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Levonorgestrel-releasing intrauterine system versus a low-dose combined oral contraceptive for treatment of adenomyotic uteri: a randomized clinical trial☆,☆☆,★

Omar M. Shaaban*, Mohammed K. Ali, Ali Mohamed A. Sabra, Diaa Eldeen M. Abd El Aal

Department of Obstetrics and Gynecology, Faculty of Medicine, Assiut University, Egypt

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Abstract

Introduction: This study compares the efficacy of a levonorgestrel-releasing intrauterine system (LNG-IUS) and a low-dose combined oral contraceptive (COC) in reducing adenomyosis-related pain and bleeding.

Materials and methods: A randomized clinical trial included 62 participants complaining of pain and bleeding that was associated with adenomyosis. Participants were randomly assigned to either LNG-IUS or COC treatment. The outcomes included the improvement of pain using a visual analogue scale, menstrual blood loss using a menstrual diary and estimated uterine volume by ultrasound for 6 months of treatment. We also compared uterine arteries and intramyometrial Doppler indices before and 6 months after treatment with both LNG-IUS and COCs.

Results: Both treatments significantly reduced pain after 6 months of use; however, the reduction was greater in the LNG-IUS group (from 6.23±0.67 to 1.68±1.25) compared with the COCs group (from 6.55±0.68 to 3.90±0.54). Both treatment arms significantly decreased the number of bleeding days, uterine volume and Doppler blood flow in the uterus from before to after treatment. These effects were more significant in the LNG-IUS arm compared with the COC arm.

Conclusion: Both LNG-IUS and COCs decreased the pain and menstrual bleeding that is associated with adenomyosis. However, LNG-IUS is more effective than the COCs in reducing pain and menstrual blood loss. This effect may be secondary to the decrease in uterine volume and the increase in blood flow resistance.

Keywords: Adenomyosis; COCs; LNG-IUS; Mirena; Dysmenorrhea

1. Introduction

Adenomyosis is a common disease in women aged 40–50 years and is considered a significant cause of dysmenorrhea and menorrhagia [1]. Until a few years ago, a hysterectomy was considered the main treatment that could definitively cure this disease [2]. Other treatment options are increasingly offered, including hormonal suppression with GnRH agonists or danazol and endometrial ablation [3]. However, deep adenomyosis responds weakly to the above treatment options, which are commonly not considered for long-term management because of the associated side effects [4].

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a reversible method of contraception that is effective in treating dysmenorrhea and menorrhagia [5]. LNG-IUS has been suggested as a treatment option for adenomyosis, secondary to its effect in down-regulation of estrogen receptors (ER) in both glandular and stromal endometrial tissues, its effect on decidualization and subsequent noticeable atrophy of the endometrium [6]. In addition, the LNG-IUS may offer pain relief because of the reduction of prostaglandin production within the endometrium as well as atrophy of the adenomyosis foci [7]. Low-dose combined oral contraceptive (COC) pills have been widely

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* Corresponding author. Faculty of Medicine, Assiut University, Women's Health Hospital, Assiut University Campus, 7111, Assiut Egypt, Egypt. Tel.: +20-882412616, +20-1223971457 (mobile).

E-mail address: omshaaban2000@yahoo.com (O.M. Shaaban).

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used as the primary treatment for menorrhagia [8]. COCs can also be used to induce endometrial atrophy and to decrease endometrial prostaglandin production, which can consequently improve menorrhagia and dysmenorrhea that are associated with adenomyosis [9].

The current study compares the efficacy of LNG-IUS with that of low-dose COCs in the treatment of adenomyosis-associated pain with or without abnormal uterine bleeding. To our knowledge, no randomized clinical trial (RCT) has been conducted to compare the above two modalities in the management of adenomyosis. In addition, in this study, we are also testing the hypothesis that adenomyosis increases uterine volume and blood flow to feed the ectopic endometrial foci, thus causing the pain and bleeding that are associated with adenomyosis. Color Doppler ultrasound has been used previously for diagnostic purposes [10,11]. However, the effects of these treatments on the uterine artery or intramyometrial blood flow have not been studied before.

2. Materials and methods

The current study is a clinically registered open, parallel, RCT (NCT01601366) comparing the effect of the LNG-IUS (Mirena) with that of low-dose COCs in treating adenomyosis-related pain with or without uterine bleeding. The ethical review board of the Faculty of Medicine of the Assiut University approved the study. The participants were recruited from the Outpatient Gynecology Clinic of the Women's Health Hospital. It was carried out in the period between the first of August 2013 and the first of November 2014. This trial was designed and reported according to the revised recommendations of ClinicalTrials.gov for improving the quality of reporting RCTs.

2.1. Eligible participants

All participants who presented to the above clinic with complaints of pelvic pain (dysmenorrhea and or chronic pelvic pain) with or without uterine bleeding were entered in a screening phase. This phase included history taking (including basal evaluation of the degree of pain and bleeding), clinical examination, two-dimensional transvaginal ultrasound (2D TV/US) and color Doppler ultrasound. Ultrasound scanning was performed using a Sonoline G60S ultrasound imaging system (Siemens, Germany) using a 4- to 7-MHz endovaginal probe. The following ultrasound criteria were used to diagnose adenomyosis: globular uterus, myometrial linear striation, myometrial cysts and uterine wall asymmetry [9]. Myometrial cysts were defined as rounded anechoic areas of 2–6 mm in diameter [10]. Color Doppler was used to differentiate the myometrial cysts from myometrial blood vessels [11]. Other inclusion criteria included the participant's request for contraception for at least 6 months, an age between 20 and 45 years, a resident in the nearby vicinity to make the follow-up easy and feasible and acceptance of use of either type of management. Exclusion criteria included history of ectopic pregnancy, puerperal sepsis, pelvic inflammatory disease, evidence of coagulopathy and/or abnormalities of the uterine cavity such as submucous fibroids distorting the cavity. Women were also excluded if they had a history of malignancy or histological evidence of endometrial hyperplasia, any adnexal abnormality on ultrasound, undiagnosed vaginal bleeding or any other contraindication to receive COCs.

2.2. Randomization

Randomization was done using a computer-generated random table. Eligible patients who consented were randomly assigned to receive either LNG-IUS or COCs. Allocation concealment was done using serially numbered closed opaque envelopes. Each envelope was labeled with a serial number and had a card noting the intervention type inside. Allocation was never changed after opening the envelopes. Preparation and sorting of the serially numbered envelopes was done by an investigator who did not participate in evaluating patients either before recruitment or in the follow-up stage.

2.3. Intervention

Eligible participants were allocated to one of two groups. The LNG-IUS group received LNG-IUS (Mirena; Bayer Schering Healthcare AG, Bayer HealthCare, Berlin, Germany), inserted according to the manufacturer's instructions [12]. Transvaginal sonography ascertained proper insertion of the device immediately after insertion. The second group received COCs (Gynera; Bayer Schering Healthcare AG, Bayer HealthCare, Berlin, Germany), which included 30 mcg of ethinyl estradiol and 75 mcg of gestodene. Participants were instructed to use the COCs as prescribed (one pill every day for 21 days followed by a 1-week pill-free interval). Both treatment groups were provided the treatment for free. Baseline assessment of the degree of pelvic pain as measured by visual analogue scale (VAS), the menstrual blood loss by menstrual diary, uterine volume and Doppler blood flow in the uterine and intramyometrial blood flow were evaluated (as described in the study outcomes section). Ultrasound evaluation and clinical visits were free of charge, and the participants were requested to come to a monthly follow-up with our clinic for at least 6 months. Each participant had a special follow-up card for the study that included the study serial number, the study group and the required follow-up schedule. The card also included contact details for reaching a trained nurse for any required help or advice between visits. The contact details of each participant, including cell phone number (if provided), were also recorded on the data collection sheet.

2.4. Study outcomes

The primary outcome of this study was the improvement of pelvic pain (dysmenorrhea and or chronic pelvic pain) as