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Comparing the effect of aromatase inhibitor (letrozole) + cabergoline (Dostinex) and letrozole alone on uterine myoma regression, a randomized clinical trial

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ABSTRACT

Objective: To evaluate the effect of letrozole in combination with cabergoline and letrozole alone on regression of symptomatic uterine myomas in women of reproductive age.
Design: Randomized controlled clinical trial.
Setting: University hospital.
Patients: Ninety-one women of reproductive age were enrolled in the study and 88 women were eligible. Eight participants were excluded from the study.
Interventions: Eighty women of reproductive age with symptomatic myomas >4 cm were evaluated in two groups. Participants in Group 1 received 2.5 mg letrozole once daily and cabergoline 0.5 mg/week from the first day of the menstrual cycle for 12 weeks, and participants in Group 2 received letrozole alone.
Main outcome measures: Changes in uterine size and volume; myoma size, volume and number; and side effects of treatment.
Results: Overall, 76 patients completed the study. Compared with baseline values, mean uterine volume was reduced significantly in both groups ($p = 0.01$), and there was no significant difference between groups ($p = 0.99$). The mean number of dominant myomas was reduced significantly in both groups ($p = 0.03$), with no significant difference between groups ($p = 0.6$). The mean volume of myomas was reduced significantly in both groups ($p = 0.01$), with no significant difference between groups ($p = 0.45$). Although a significant decrease in number and volume of myomas was documented in each group ($p < 0.05$), the intergroup analyses did not reveal significant differences between the two groups in terms of the change in number ($p = 0.28$) and volume ($p = 0.96$) of myomas. Headache was significantly more common in the letrozole + cabergoline group (nine vs two cases, $p = 0.02$), but the two groups were comparable for the remaining minor side effects.
Conclusion: This study showed that 12 weeks of treatment with letrozole with and without cabergoline improved the size and volume of the uterus and myomas, led to symptom improvement, and could be used for short-term treatment prior to surgery or fertility programmes.
Condensation: Condensation letrozole in combination with cabergoline in the management of uterine fibroids.

Introduction

Uterine myomas are the most common benign gynecological tumours [1–3]. Although the exact aetiology is not well established, it appears to be due to the influence of several risk factors. There is evidence suggesting the role of oestrogen and progesterone [1]. The risk factors include increasing age, black ethnicity, early menarche, nulliparity, obesity, inactivity, alcohol consumption, caffeine use, stress, family history and environmental factors [2].

The strategy for treating uterine myomas usually relies on the severity of symptoms, size and location of the myoma, patient's age, proximity of menopause and patient's desire for pregnancy. Approximately 40% of patients need medical/surgical intervention [1–3]. Current treatments for uterine fibroids include a variety of surgical techniques. The therapeutic options include monitoring of patients, medical treatments, and less invasive surgical and radiological approaches [4,5]. Medical treatment is the only

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short-term option at present, and this could be developed to provide alternatives to surgical intervention [6].

Various medications have been tried in this regard, including gonadotropin-releasing hormone (GnRH) agonists and antagonists [7,8], dopamine agonists [9,10], aromatase inhibitors [11,12], antiprogestins [13,14], specific modulators of oestrogen and progesterone receptors [15–17], intrauterine progesterone releasing systems [18], danazol [19], gestrinone [20], vitamin D [21], progestins [22] and herbal agents [23].

Aromatase inhibitors prevent the production of ovarian and environmental oestrogens through a mechanism that involves inhibition of aromatase enzymes and prevention of the conversion of androgens to oestrogen [24]. In previous studies, letrozole was able to decrease the size of myomas, uterine bleeding and dysmenorrhoea with fewer common complications than the problems associated with GnRH agonists [11,24].

Cabergoline, a dopamine agonist, is also used for treating myomas [9]. Although the definitive treatment in patients with uterine myomas is surgical, this may be associated with complications and loss of fertility.

This study aimed to compare the effects of an aromatase inhibitor (letrozole) plus cabergoline with letrozole alone on the growth of uterine myomas.

Materials and methods

This randomized controlled clinical trial was conducted from April 2015 to March 2016 at Alzahra Teaching Hospital, Tabriz University of Medical Sciences, Iran. The study was registered at the Iranian Registry of Clinical Trials (www.irct.ir, No. IRCT201506205283N12), and written informed consent was obtained from patients. The Ethics Committee of Tabriz University of Medical Sciences approved this study (Ref. No. TBZMED. REC.1394.264). Ninety-one participants with one to five uterine submucosal or intramural myomas between 4 and 10 cm who were candidates for myomectomy due to fibroid-related problems [e.g. excessive and heavy menstrual bleeding (>80 cm^3 and/or menstrual bleeding that lasted for >7 days) or irregular menstrual bleeding (such as periods that occur <21 days apart or last for >7 days), pain or pressure in the pelvis, or problems with pregnancy or infertility] were enrolled, and 88 of them were eligible. Finally, 80 patients were randomized (Fig. 1).

Parsanezhad et al. [11] found that letrozole decreased the size of myomas in 45.6% of their patients, and Sayyah-Melli et al. [9] reported that cabergoline led to a 46–53% reduction in the size of myomas. Thus, using Power and Sample Size Calculation software, based on a 45% reduction in the volume of myomas in the letrozole + cabergoline group and a further 12% reduction in the letrozole group, and comparing the letrozole + cabergoline group with 80% power, 38 cases were calculated for each group, resulting in a total of 76 cases. This figure was augmented to 80 cases to allow for possible dropouts. The patients were randomized using Rand Version 2.1 (DatInf GmbH, Tübingen, Germany) with sequentially numbered containers in two groups receiving either letrozole + cabergoline or letrozole alone.

The exclusion criteria were age >45 years, fibroids >10 cm, more than five fibroids, fibroids with subserosal location, a positive history of abnormal endometrial or cervical pathology, uterine infection, renal disease, hepatic disease, pregnancy-related toxaemia, cardiovascular disease, peptic ulcer, use of antipsychotic medications, receipt of oestrogen and progesterone in the last month, a hormone-based implant in the last 3 months, and previous history of medical/surgical treatment for uterine myomas.

After patients' demographic characteristics were recorded, Group 1 received letrozole 2.5 mg/day (Letrofem, Iran Hormone, Tehran, Iran) orally from the first day of the menstrual cycle and cabergoline 0.5 mg/week (Dostinex, Pharmacia, and Upjohn SPA, Milan, Italy) orally for 12 consecutive weeks. Group 2 received letrozole alone.

All patients were checked for changes/improvement in uterine bleeding in terms of amount, duration, frequency and blood tests to rule out anaemia. In addition, all patients were evaluated for headache, flushing, nausea, vomiting and musculoskeletal tenderness/pain.

Uterine size, and number and size of uterine myomas were determined before and at the end of interventions using

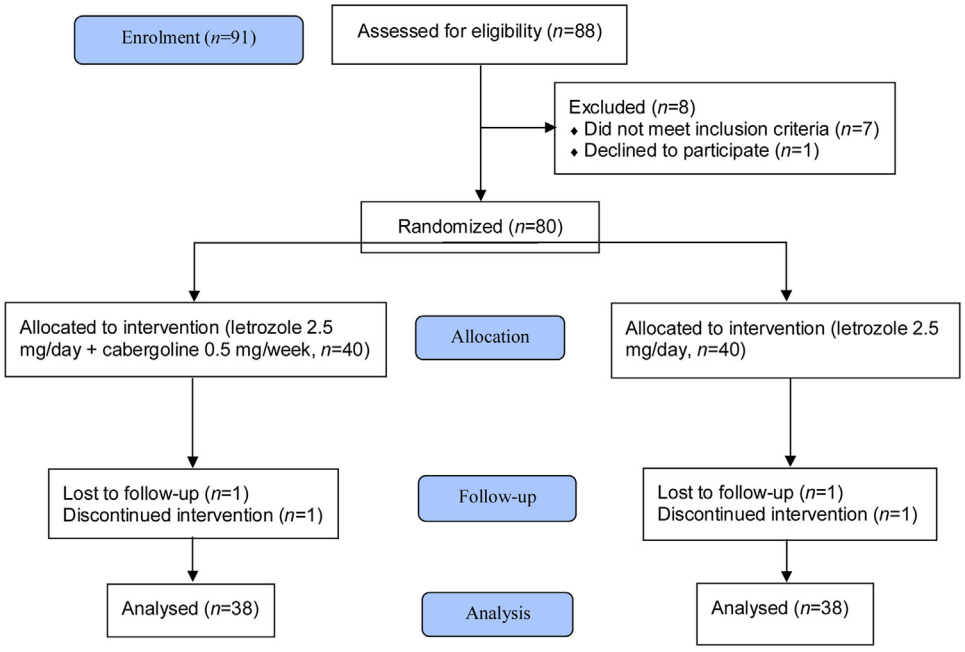

Fig. 1. Consort flowchart of study population.