Ulipristal Acetate vs Gonadotropin-Releasing Hormone Agonists Prior to Laparoscopic Myomectomy (MYOMEX Trial): Short-term Results of a Double-blind Randomized Controlled Trial

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ABSTRACT

Two agents used for pretreatment of fibroids before myomectomy are gonadotropin-releasing hormone agonists (GnRHa)—considered a criterion standard—and ulipristal acetate (UPA), a selective progesterone receptor modulator (SPRM) recently approved for preoperative treatment. No randomized trials have compared pretreatment of uterine fibroids with GnRHa or UPA prior to laparoscopic myomectomy.

The aim of this double-blind randomized controlled trial was to determine whether pretreatment with UPA was noninferior to pretreatment with GnRHa for intraoperative and postoperative outcomes of laparoscopic myomectomy. The study was conducted in 9 hospitals in the Netherlands. All participants were enrolled between May 2015 and July 2017. Surgery was performed by surgeons experienced in laparoscopic procedures (>150 per year). Premenopausal women older than 18 years were randomized to receive daily oral UPA for 12 weeks and single placebo injection or single intramuscular injection with GnRHa (leuprolide acetate, 11.25 mg) and daily placebo tablets for 12 weeks. The primary study outcome was intraoperative blood loss, and secondary outcomes included reduction of fibroid volume, time of suturing, total surgery time, and ease of surgery.

A total of 55 women were randomized: 30 to UPA and 25 to leuprolide acetate. Noninferiority of UPA to GnRHa with respect to intraoperative blood loss was not demonstrated. Compared with GnRHa pretreatment, pretreatment with UPA significantly increased median intraoperative blood loss (525 [interquartile range, 348–1025] mL vs 280 mL [100–500] mL; \( P = 0.011 \)) and increased suturing time for the largest fibroid (40 [28–48] minutes vs 22 [14–33] minutes; \( P = 0.003 \)). Pretreatment with UPA resulted in a significantly smaller reduction in uterine fibroid volume compared with GnRHa (−7.2% [−35.5% to 54.1%] vs −38.4% [−71.5% to −19.3%]; \( P = 0.001 \)). Subjectively, surgeons found laparoscopic myomectomies in women pretreated with UPA to be more difficult than in women pretreated with GnRHa. There was no significant difference between the 2 groups in the most common adverse effects, headaches, and hot flushes.

These data do not demonstrate noninferiority of UPA to GnRHa with regard to intraoperative blood loss. Although this can be explained by the limited sample size, it cannot be excluded that UPA pretreatment for laparoscopic myomectomy is inferior to GnRHa. Pretreatment with GnRHa appears to be more favorable than UPA for several objective operative outcomes.
including fibroid volume reduction, intraoperative blood loss, hemoglobin reduction postoperatively, time of suturing of largest fibroid, and several subjective surgical ease parameters. Confirmation of these findings in larger studies with superior design is needed to make any final conclusions.

EDITORIAL COMMENT

(Symptomatic uterine fibroids can be treated with hysterectomy or surgical alternatives that preserve the uterus and may preserve fertility. The advantages of hysterectomy include ligation of uterine blood vessels to prevent excessive blood loss as well as complete removal of current and future fibroids. Transvaginal destruction or removal of small, accessible fibroids can be accomplished with minimal blood loss, with pretreatment needed only in the most challenging cases involving larger fibroids. Transabdominal myomectomy facilitates removal of multiple fibroids but is associated with excessive blood loss during the time between each uterine incision and hemostatic closure. A systematic review including 38 randomized controlled trials showed that pretreatment with a GnRHa reduces uterine and fibroid volume and increases preoperative hemoglobin levels as compared with placebo, no pretreatment, or other hormonal treatments. In the same review, 4 trials comparing SPRMs to placebo showed similar benefits (Cochrane Database Syst Rev 2017;11:CD000547).

The abstracted trial was designed to demonstrate that pretreatment with a newly approved SPRM (UPA) works just as well as pretreatment with GnRHa. "Just as well" is defined in noninferiority trials as a difference so small with a confidence interval so narrow that, if present, the difference is unlikely to be clinically unimportant. The MYOMEX trial was well designed and included blinding of surgeons to which pretreatment patients received, adding credibility to subjective outcomes such as surgical ease. Other outcomes of interest included estimated blood loss and postoperative change in hemoglobin concentration.

For most outcomes, the investigators found much larger differences than they hypothesized favoring the superiority of GnRHa over UPA. Both estimated blood loss and drop in hemoglobin concentrations were twice the magnitude after UPA pretreatment as GnRH pretreatment, a large, clinically important, and statistically significant difference. Fibroid volume, difficulty with dissection, and suture closure time were also greater after UPA pretreatment, explaining the differences in blood loss. There is strong consistency across these outcomes supporting their validity.

In their conclusions, the investigators were appropriately cautious not to draw sweeping inferences from this 1 small trial. However, they were also hesitant to conclude that UPA is inferior to GnRH, citing the study's small sample size and recommending that larger studies be carried out. The logic here is challenging, in that a limited sample size would also decrease the study’s power to detect superiority of one treatment over the other. In this case, large differences were found in most outcomes favoring the superiority of GnRHa. The differences identified were so large that they were very unlikely to be due to chance. Instead, readers should be cautioned about threats to the study’s external validity. As noted by the authors, the mean diameter of the largest fibroids in the 2 randomized groups was approximately 8 cm, and it is possible that the UPA and GnRHa would be more similar in effectiveness in patients with smaller fibroids. Unfortunately, subgroup analyses were planned to look at treatment effectiveness as a function of disease burden. Because of these limitations, readers are advised not to implement changes in their practice until larger trials with planned subgroup analyses are conducted in different settings.—LAL)