

Treatment of Endometriosis and Chronic Pelvic Pain with Letrozole and Norethindrone Acetate

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Abstract

Background: Endometriosis is encountered in 7-10% of actively menstruating women, with a suspected prevalence as high as 22% in asymptomatic women. It is an important cause of chronic pelvic pain. The aim of this study was to evaluate the efficacy and safety of letrozole in combination with norethindrone acetate and calcium in the management of endometriosis associated pelvic pain.

Methods: Prospective non-randomized open label study was carried out including 20 patients with endometriosis related pelvic pain that was refractory to previous treatments.

Result: In all 14 patients completed the study. All patients showed significant improvement of pain scores and revealed significant improvement of features of endometriosis on being given letrozole in combination with norethindrone acetate and calcium.

Conclusion: Letrozole is an effective drug for treatment of endometriosis.

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Key Words : Endometriosis; Letrozole

Introduction

Endometriosis is a chronic inflammatory disease that responds to steroidal manipulation. It is characterized by the presence of fragments of functional endometrial glands and stroma outside the uterine cavity. The pelvic cavity is the most common site for endometriosis. The disorder is encountered in 7-10% of actively menstruating women, with a suspected prevalence as high as 22% in asymptomatic women, 60% in women with dysmenorrhoea and 30% in women with subfertility. It is an important cause of chronic pelvic pain. The lesions of endometriosis may range from microscopic endometriosis implants to large ovarian endometriomas and deep peritoneal lesions.

Medical and surgical therapy is used for endometriosis and both are usually complimentary to each other. Surgery done by the endoscopic route is the preferred choice among surgical methods. The basis of the medical treatment is to prevent the stimulation of the endometrial tissue by the suppression of the estrogen secretion or antagonising the estrogen action. This is achieved by the drugs that suppress the ovarian steroids and induce a hypo-estrogenic state that causes atrophy of the ectopic endometrium. Gonadotrophin-releasing hormone (GnRH) analogues, danazol, progestogens and estrogen progestin combinations have all proven effective in relieving pain and reducing endometriosis implants.

Letrozole is a new group of drug - aromatase inhibitor which prevents the secretion of estrogen and prevents the activation of the endometriosis implants. As the drug brings a state of hypo-estrogenism in these women, calcium is added as an add-back therapy along with letrozole. Norethistrone is used as studies have shown it to increase apoptosis locally in endometrial implants and supplement the efficacy of letrozole. The objective of this study was to evaluate the efficacy and safety of letrozole in combination with norethindrone acetate and calcium in the management of endometriosis associated pelvic pain.

Material and Methods

Prospective non-randomized open label study was carried out in a tertiary care centre. The study included 20 patients with endometriosis related pelvic pain that was refractory to previous treatments or had a recurrence after the treatment. The inclusion criteria included:

1. Reproductive age women
2. Cyclic predictable menses
3. Endometriosis documented by laparoscopy
4. Pelvic pain persisting or recurring after one or more previous treatment
5. Chronic pelvic pain or dysmenorrhoea experienced for at least two weeks in last three months.

The exclusion criteria were:

1. Undiagnosed vaginal bleeding

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2. Endometriomas >2cm
3. Sensitivity to letrozole
4. Seizure disorder
5. Pregnancy
6. Pulmonary, cardiac, renal or hepatic disease

All the selected patients were given a 30 days period for hormonal washout before enrolling in the study. An ultrasonography of the pelvis was done to see the presence of ovarian cysts at start, three and six months. Hormonal profile of luteinizing hormone (LH), follicle stimulating hormone (FSH), estradiol (E2) and testosterone levels were done on day2/day3 before initiation of the therapy and completion of the therapy. The patients underwent diagnostic laparoscopy to determine the severity of the endometriosis. No ablative surgery was performed at this time. The scoring of the severity of the disease was done as per the American Society of Reproductive Medicine (ASRM). These women were given tab letrozole 2.5 mg, tab norethindrone acetate 2.5mg and 1000 mg of calcium carbonate per day for six months starting from 3rd day of menses. All the patients recorded daily pain scores 30 days before starting the therapy, during the treatment and four weeks after the completion of the therapy. They were told to record vaginal bleeding, spotting, length, duration and severity of pain during treatment. The patients were also told to record any side effects. The patients also underwent complete blood count, renal and hepatic function tests monthly. Repeat laparoscopy was also done by the same group of surgeons 6-8 weeks after completion of the therapy. The patients were staged as per the ASRM scoring. Surgical intervention, if required, was done at this time.

The analysis of the data was done to compare the pain scores and laparoscopic scores using Microsoft Excel 2007.

Results

A total of 20 patients were recruited in the study and first look laparoscopy was done for all of them. Only 14 patients completed the study. Two patients were lost after two months of treatment protocol, three patients were lost after five months and one patient did not consent for the second look laparoscopy.

Table 1
Details of the patients

Parameter	Value
Age (years)	28.9 (24-40)
Gravidity	
Nullipara	16
Prior pregnancy	4
Prior therapy	
Oral contraceptive pills	17
Leuprolide	7
Laparoscopic ablation	3
Danazol	9
Progestogens	15
Presacral neurectomy	Nil

Table 1 summarises the demographic characteristics of the patients included in the study. All the patients were in the reproductive age group and the mean age was 28.9 years. All the patients had not shown any response to the prior therapy. Four patients had history of prior pregnancy and three had living issues.

The analysis of the hormonal profile in the pre and post treatment showed no significant changes in the levels of LH, FSH and E2. The ultrasound done at three and six months did not show any evidence of functional ovarian cysts during the study.

All the patients completing the study showed an improvement in the ASRM score of the disease and reduction in the severity of the pain.

Discussion

Endometriosis is considered an important cause of

Table 2
Pain scoring in patients

Patient	Pre-treatment score	Post-treatment score
1	9	2
2	8	2
3	5	1
4	7	1
5	6	2
6	8	1
7	3	<1
8	4	4
9	8	<1
10	7	2
11	6	6
12	5	2
13	4	2
14	6	<1
Mean	6.14	1.89
SD	1.79	1.5

Table 3
American Society of Reproductive Medicine (ASRM) scoring of the patients

Patient	Pre-treatment score	Post-treatment score
1	56	10
2	22	6
3	38	4
4	46	6
5	68	7
6	80	14
7	26	8
8	60	10
9	58	24
10	56	6
11	62	4
12	48	8
13	50	10
14	30	12
Mean	50	8.57
SD	16.47	5.33

chronic pelvic pain [1,2,8-10]. Despite its high prevalence, controversy still exists regarding true association between extent of endometriosis and severity of the symptoms. Despite the effectiveness of available treatments, novel therapeutic strategies may eliminate endometriosis lesions when present and prevent its recurrence after surgical treatment [3,5-7]. The blockade of aromatase activity in the endometriosis lesions with the aromatase inhibitor represents a new step in the medical treatment of endometriosis. Preliminary clinical studies have demonstrated the efficacy of the 3rd generation non-steroidal aromatase inhibitors i.e. letrozole, in reducing the intensity of pain symptoms associated with endometriosis [2,3,5,12].

In the last few years, our understanding of the pathogenesis of endometriosis at the cellular and molecular levels has improved significantly. Aromatase overexpression has been detected in the endometriosis tissue. Aromatase is responsible for the conversion of C19 androgens to estrogen in several human tissues. Aromatase activity gives rise to local estrogen biosynthesis, which, in turn stimulates prostaglandin E2 production by up regulation of cyclooxygenase, thus establishing a positive feedback cycle. Another abnormality detected in endometriosis is the deficiency in 17 β -hydroxysteroid dehydrogenase type II expression, impairs the inactivation of estradiol to estrone. In contrast to the eutopic endometrium, these molecular aberrations collectively favour accumulation of increasing amount of local estradiol and prostaglandin E2 in endometriosis. This may give us the opportunity to use new, specific agents for treatment of this disorder [4,5,8].

Letrozole, a 3rd generation aromatase inhibitor, is a highly potent and specific suppressors of estrogen production locally and systemically. It has been used in a variety of indications from breast cancer to ovulation induction in infertility [2,3,5]. The literature has very few studies similar to this, where the effect of the drug has been evaluated in the pre and post-treatment endoscopy. The drug is used along with progesterone, calcium and vitamin D supplements in endometriosis as add back therapy to prevent the potential risk of bone loss and osteopenia. The results of the study have been promising but require detailed evaluation for further recommendation as regular treatment of endometriosis related pain.

In conclusion, letrozole is an effective drug for treatment of endometriosis. The drug has not shown any significant side effects during its use for a period of six months.

Conflicts of interest

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