Treatment strategies for pelvic pain associated with adenomyosis

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Abstract

Objective: To observe the effects of levonorgestrel-releasing intrauterine system (LNG-IUS) in treatment of chronic pelvic pain associated with adenomyosis (AM) and in prevention of its recurrence.

Methods: A prospective continuing study including 180 patients with chronic pelvic pain associated with AM who received insertion of LNG-IUS who were divided into three groups depending on the pain severity. The visual analog scale (VAS) was used for pain assessment before and during the treatment and transvaginal ultrasonic measurement of the uterine size, while various side effects, were observed and recorded.

Results: After placement of LNG-IUS, scores of pain and ratio of severe pelvic pain decreased significantly compared with baselines ($p<0.01$), the scores of VAS were $9.0 \pm 0.8$, $6.5 \pm 2.8$, $4.3 \pm 1.8$, $3.3 \pm 2.2$, $2.2 \pm 2.1$, $2.2 \pm 1.8$, $1.4 \pm 1.6$ and $1.3 \pm 1.3$ at 0, 3, 6 and 12 months, respectively. During 12 months after placement of LNG-IUS, scores of pain had improved significantly compared with preceding period ($p<0.01$). We found no universal dependent factors predicting improvement of pain, which was neither relevant with simultaneous changes of menstruation patterns nor with adverse effects ($p>0.005$).

Conclusion: The obtained results allowed to confirm the possibility of using LNG-IUS in the treatment of pelvic pain syndrome associated with AM, particularly with mild and moderately severe pelvic pain syndrome. This is a cost effective, reversible and long-term treatment for women with pelvic pain associated with AM, which reduces the need for surgical interventions.

Introduction

Adenomyosis (AM) is a widespread disease that affects women of the reproductive age [1]. This is a gynecological disorder characterized by a benign invasion of ectopic endometrium tissue within the wall of the uterus with the adjacent smooth muscle hyperplasia [2]. But, today the definition of AM is characterized by the presence of heterotopic endometrial glands and stroma within the myometrium, >2.5 mm in depth in the myometrium or more than one microscopic field at 10 times magnification from the endometrium–myometrium junction and a variable degree of adjacent myometrial hyperplasia, causing globular and cystic enlargement of the myometrium, with some cysts filled with extravasated, hemolyzed red blood cells, and siderophages. The etiology is unclear, but as risk factors, in addition to hereditary ones, include uterine trauma during the delivery or abortion, chronic endometritis and hyperestrogenemia [3]. In various sources, its prevalence is estimated from 5 to 70%, but it is difficult to be precisely determined for many reasons. In one third of the cases, AM is an asymptomatic disease and consequently can be occasionally diagnosed by pelvic ultrasound or it is found in hysterectomy specimens performed for other medical reasons. In these cases, diagnosis can be also mistaken from 10 to 90% among pathologists if histological criteria are not strictly followed. AM does not present pathognomonic clinical features: enlarged uterus, dysmenorrhea (30%) and menorrhagia (50%) can be associated with other diseases [1].

Chronic pelvic pain has recently been defined as “chronic or persistent pain perceived in structures related to the pelvis of women. It is often associated with negative cognitive, behavioural, sexual and emotional consequences as well as with symptoms suggestive of lower urinary tract, sexual, bowel, pelvic floor or gynaecological dysfunction”. Despite this definition acknowledging that the patient and clinician localize the pain as being perceived in the specified anatomical area, the conscious experience of pain is the result of co-ordinated activity within the central nervous system (CNS). If the focus is shifted away from the pelvis and onto the CNS, it can be seen that women with CPP do exhibit central changes analogous to those observed in other chronic pain conditions.

It is an important cause of chronic pelvic pains, dysmenorrhea and heavy menstrual bleeding (HMB), which occur in ~65% of women with AM and can result in a poor quality of life [4].
Traditionally, the diagnosis of AM was based on clinical findings and pathologic confirmation after hysterectomy. However, transvaginal ultrasonography (TVS) and magnetic resonance imaging have shown to be accurate, noninvasive methods for diagnosis [5].

Hysterectomy is a ‘‘gold standard’’ and definitive therapy for uterine AM associated with pelvic pain, and many cases of AM have been diagnosed by pathological review retrospectively. As such, the diagnosis of AM is difficult, and this subsequently results in difficulty in the management of these patients, particularly those who are symptomatic but have a strong desire to preserve their uterus. The use of uterine-sparing surgery in the management of uterine AM still remain controversial, however, some data support its feasibility. This is why conservative treatment is still needed in the group of patients with pelvic pain syndrome that requires preservation of fertility and improvement of quality of life. However, studies focusing on the topic of medical treatment for AM are rare.

Medical treatment for AM always follows the principles of the management of endometriosis, which are usually aimed at reducing the production of endogenous estrogen or inducing endometrial differentiation with progestins. Clinical evidence points to the clear and deleterious effect of uninterrupted ovulatory cycles on the development and persistence of AM; symptoms of AM usually appear after menarche and vanish after menopause. The objectives of medical treatment are the inhibition of ovulation, abolition of menstruation and achievement of a stable steroid hormone milieu, based on the concept that the responses of the eutopic and ectopic endometria are substantially similar [6]. Medical therapies primarily aimed at the relief of pelvic pain and commonly used in the treatment of AM, similar to those for endometriosis, are mainly based on the fact that the hypothalamic–pituitary–gonadal axis plays a pivotal role in every phase of mammalian reproduction, and include gonadotropin-releasing hormone agonist (GnRH agonist), oral contraceptives (OCs), progestins, danazol, and recently, selective estrogen receptor modulators (SERMs), selective progesterone receptor modulators (SPRMs) or aromatase inhibitors (AIs). These agents create a hypoestrogenic (GnRH agonists, AIs), hyperandrogenic (danazol, gestrinone), or hyperprogestogenic (OCs, progestins) environment, with suppression of endometrial cell proliferation [6]. However, medical treatments are symptomatic and not cytoreductive: lesions survive the use of any drug, at any dose, for any length of time, and are ready to resume their metabolic activity at treatment discontinuation [7]. Medical treatments of pelvic pain caused by AM may represent hormonal therapies but are associated with adverse events impacting long-term use and adherence this is why the use of drugs with minimal systematic side effects is the target basis of the modern therapy of pelvic pain associated with AM.

The aim of the study was to study immediate and remote results of the relief of chronic pelvic pain in women of reproductive age with AM, with the use of the levonorgestrel-releasing intrauterine system.

Materials and methods

A total of 180 reproductive age patients (31–46 years) 31, 56 ± 2, 32 years participated in a retrospective study conducted from January 2014 to December 2015 on the basis of the Peoples’ Friendship University of Russia, Department of Obstetrics and Gynecology with a Course in Perinatology of the Faculty of Medicine. The patients were diagnosed with AM using TVS and had a uterine size ≥ 12 gestational weeks during the pelvic examination along with chronic pelvic pains. The diagnostic criteria for AM with TVS were as follows: globular and/or asymmetric thickening of the uterine wall, myometrial cysts, distorted and heterogeneous myometrial echotexture, focal or diffuse heterogeneous myometrial echotexture, a poorly defined endometrial–myometrial junction, and a poorly defined focus of abnormal myometrial echotexture. The uterine volume was calculated using the formula for an ellipsoid (volume = 0.52 × length × anteroposterior diameter × transverse diameter). All patients refused to undergo hysterectomy or use oral contraceptives, and provided informed consent for treatment of symptomatic AM with the LNG-IUS.

The inclusion criteria in the group was the lack of hormonal therapy for six cycles prior to installation and the use of LNG-IUS, the presence of varying severity pelvic pain associated with AM.

Exclusion criteria were the presence of fibroids of the uterus, acute inflammatory diseases of the pelvic organs, external endometriosis, ovarian formation, deformation of the uterine cavity and the generally accepted contraindications for the installation of LNG-IUD.

The duration of the presence of symptoms of chronic pelvic pain ranged from 1 to 15 years.

Depending on the severity of pelvic pain patients were equally allocated to three groups:

- Group I – 60 (n = 60) women with a pelvic pain syndrome low degree of severity;
- Group II – 60 (n = 60) women with a pelvic pain syndrome of moderate severity;
- Group III – 60 (n = 60) women with severe pelvic pain.

The LNG-IUS was installed into the uterine cavity during days 5–7 of the menstrual cycle of all patients. After the installation of the LNG-IUS, we recommended follow-up visits every 3–12 months during the first year. Each follow-up visit typically entailed TVS examinations to confirm the uterine volume and location of the LNG-IUS. Pain assessment was done with a visual analog scale (VAS). Pre insertion symptoms of pelvic pain were assessed using a linear scale, with the left extreme defined as ‘‘no pain or no bleeding’’ (0 mm) and the right extreme defined as ‘‘worst pain I have ever felt’’ (100 mm). The score itself was determined by measuring the distance from the left side of the scale to the point marked by patients as their level of pain. All follow-up data (i.e. symptom changes, side effects and TVS findings) were retrospectively collected and analyzed.

Statistical analyses were performed using SPSS software for Windows version 20 (SPSS Inc., Chicago, IL). The Shapiro–Wilk test was used to test the normality of the data. Descriptive data were expressed as the mean ± standard deviation. Skewed data were within the median and range. A Wilcoxon signed rank test was used to compare the subjective changes in symptoms and the uterine volume prior to and after the LNG-IUS insertion. Statistical significance was set at p < 0.05. All statistical tests were two-sided.

Results

Of the 180 (n = 180) patients 178 (98.8%) completed the study. Two (1.25%) patients refused from the study due to the non-effectiveness of treatment within the first month. Expulse IUD occurred in two women during the first three months (1.1%) and they produced re-introduction of the LNG-IUD.

The main emphasis was on the reduction of pain syndrome.

Totally 180 women meet inclusion criteria, among which 178 cases (98.8%) had pelvic pains of varying severity, with median follow-up period of 12 months (range 1–12 months). After placement of LNG-IUS, scores of pain and ratio of severe pelvic pain decreased significantly compared with baselines (p < 0.01), the scores of VAS were 9.0 ± 0.8, 6.5 ± 2.8, 4.3 ± 1.8, 3.3 ± 2.2, 2.2 ± 2.1, 2.2 ± 1.8, 1.4 ± 1.6 and 1.3 ± 1.3 at 0, 3, 6 and 12 months.
12 months respectively. During 12 months after placement of LNG-IUS, scores of pain had improved significantly compared with preceding period \( (p<0.01) \). We found no universal dependent factors predicting improvement of pain, which was neither relevant with simultaneous changes of menstruation patterns nor adverse effects \( (p>0.005) \).

In the group with pain of low intensity, improvement was observed already at the end of the first (20%) month in 12 patients, at the end of the second month – in 38 (66.3%) patients and in the remaining 10 (16.65) patients – at the end of the third month, thus a complete pain syndrome reduction was registered already at the end of the third month in all patients. In the group with moderate pelvic pain, reduction of pain was observed in 15 (25%) patients at the end of the third month, in 32 (53.3%) women on the sixth month of treatment, in 13 (21.6%) patient’s pain persisted until the 12th month.

In the group with severe pelvic pain syndrome, a reduction of pain was observed in 14 (24.1%) patients at the end of the third month, in 27 (46.5%) patients – at the end of the sixth month, and in 6 (10.3%) patients – at the end of 12th month. Unfortunately, of the 58 patients of this group, pain persisted in the remaining 11 patients and this was the basis for changing of the treatment tactics.

By the end of the 12th month of observation in the first and in the second group of 36 women on the background of the therapy amenorrhea was registered.

During the year of observation no patient became pregnant, what demonstrates the high-contraceptive effectiveness of the method.

Side effects were as follows: the most frequent of them was a violation of the menstrual cycle by the type intermenstrual bleeding and also in the follow up period after 1 year of the beginning of treatment with LNG-IUD, 3.3% of patients registered headache and acne vulgaris.

The mean uterine volume was \( 162 \text{ mm}^3 \) (range \( 39–842 \text{ mm}^3 \)). Among the total participants, 2 (1.25%) discontinued the treatment prematurely. However, there was significant difference in uterine volume between Group 1 and Group 2 \( (176 \pm 12.5 \text{ and } 138 \pm 6.2 \text{ mm}^3, p=0.010) \). Based on the receiver operator characteristic analysis, the optimum cutoff value of uterine volume less than 140–148 mm\(^3\) was observed in the group with a moderate pelvic pain \( (p>0.005) \).

**Discussion**

The natural desire to preserve the specific function of the reproductive system in women requires addressing the discussion question about the possibilities of conservative therapeutic methods of pelvic pain, place and time of the surgery.

The modern concept of conservative treatment is the basis for the use of a rather broad spectrum of therapeutic measures as with isolated in the mono-therapy mode, and in combined therapy; from direct or indirect impacts on the centers governing the reproductive system, including the application of agonists GN-WP, antigonadotropins or synthetic analogs of progesterone. Due to the high frequency of comorbidity and the development of a number of side effects, the use of these hormonal drugs may be limited. One of the possible solutions is to define algorithm of complex conservative therapy including long-acting drug inhibiting the pathogenic mechanisms and providing a stable effect. In this regard, the development of a comprehensive, personalized management of reproductive age patients with pelvic pain associated with AM remains a challenge.

This study shows that there is a vast number of scientific literatures, which recommends different groups of hormonal drugs for reduction of pelvic pain caused by AM, each of them having its limitations, both in the effectiveness and safety criteria and side effects. Chronic pelvic pain restricts and modifies the daily routine of these patients, directly affecting their quality of life. Despite the use of instruments to measure pain, such analysis is complex due to its subjective nature and the influence of factors, such as personality, psychiatric disorders (depression) and psychosocial factors. The severity of pain may be related to the degree of depression and anxiety, present in 90% of women with endometriosis, namely with AM, this is why all hormonal drugs must be prescribed in the way excluding neurotic disorders (such as depression and anxiety). Some authors indicate that depression is a direct consequence of chronic pelvic pain, but there is no consensus on this temporal issue when defining which condition precedes the other [7]. However, it is possible to affirm that the two conditions coexist, and that one worsens the experience of the other [8]. Whenever endometriosis patients exhibit depression, it is clinically important to assess the condition and start appropriate treatment as soon as possible. Depression, if left untreated, has a negative effect on the patient’s ability to deal with the chronic pelvic pain, daily functioning and especially their quality of life. In addition, the impact of a chronic disease, such as endometriosis, associated with persistent painful symptoms in the pelvic area, causes the patient to become isolated, damaging relationships given that women with endometriosis are labeled as “hypochondriac” and their circle of friends ends up getting tired of so many complaints [5]. In this study, we found that LNG-IUS was an effective and simple alternative method for the treatment of chronic pelvic pain. Our finding was in accordance with many previous studies [2–4]. With LNG-IUS local endometrial concentration of levonorgestrel is high and uniform as compared to blood concentration and this account for lesser side effects. Four women achieved amenorrhea after 12 months and many complained of intermittent spotting at 3 months, which further decreased at 6 and 12 months post insertion. The treatment with LNG-IUS seemed to be an appropriate alternative to hysterectomy for all women who perceived with chronic pelvic pain of varying severity.

**Conclusion**

Thus, the obtained results allowed to confirm the possibility of using LNG-IUS in the treatment of pelvic pain syndrome associated with AM, particularly with mild and moderately severe pelvic pain syndrome. This is a cost effective, reversible and long-term treatment for women with pelvic pain associated with AM, which reduces the need for surgical interventions.

**Declaration of interest**

The authors declare that they have no competing interests.

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