0.8 (1.45)	−4.0 (2.84)	0.8 (1.45)	−4.0 (2.84)
Range	0, 10	−10, 6	0, 10	−10, 6
Last visit				
N (Nmiss)	414 (0)	414 (0)	410 (0)	410 (0)
Mean (SD)	0.9 (1.71)	−3.9 (2.97)	0.9 (1.72)	−3.9 (2.97)
Range	0, 10	−10, 6	0, 10	−10, 6

N (Nmiss): N indicates non-missing cases of the respective parameter, and Nmiss indicates missing cases: the sum of both is the number of patients in the analysis set. SD: Standard deviation, FAS: Full analysis set, PPS: Per protocol set, VAS: Visual analog scale

Table 4: Pregnancy rates at last visit (FAS/PPS)

Pregnancy rates	FAS (N=414)		PPS (N=410)	
	n (%)	95% CI	n (%)	95% CI
Pregnancy rate[1] (n [%] of subjects)	18 (33.3)	21.1, 47.5	18 (33.3)	21.1, 47.5
Pregnancy rate[2] (n [%] of subjects)	1 (11.1)	0.3, 48.2	1 (11.1)	0.3, 48.2
Pregnancy rate[3] (n [%] of subjects)	26 (23.2)	15.8, 32.1	26 (23.4)	15.9, 32.4
Pregnancy rate[4] (n [%] of subjects)	4 (1.7)	0.5, 4.2	4 (1.7)	0.5, 4.3

[1]Patients with infertility history and with desire for pregnancy, the denominators of FAS and PPS are both 54; [2]Patients with infertility history and without desire for pregnancy, the denominators of FAS and PPS are both 9; [3]Patients without infertility history and with desire for pregnancy, the denominator of FAS is 112 and the denominator of PPS is 111; [4]Patients without infertility history and without desire for pregnancy, the denominator of FAS is 239 and the denominator of PPS is 236. Every patient in FAS and PPS has pregnant status at the last visit. FAS: Full analysis set, PPS: Per protocol set, CI: Confidence interval

of goserelin acetate. A total of 114 patients in the FAS (27.5%) received add-back treatments. The majority of patients (n=114, 76.3%) did not receive add-back treatment concomitantly with goserelin acetate. Add-back treatments in both FAS and PPS groups are presented in Table 6.

Safety of goserelin acetate was not evaluated in this study. No SAE was reported during the study period.

Safety outcome

In this study, no SAE was reported during the study phase.

DISCUSSION

Endometriosis is defined as the presence of endometrial-like tissue outside the uterus, which induces a chronic, inflammatory reaction [12]. This gynecological medical condition is increasingly common in women of reproductive age [13]. The main clinical symptoms of endometriosis are severe dysmenorrhea, deep dyspareunia, chronic pelvic pain, ovulation pain, cyclical or perimenstrual symptoms (bowel or bladder associated) with or without abnormal bleeding and infertility (30-50% patients with endometriosis) [12]. Conservative surgery at laparoscopy or laparotomy is frequently the treatment of choice for symptomatic endometriosis, especially in advanced forms [5]. However, this approach does not seem to be highly effective in preventing recurrence of the disease. Hence, in this context, the use of a short course of post-surgical estrogen-lowering medical therapy to increase the efficacy has been suggested [14]. GnRHa is the most effective medical therapy for endometriosis [15].

A study conducted among 225 Chinese patients with severe endometriosis who underwent laparoscopic surgery for severe endometriosis demonstrated that the endometriosis recurrence rate after 2 years from the laparoscopic surgery was approximately 10.3% following goserelin treatment compared with the treatment with gestrinone (23.4%), danazol (24.1%), and no medication (42.2%) [16].

The current study demonstrated a lower recurrence rate of endometriosis (8.2%; 95% CI, 5.8-11.3%) compared with previous studies. Similarly, pelvic symptom recurrence rate was also lower than previously reported (5.6%; 95% CI 3.6-8.2%) [5,14,16,18]. The VAS score at visit 2 decreased significantly by 85% from baseline (4.8-0.7). The mean VAS score remained slightly above 0 and the median was 0 for all the following visits during the study. This suggested that most patients were free of pelvic pain after visit 2 and that goserelin acetate had a significant effect on pelvic pain control.

Table 5: Administration of goserelin (FAS/PPS)

	FAS (N=414)	PPS (N=410)
Medication by menstrual cycle (n [%] of subjects)		
No	190 (45.9)	188 (45.9)
Yes	224 (54.1)	222 (54.1)
Total dose (vials)		
Mean (SD)	4.0 (1.28)	4.0 (1.28)
Total dose (n [%] of subjects)		
1	5 (1.2)	5 (1.2)
2	8 (1.9)	8 (2.0)
3	195 (47.1)	193 (47.1)
4	93 (22.5)	92 (22.4)
5	16 (3.9)	15 (3.7)
6	97 (23.4)	97 (23.7)

SD: Standard deviation, FAS: Full analysis set, PPS: Per protocol set

Table 6: Summary of add-back therapy

	FAS (N=414)	PPS (N=410)
Proportion of add-back treatment (n [%] of subjects)		
No	300 (72.5)	297 (72.4)
Yes	114 (27.5)	113 (27.6)
Concomitant with goserelin (n [%] of subjects)		
No	87 (76.3)	86 (76.1)
Yes	27 (23.7)	27 (23.9)
Total	114 (100.0)	113 (100.0)

FAS: Full analysis set, PPS: Per protocol set

The pregnancy rate of the infertile patients who underwent surgery and post-operative GnRHa was 11.6%, 33%, and 46.2% in some studies in Western populations [5,14,18]. The present study demonstrated that among 54 infertile patients treated, 18 patients conceived with a corresponding pregnancy rate of 33.3% (95% CI, 21.1-47.5%), which was similar to that of a previous report.

Supplementing GnRH agonist treatment with add-back therapy efficiently alleviates the side-effects of GnRHa treatment without reducing its efficacy in terms of controlling endometriosis-related symptoms and preventing endometriotic lesion recurrence. Among the 414 patients in FAS population, 114 (27.5%) received add-back therapy, which indicates that GnRHa treatment was efficacious in the majority of the patients. Of the 114 patients, only 27 (23.7%) patients received the add-back therapy concomitantly with goserelin. Slightly greater than one-half of the patients (n=224, 54.1%) received goserelin acetate by menstrual cycle. An average of four doses of goserelin acetate was administered to the patients in this study, indicating that the mean duration of goserelin treatment was 4 months. Nearly ½ (49.8%) of patients received more than four doses of goserelin.

To our knowledge, this is one of the largest non-interventional, observational studies conducted in China, evaluating the efficacy of goserelin acetate as a post-operative treatment for moderate to severe endometriosis in normal clinical practice. Given the difficulty to measure disease relapse by invasive examination in routine practice, we selected a symptom rating scale to document the presence of relevant symptoms. The large number of women enrolled from gynecology departments at 15 medical centers in China may have caused differences in patients' symptom score though the study procedures were described in detail in the protocol. Increasing numbers of discontinued patients during the study corresponded with an increasing number of missing VAS scores.

CONCLUSION

This study examined the real life efficacy of goserelin acetate, and was found to be effective in reducing symptom and total recurrence rate when used post-operatively in Chinese patients with mild to severe endometriosis. Goserelin acetate therapy after invasive treatment revealed that the total recurrence rates and symptom recurrence rates up to 18 months post-operation were lower than those previously reported, and pregnancy rates were comparable to the previously published results. The authors therefore offered goserelin acetate as a viable treatment for Chinese patients with moderate to severe endometriosis.

ACKNOWLEDGMENTS AND DECLARATION OF INTERESTS

This study was funded by AstraZeneca. We are grateful to the patients, their families and the investigators for their participation in this study. The authors acknowledge Amit Bhat and Sandeep Gantotti, Indegene Lifesystems Pvt., Ltd. (Bangalore, India) for providing the necessary writing assistance and editorial support towards the development of the manuscript. The authors have no conflicts of interest to disclose. All authors planned the study and contributed to the interpretation of the data, revisions and gave input at all stages of the study. All authors have approved the final version of the manuscript.

REFERENCES

1. Ozawa Y, Murakami T, Terada Y, Yaegashi N, Okamura K, Kuriyama S, *et al*. Management of the pain associated with endometriosis: an update of the painful problems. Tohoku J Exp Med 2006;210(3):175-88.

2. Crosignani PG, Vercellini P. Conservative surgery for severe endometriosis: should laparotomy be abandoned definitively? Hum Reprod 1995;10(9):2412-8.
3. Crosignani PG, Vercellini P, Biffignandi F, Costantini W, Cortesi I, Imparato E. Laparoscopy versus laparotomy in conservative surgical treatment for severe endometriosis. Fertil Steril 1996;66(5):706-11.
4. Bergqvist A, Bergh T, Hogström L, Mattsson S, Nordenskjöld F, Rasmussen C. Effects of triptorelin versus placebo on the symptoms of endometriosis. Fertil Steril 1998;69(4):702-8.
5. Vercellini P, Crosignani PG, Fadini R, Radici E, Belloni C, Sismondi P. A gonadotrophin-releasing hormone agonist compared with expectant management after conservative surgery for symptomatic endometriosis. Br J Obstet Gynaecol 1999;106(7):672-7.
6. Henzl MR, Corson SL, Moghissi K, Buttram VC, Berqvist C, Jacobson J. Administration of nasal nafarelin as compared with oral danazol for endometriosis. A multicenter double-blind comparative clinical trial. N Engl J Med 1988;318(8):485-9.
7. Telimaa S, Apter D, Reinilä M, Rönnberg L, Kauppila A. Placebo-controlled comparison of hormonal and biochemical effects of danazol and high-dose medroxyprogesterone acetate. Eur J Obstet Gynecol Reprod Biol 1990;36(1-2):97-105.
8. Winkel CA. Evaluation and management of women with endometriosis. Obstet Gynecol 2003;102(2):397-408.
9. Reichel RP, Schweppe KW. Goserelin (Zoladex) depot in the treatment of endometriosis. Zoladex Endometriosis Study Group. Fertil Steril 1992;57(6):1197-202.
10. Shaw RW. An open randomized comparative study of the effect of goserelin depot and danazol in the treatment of endometriosis. Fertil Steril 1992;58:265-72.
11. Rock JA, Truglia JA, Caplan RJ. Zoladex (goserelin acetate implant) in the treatment of endometriosis: a randomized comparison with danazol. The Zoladex Endometriosis Study Group. Obstet Gynecol 1993;82(2):198-205.
12. Kennedy S, Bergqvist A, Chapron C, D'Hooghe T, Dunselman G, Greb R, *et al.* ESHRE guideline for the diagnosis and treatment of endometriosis. Hum Reprod 2005;20(10):2698-704.
13. Lang J. The guideline of diagnosis and treatment of endometriosis. Chin J Obstet Gynecol 2007;42:645-8.
14. Busacca M, Somigliana E, Bianchi S, De Marinis S, Calia C, Candiani M, *et al.* Post-operative GnRH analogue treatment after conservative surgery for symptomatic endometriosis stage III-IV: a randomized controlled trial. Hum Reprod 2001;16(11):2399-402.
15. Zhou Y. The guideline of diagnosis and treatment of endometriosis. Prog Obstet Gynecol 2006;15:161-72.
16. Xiong Y, Zhu B, Ling Y. The guideline of diagnosis and treatment of endometriosis. Prog Obstet Gynecol 2005;14:492-4.
17. Shen X, Feng Z. The efficacy of laparoscopy in combination with medical treatment on endometriosis. Jiangxi Pharmacol 2006;42:586-8.
18. Loverro G, Carriero C, Rossi AC, Putignano G, Nicolardi V, Selvaggi L. A randomized study comparing triptorelin or expectant management following conservative laparoscopic surgery for symptomatic stage III-IV endometriosis. Eur J Obstet Gynecol Reprod Biol 2008;136(2):194-8.