Endocrine Care
doi: 10.4183/aeb.2012.231

TRIPTORELIN MODULATION OF GONADAL STEROIDOGENESIS AS A PREOPERATIVE TREATMENT IN LEIOMYOMATA UTERI

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Abstract

Introduction. The gold standard for surgery of fibroids is vaginal surgery and a preoperative treatment that facilitates this approach through reduction of the uterine volume is of utmost importance. GnRH agonists and selective progesterone receptor modulators (SPRM) have both been tested to this effect.

Objective. To evaluate whether uterine shrinkage induced by preoperative GnRH agonists in women with uteruses > 280g may facilitate vaginal hysterectomy (VH).

Material and methods. 23 women scheduled to have an abdominal hysterectomy based on the uterine size over 280 g were allocated to receive the GnRH agonist triptorelin 3.75 mg monthly for three months. Uterine weight (estimated by ultrasound), serum levels of estradiol and Hb were assessed before treatment and monthly afterwards three times.

Results. Estradiol levels decreased from 235.9±15 to 38±3.7pg/mL at three months ($p<0.0001$), after an initial flare up. Hb increased from 11.85±1.8 to 12.7±0.74 g/dL. The uterine weight decreased from 443.5±39 to 294.8±31 g (by 33.5%), all patients benefitting from a VH.

Conclusion. In women with a large uterus impending an abdominal hysterectomy, a 3-month preoperative course of GnRH agonists facilitates VH by decreasing uterine size by 30%.

Key words: GnRH agonists, fibroid, vaginal hysterectomy.

INTRODUCTION

Hysterectomy is one of the most prevalent surgeries worldwide. Nine out of every ten hysterectomies are performed for non-cancerous conditions that are not life threatening but have a negative impact on quality of life (1).

The majority of gynecologic surgeons continue to perform abdominal hysterectomies by means of a laparotomy, although less invasive approaches are now considered gold standard.

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Many gynecologic organizations recommend avoiding laparotomy, and advise abdominal hysterectomy (AH) only when the vaginal or laparoscopic route is ruled out (2,3). Vaginal hysterectomy (VH) is the safest route and has the best cost–effectiveness ratio, making it the first-choice option in clinical practice (4).

There are countries where this approach was introduced into national programs promoting minimally invasive hysterectomies. During such a program, FINHYST, in Finland the ratio between different types of hysterectomies dramatically shifted from 58% abdominal hysterectomies in 1996, to 76% minimally invasive hysterectomies (44% vaginal, 32% laparoscopic) ten years later, with a significant shortening of hospital stay and of convalescence time (5). Therefore, it became imperative to make efforts to increase the ratio of minimally invasive hysterectomies in every medical system.

Large uterine size is the first impairment to vaginal hysterectomy. Pre-operative uterine size estimated to more than 280 g (clinically, the equivalent of a 12 week pregnant uterus) is a universally accepted contraindication for vaginal hysterectomy (6).

Fibroids response to estro-progestative stimulation is well described, and therefore different regimens of estro-progestative modulation have been tested to reduce pre-operative uterine size (7,8).

GnRH agonists are known to produce profound hypoestrogenism and have been used for medical treatment of leiomyomas (fibroids). Preoperative treatment with GnRH agonists seems to be useful for producing a significant reduction of uterine volume, thus allowing, in selected cases, vaginal hysterectomy. In patients with severe anemia these drugs proved to be very effective in temporarily improving the hematologic parameters (4).

PATIENTS AND METHODS

Twenty-three women who were scheduled to have abdominal hysterectomy for leiomyomas based on the criteria that the estimated uterine weight was above 280 g (as measured by transvaginal sonography) had been identified for treatment with the long-acting GnRH agonist triptorelin (Diphereline®) and volunteered to participate in the study. Patients were excluded from this analysis if they had contraindications for vaginal hysterectomy other than uterine size. The study was approved by the Local Ethics Committee and an informed consent was obtained in all cases.

Triptorelin was administered by intramuscular injection once per month at a dose of 3.75 mg for three months. Uterine weight and serum levels of estradiol were assessed before initiation of treatment (in the 14th day of menstrual cycle) and afterwards every month. Hormonal measurements have been made by ELISA.

Uterine weight was assessed pre- and post- GnRH agonist administration. Uterine size was estimated by ultrasound using the formula for a prolate ellipsoid: *longitudinal diameter x anterio-posterior diameter x transverse diameter x 0.5233.*

Standard clinical evaluations and laboratory tests, including hematological,

renal function and liver function tests, and microscopic examinations of sediment from midstream urine specimens were performed before treatment, and after three cycles of treatment. In women with metrorrhagia an endometrial histology was obtained prior to surgery. All women agreed to use barrier contraception throughout the study.

Statistical analysis was made using SPSS 17.0 (*IBM Corporation, USA*).

RESULTS

Patients. Average age at the admission was 45 ±3.5 years. BMI was 27.2 kg/m²±2.4. At presentation, 11 out of the 23 patients enrolled had menometrorrhagia caused by leiomyoma. In 8 of them who were anemic (defined as Hb levels < 10.5 g/dL) we initiated iron supplementation along with triptorelin treatment. All women with metrorrhagia benefitted of endometrial biopsy and had benign results prior to surgery.

In all patients, except one, treatment induced an efficient suppression of estradiol (E2), illustrated by a significant decrease from 235.9±15 pg/mL to 38±3.7pg/mL at three months (ANOVA $p<0.0001$), after an initial flare up from 235.9±15 pg/mL to 259.8 pg/mL at 2 weeks after initiation of treatment (Wilcoxon test, $p<0.036$) (Fig. 1).

Hematological parameters improved prior to surgery, with an average hemoglobin increase of 1g, from 11.85±1.8 to 12.7±.74 g/dL (Fig. 2).

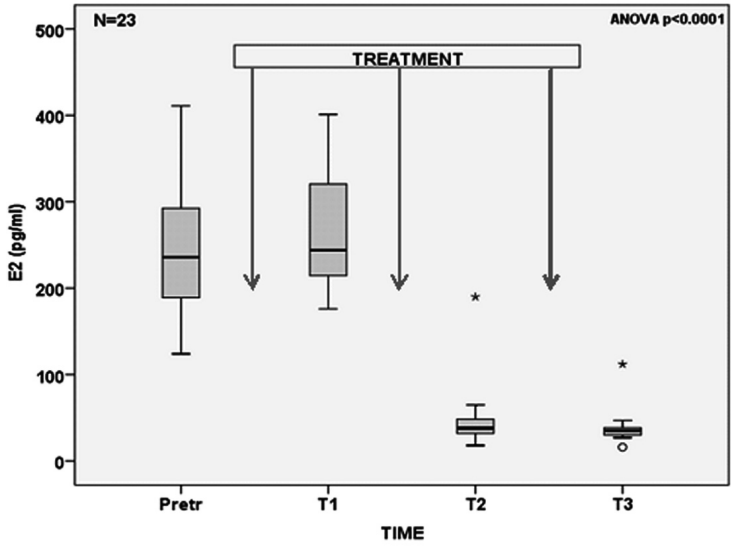

Figure 1. E2 (estradiol) levels significantly decrease at 6 weeks (T2) and 10 weeks (T3) after triptorelin (Diphereline®) initiation, after an initial flare-up at 2 weeks (T1), (ANOVA $p<0.0001$) (N=23).

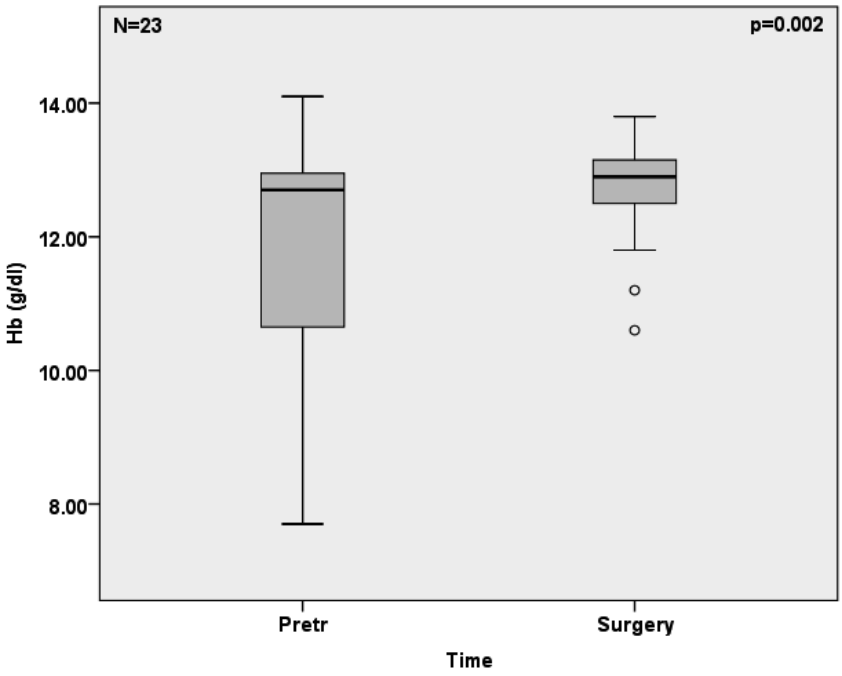

Figure 2. Hb (g/dL) levels improved after a 3 months course of triptorelin (Diphereline®). (N=23, Wilcoxon test p=0.002).

In patients presenting with metrorrhagia, bleeding became minimal after 14 days and stopped after a maximum of 21 days in all cases in which was present.

Side-effects during triptorelin treatment included hot flushes, 78.26 %, vaginal dryness, 52.17%, asthenia, 13.04% (Table 1). For hot flashes, symptomatic treatment with 2.5 mg tibolone q.d. was initiated in 6 patients. In patients who did not ask for alleviation, the mean number of hot flushes per day increased significantly ($P < 0.05$) in the first 15 days of triptorelin treatment and remained constant for all three cycles of treatment.

The average uterine weight preoperatively, after a three months course of triptorelin, decreased from 443.5±39 g to 294.8 g±31 g. We found a significant reduction in uterine weight by 33.5% (Fig. 3).

Subsequent to uterine reduction, all patients benefited of a vaginal hysterectomy. In all cases VH was performed 4-6 weeks after the last dose of triptorelin. In 5/23 cases procedures for stress urinary incontinence were associated.

DISCUSSION

Definitive treatment of uterine fibroids still relies on surgery, although various regimens of medical treatment have been tested mainly to control symptoms such as heavy bleeding, secondary anemia, pelvic pain, infertility

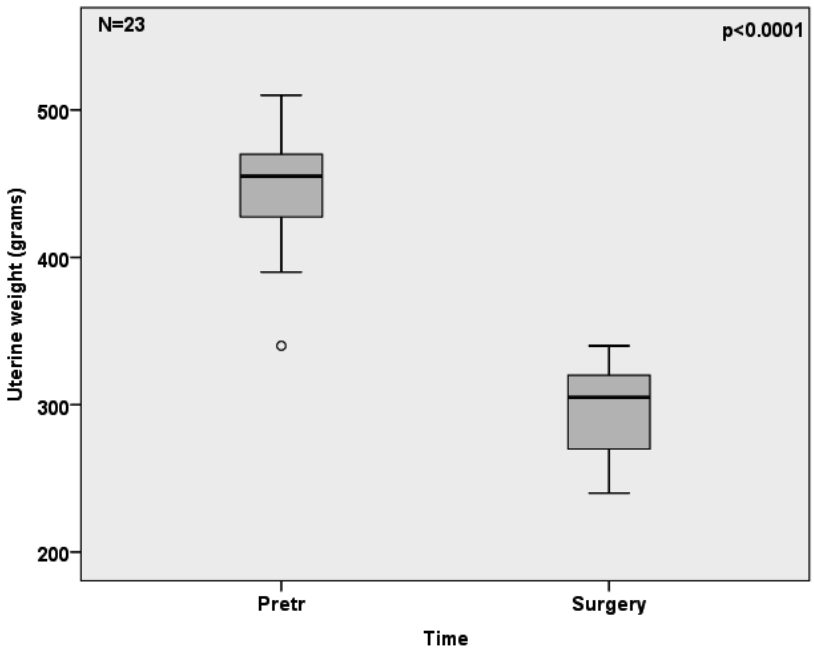

Figure 3. Uterine weight decreased significantly (p<0.0001) after a three months course of triptorelin (Diphereline®) (N=23). All patients benefitted of a vaginal hysterectomy.

Table 1. Effects during triptorelin (Diphereline®) treatment

Uterine size reduction	100% cases	23/23
Stopped vaginal bleeding	100% cases presenting with menorrhagia	11/11 who presented with menorrhagia
Improved Hb	52,17%	12/23, and the rest were stable, none decreased
Hot flashes	78,26% cases	18/23, 6 requesting symptomatic treatment
Vaginal dryness	52,17% cases	12/23, 6 requesting symptomatic treatment

and reduced quality of life (4, 7,8).

No medical treatment is currently used long-term due to their important side-effects. However, the use of GnRH agonists prior to uterine surgery has been promoted for several reasons. A reduction was expected in intraoperative blood loss and in the need for pre-, per- and postoperative blood transfusions on the basis of size reduction alone. Selective removal of fibroids was thought to become technically easier, thereby reducing the risk of postoperative formation of adhesions and increasing the fertility potential after conservative surgery (9,10). Total removal of the enlarged uterus in cases of symptomatic fibroids was expected to become easier,

for instance by changing the route of operation from abdominal to vaginal. Finally, application of GnRH agonists before endoscopic fibroid surgery is promoted for reduction of blood loss in hysteroscopy and enabling the endoscopic removal of larger fibroids in general. Studies addressing these expectations and questions are far from numerous. Comparative studies often lack randomization and for the endoscopic approach comparison to other hormonal regimens or placebo is virtually absent.

Our present study argues that with the use of GnRH agonists the volume of the uterus can be reduced by 33.5%, which permitted in all our cases a change in the choice of surgical route to a less invasive vaginal hysterectomy.

Our data, consistent with previous studies that used magnetic resonance imaging for uterine assessment under GnRH agonists showed that uterine fibroids volume response is approximately 30-35% (11). In addition to size reduction, the blood flow through the uterine vessels is decreased, presumably caused by the lack of normal estrogen stimuli on the uterine vasculature (12).

Until recently the treatment with GnRH agonists was the only effective option to accomplish all these purposes. The main drawbacks for GnRH agonist treatment are signs and symptoms of hypoestrogenism including hot flushes, headaches, and osteoporosis, which limit long-term use. In our study, while heavy vaginal bleeding was well controlled under medical treatment, 78.26% of patients complained of hot flushes and 52.17% of vaginal dryness, some necessitating symptomatic treatment.

Recently, a collaborative study on ulipristal, a selective progesterone receptor modulator (SPRM), showed encouraging results on symptom-control of patients with fibroids compared to placebo (13) and similar to GnRH agonists (leuprolide) (14) with apparently less side-effects and a better patient compliance. Selective progesterone receptor modulators have mixed agonist–antagonist properties, and occupy an intermediate position of the spectrum of large family of progesterone receptor ligands. Some of them display direct antiproliferative effects in the myometrium, although with variable actions which seem product- and dose-dependent. This property justifies their use in the treatment of myomas. In the PEARL I trial, 237 women with fibroids, excessive uterine bleeding, and anemia were randomized to ulipristal 5 mg daily, ulipristal 10mg daily, or placebo. At the end of the 13-week trial, uterine bleeding was controlled for about 92% of ulipristal-treated women compared to only 19% of the placebo-treated group ($p<0.001$ *vs.* either ulipristal group). The fibroid volume shrunk for the ulipristal groups (21% smaller in size for the 5mg group and 12% smaller for the 10mg group) to a greater extent than it did for the placebo group (3% larger in size; $p<0.01$ vs. either ulipristal group). From these data, the authors conclude that ulipristal is more effective than placebo for the medical treatment of symptomatic fibroids (13).
Run in a clinical setting similar to that of PEARL I, the PEARL II trial provides evidence that daily oral ulipristal is non-inferior to monthly intramuscular leuprolide acetate for the medical treatment of symptomatic fibroids prior to planned uterine surgery (14). Notably,

the ulipristal groups experienced significantly fewer hot flashes than the leuprolide acetate group, suggesting that ulipristal is the better-tolerated treatment.

However, from the existent data, GnRH agonists seem to be superior to ulipristal in the reduction of the uterine size (53% v*s* 42% in the group receiving 10 mg of ulipristal acetate), although ulipristal appears superior to GnRH agonists in rapidly controlling the uterine bleeding. The main concern on ulipristal usage is the unusual histological pattern of benign, "non-physiologic" endometrial change occurred in the majority of ulipristal-treated women. Although the changes resolved within six months of drug discontinuation, the potential long-term adverse effects of ulipristal on the endometrium are somewhat concerning. For these reasons longer-duration trials are necessary.

Regarding definitive treatment of fibroids through surgery, and giving the patients the chance of a minimally invasive procedure, an adjuvant pre-operative three months course of GnRH agonists remains the better option.

In conclusion, the use of a GnRH agonist for 3 months prior to fibroid surgery was found to reduce significantly, by 33.5%, the uterine volume and fibroid size with short term and long term benefits. During treatment vaginal bleeding is controlled and hematological parameters, such as anemia, improve. For patients undergoing hysterectomy, a minimally invasive vaginal procedure becomes possible following the use of a three months course of GnRH agonists.

Conflict of interest

The authors declare that there is no conflict of interest.

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