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Preoperative treatment with letrozole in patients undergoing laparoscopic myomectomy of large uterine myomas: a prospective non-randomized study

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ABSTRACT

Objective: To assess the efficacy of preoperative treatment with aromatase inhibitors (AIs) in premenopausal women undergoing laparoscopic myomectomy of large uterine myomas.
Study design: Prospective non-randomized assessor-blind comparative trial.
Results: This study included 80 patients undergoing laparoscopic myomectomy of large uterine myomas (≥8 cm). Forty patients were treated with a combination of oral letrozole (2.5 mg/day) and norethindrone acetate (2.5 mg/day) continuously in the three months prior to surgery (group A) and 40 patients received no treatment before surgery (group B). The total operative time (mean ± SD, range) was significantly lower in group A (121.5 ± 19.9 min; 89–181 min) than in group B (134.4 ± 16.8 min; 111–185 min; $p < 0.001$). The time required to close the hysterotomies (mean ± SD, range) was lower in group A (27.1 ± 5.1 min; 16–39 min) than in group B (37.1 ± 9.6 min; 17–57 min; $p < 0.001$). The intraoperative blood loss (mean ± SD, range) was lower in group A (271.0 ± 125.6 ml; 95–625 ml) than in group B (460.4 ± 205.7 ml; 180–1115 ml; $p < 0.001$). No major complication occurred in any case. The cleavage plane was better defined in group B compared with group A ($p < 0.001$). The quality of the myometrial scar, defined by ultrasound evaluation, was similar in the two study groups both at one-week ($p = 0.356$) and at 3-month follow-up ($p = 0.201$).
Conclusions: The total operative time, the time required to close the hysterotomies and the intraoperative blood loss significantly decrease after preoperative treatment with letrozole. Future randomized studies should compare the efficacy of preoperative administration of AIs and GnRHa prior to laparoscopic myomectomy.

Introduction

Laparoscopic myomectomy has several advantages over the laparotomic and minilaparotomic techniques, such as lower intraoperative hemoglobin drop, shorter hospital stay, less postoperative pain, and faster recovery [1–5]. Large myomas may be difficult to be excised by laparoscopy and the repair of the uterine wall defects may be challenging for surgeons with limited experience in laparoscopic suturing.

Gonadotropin-releasing hormone analogs (GnRHa) have been used in the 3–4 months before surgery to decrease uterine volume and fibroid size [6]. In addition, the preoperative treatment with GnRHa is beneficial in the correction of pre-operative iron deficiency anemia if present and reduces intra-operative blood loss [6,7]. Similarly, aromatase inhibitors (AIs) block estrogen synthesis and have been used in the medical treatment of myomas [8–12].

This non-randomized assessor-blind comparative study investigated the efficacy of preoperative treatment with AIs in premenopausal women undergoing laparoscopic myomectomy of large uterine myomas.

Materials and methods

This was a non-randomized assessor-blind comparative study. The study was approved by the local ethics committee and conducted according to the declaration of Helsinky. Patients signed a written consent form.

The primary end-point of the study was to evaluate whether the preoperative administration of AIs decreases the total operative

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time. The secondary objectives of the study were: to assess the changes in myoma volume caused by preoperative treatment; to evaluate the effect of preoperative treatment on intraoperative blood loss, time required to close the hysterotomies, difficulty encountered by the surgeon in the identification of the cleavage of the myomas; to evaluate the quality of the myometrial scars at 1 week and 3 months from surgery.

The criteria for inclusion in the study were: reproductive age; one uterine intramural myoma with larger diameter ≥8 cm (first myoma); number of myomas ≤3; largest diameters of the other myomas respectively ≤5 cm (second myoma) and ≤3 cm (third myoma). Exclusion criteria were: previous uterine surgery; additional diseases requiring surgical treatment (such as endometriosis, tubal surgery, appendicitis); use of hormonal therapies in the 6 months prior to inclusion in the study; previous use of AIs; unwillingness to tolerate menstrual changes; undiagnosed vaginal bleeding; osteopenia or osteoporosis; current or past history of seizure disorders; pulmonary, cardiac, hepatic or renal diseases; thromboembolic or cerebrovascular events; pregnancy; contraindications for general anesthesia; psychiatric disorders precluding informed consent.

The diagnosis of uterine myomas was based on a transvaginal ultrasonography performed by using a Voluson E6 ultrasound machine (General Electric Medical Systems, Milwaukee, WI, USA). Size, location (with respect to uterine layers), position (with respect to the uterine axis), and number of myomas were recorded. The myomas were categorized according to the FIGO classification [13]. The volume of the myomas was estimated by using the virtual organ computer-aided analysis (VOCAL, GE Healthcare, Milwaukee, WI, USA) [14]. Total myoma volume was defined as the addition of the volume of the myomas affecting each uterus.

Transvaginal ultrasonography was performed before preoperative hormonal treatment and on the day of surgery (after 3 months of treatment). Hemoglobin concentration was measured on the day before surgery and 24 h after surgery, the difference in hemoglobin concentration (ΔHb) was recorded. Total operative time, estimated blood loss and intraoperative complications were recorded. The surgeons assessed the degree of difficulty encountered in the identification of the cleavage of the myomas using a 5-point Likert scale (very easy, easy, neutral, difficult, very difficult). Transvaginal ultrasonography was used to assess the quality of the myometrial scars at 1 week and 3 months from surgery by using a 3-point Likert scale (good, neutral and bad) [15–18]. The ultrasonographer was blinded to the use of preoperative treatment. At 1 week from surgery, bad quality of the myometrial scar was defined as the presence of fluid-filled anechoic areas with diameter >5 mm, which could be due to hematomas (Fig. 1); neutral quality of the myometrial scar was defined as the uterine scar appearing as a echogenic area with heterogeneous myometrial texture with few small (<5 mm) anechoic areas (Fig. 2); good quality of the myometrial scar was defined as uterine scar appearing as a echogenic area with heterogeneous myometrial texture without anechoic areas [17]. At 1 week from surgery, the stitches appear as small linear hyperechoic points (Fig. 2). At 3 months from surgery, bad quality of the myometrial scar was defined as persistence of anechoic areas in the site of the uterine scar (Fig. 3); neutral quality of the myometrial scar was defined as visible uterine scar (without anechoic areas); good quality of the myometrial scar was defined as normal echogenic myometrial texture.

Study subjects were either treated with a combination of oral letrozole (2.5 mg/day, Femara; Novartis Farma, Varese, Italy), norethindrone acetate (2.5 mg/day, Primolut-Nor; Schering, Milan, Italy) elemental calcium (1000 mg/day) and vitamin D3 (880 IU/day, Cacit-Vitamina D3; Procter & Gamble, Rome, Italy; group L) continuously in the three months prior to surgery (group A) or received no treatment before surgery (group B). The choice of

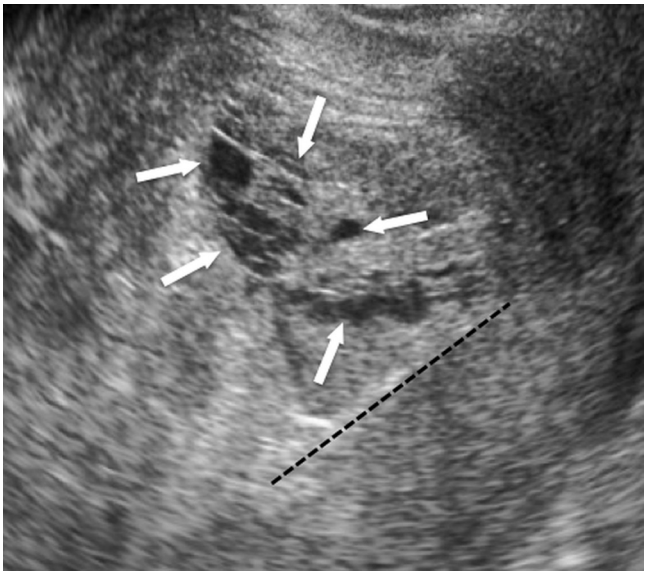

Fig. 1. *Bad quality of myometrial scar at 1 week from surgery*. Multiple fluid-filled anechoic areas (arrows) can be observed in the myometrial scar. The line indicates the endometrium.

treatment was not randomized. The possibility to receive the preoperative treatment with AIs was offered to all patients referred to our institution because of laparoscopic myomectomy fitting the inclusion criteria. Patients were informed on the potential benefits and adverse effects of treatment and they were told that AIs are not approved for the treatment of uterine myomas and, therefore, the use of these drugs should be considered experimental. Patients were informed that AIs have been used to treat uterine myomas [8–12] but that no previous study investigated the efficacy of the treatment with AIs before surgery for uterine myomas. A list of potential adverse effects of the hormonal therapies was given to the patients [19]. Patients were told that the decrease of myoma volume caused by AIs might facilitate the surgical procedure. Patients accepting to receive the preoperative treatment were assigned to group A while those refusing hormonal therapy were assigned to group B. Patients were requested to report the adverse effects experienced during the 3-month treatment.

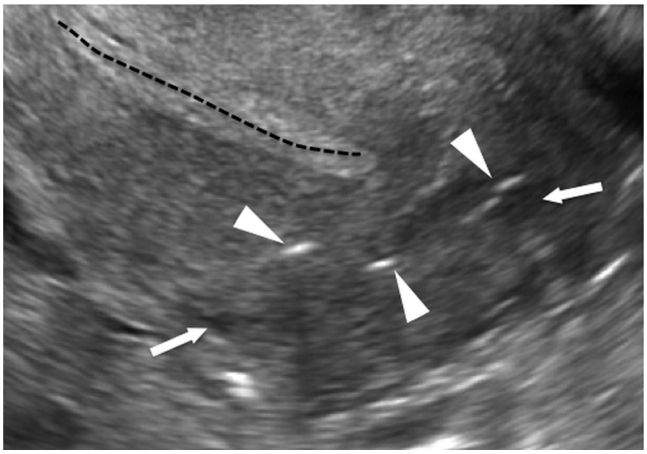

Fig. 2. *Neutral quality of myometrial scar ad 1 week from surgery*. The myometrial texture is heterogeneous with few small anechoic areas (arrows); the stitches appear as small linear hyperechoic points (arrowhead). The line indicates the endometrium.