Short Communication

Oral Gonadotropin-Releasing Hormone Antagonist Relugolix Has the Same Effect as Gonadotropin-Releasing Hormone Agonist Injections in Terms of Preparation for Transcervical Resection Myomectomy

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Abstract

For preparing the optimal condition in transcervical resection (TCR) surgery, gonadotropin-releasing hormone (GnRH) agonist has been utilized. Recently, an oral GnRH antagonist (relugolix) is available and acts directly on GnRH receptor, avoiding flare up and reducing blood E2 levels rapidly. We retrospectively compared the oral GnRH antagonist (n = 14) effect to that of subcutaneous GnRH agonist (n = 19) for the pretreatment of endometrium in TCR myomectomy. Endometrial thickening was determined by intraoperative videos. The color tone of the endometrium in the normal part was assessed by digital image processing. The median duration of the first GnRH agonist injection and the surgery was 67 days (21–136 days), which is significantly longer than that of the oral GnRH antagonist group, 18.5 days (7–157 days $P < 0.01$). Both the GnRH agonist and antagonist groups did not exhibit prominence in the endometrium. The GnRH antagonist group showed the same degree of whiteness in the normal endometrium as the GnRH agonist group. The oral GnRH antagonist administration could rapidly atrophy the endometrium and create an optimal surgical field for TCR in a short period.

Keywords: Gonadotropin-releasing hormone antagonist, relugolix, transcervical resection

Introduction

Transcervical resection (TCR) surgery is indicated for infertility cases and for patients who want to control their menstrual bleeding volume.[1,2] The advantages of TCR over transabdominal surgery, such as a shorter operating time and hospital stay with improved cost-effectiveness, quicker recovery, and return to work, have been well documented.[3] Above all, TCR is the preferred technique because it is less painful for patients.

TCR may be technically challenging if the endometrium is thick, as in the late secretory phase of the menstrual cycle.[1] Therefore, TCR surgeries are suggested to be performed during the period of thin endometrium immediately after menstruation. However, it is not always possible to schedule the procedure at the appropriate time. Therefore, the use of hormonal agents which induce endometrial thinning or atrophy before surgery has been performed. The most commonly evaluated agents have been progestogen, gonadotropin-releasing hormone (GnRH) agonist, and danazol.[4] Among these drugs, for the pretreatment of the endometrium for TCR operation, few data were available to assess the effectiveness of progestogens as endometrial

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thinning agents.[2] GnRH agonist produces slightly more consistent endometrial thinning than is produced by danazol.[2] Moreover, both GnRH agonist and danazol produced side effects in a significant proportion of women, including menopausal symptoms such as hot flushes, vaginal dryness, hirsutism, decreased libido, and voice changes, as well as other side effects such as headache and weight gain.[2,5] Therefore, for preparing the optimal condition, a GnRH agonist has been utilized before TCR operations, but side effects related to a long-term hypoestrogenic condition should be considered.[2]

Recently, an oral GnRH antagonist is available for fibroid[6] and can be used for the preparation of TCR-myomectomy. With GnRH agonist, a transient increase in estradiol (E2) concentration (i.e. flare-up) is observed while gonadotropin secretion is accelerated, increasing the risk of bleeding.[7] It takes 2–3 weeks after administration to induce a reduction in E2 concentrations. On the other hand, a GnRH antagonist (relugolix) acts directly on GnRH receptors, avoiding flare up and reducing blood E2 levels rapidly after administration.[7] Therefore, we hypothesized that the oral GnRH antagonist might be able to rapidly atrophy the endometrium and create an optimal surgical field for TCR in a short period. In the present study, we retrospectively compared the oral GnRH antagonist effect to that of subcutaneous GnRH agonist for the pretreatment of endometrium in TCR-myomectomy.

Methods

Patients

Eligible patients were those who underwent TCR-myomectomy at our hospital and affiliated hospital (Kitasato University Medical Center Hospital) between 2016 and 2019. All patients were confirmed to be negative for endometrial malignant cells by smear before surgery. Preoperative diagnoses of all cases with ultrasonography were submucosal type fibroids, and the average preoperative fibroid size was 23 ± 10 mm. Details of fibroid size in each group are shown in Table 1. Surgery was performed using a continuous flow resectoscope (Olympus Co, Tokyo, Japan). Nineteen patients who underwent TCR-myomectomy after receiving GnRH agonist (leuprorelin acetate) injections, and 14 patients treated with oral GnRH antagonist (relugolix) were included. Furthermore, patients who underwent TCR-myomectomy during the proliferative (n = 4) and secretory (n = 7) phases were included in the nonhormone group. The main complaints were as follows, in the GnRH agonist group: abnormal uterine bleeding (AUB) n = 9 and infertility n = 10, GnRH antagonist group: AUB n = 4 and infertility n = 10, and in the nonhormone treatment group: AUB n = 4 and infertility n = 7. Data were extracted from medical records in a retrospective manner for these cases and analyzed. Ethical approval for the study was obtained in the institute (B19-178, 2020118).

Table 1: Background of patients

	GnRH agonist (leuprolerin)	GnRH Antagonist (relugolix)	Prolierative Phase	Secretory Phase
number	19	14	4	7
age (mean)	40.0±7.5	38.5±8.2*	39.5±3.4	45.4±4.5*
size (mean)	23.3±3.1	22.7±2.3	11.7±2.3 **	29.5±3.2 **
Hormonal treatment days (median)	67 (21-136)***	18.5 (7-157)***	N/A	N/A

*Significant difference in age (P<0.05) GnRH antagonist vs secretory phase. **Significant difference in size (P<0.05) proliferative vs secretory phase. ***Significant difference in days (P<0.01) GnRH agonist vs GnRH antagonist

Hormonal treatments

Relugolix (40 mg), a GnRH antagonist, was administered orally as one tablet a day until the day before surgery. A GnRH agonist, leuprorelin acetate (1.88 mg) was administered subcutaneously every 4 weeks. Patients were basically assigned to the GnRH antagonist group after the start of relugolix sales in 2019, and to the GnRH agonist group before that. The median number of GnRH agonist injections was two times,[1-4] while oral GnRH antagonists were administered for 18.5 days (7–157 days). Patients whose physicians determined that preoperative hormone therapy was unnecessary were assigned to the nonhormone group. The nonhormone-treated patients had a regular menstrual cycle (25–38 days), and the proliferative and secretory phases were examined according to the menstrual cycle.

Transcervical resection and the evaluation of the endometrium

The presence or absence of endometrial thickening was determined by watching intraoperative videos. The endometrium was considered thickened if there was prominence in the normal endometrial area, while the endometrium was considered nonthick when it was flat without prominence. The endometrium was then assessed using objective indicators for the coloration of the endometrium [Figure 1]. The part where the normal endometrium and the yellow part of the electrodes of the hystero-scope is photo-captured from the surgical video. The image is processed in black and white using Image software (Image J, Ver. 1.52a). This will make the red areas of the endometrium appear black and the white areas white. The endometrial luminance where there was no fibroid lesion was measured with Image J. The yellow part of the TCR electrode was also measured, and the value obtained for the endometrium was divided by the value of the electrode to obtain the corrected value. We evaluated the values of the electrode yellow part where we used as a reference and found that there was no statistical difference among the four groups.

Statistical analysis

Data were analyzed using Fisher's exact test and continuous variables using the Mann–Whitney *U*-test.

Results

The mean age of patients in each group was 40.0 years in the GnRH agonist group (n = 19), 38.5 years in the GnRH antagonist group (n = 14), 39.7 years in the proliferative phase (n = 4), and 45.4 years in the secretory phase (n = 7), with a significant difference between the GnRH antagonist group and secretory groups [$P < 0.05$, Table 1]. The mean size of fibroid before hormonal treatment was comparable between the GnRH agonist group (23.3 ± 3.1 mm: mean ± standard error of the mean [SEM]) and the antagonist group (22.7 ± 2.3 mm), while there was a significant difference in the size of fibroid between the proliferative and secretory phase ($P < 0.05$). The median number of GnRH agonist injections was two times,[1-4] and the median duration between the date of the first GnRH agonist injection and the surgery was 67 days (21–136 days), which is significantly longer than that of GnRH antagonist group, 18.5 days (7–157 days $P < 0.01$). In all cases, the uterine lesions could be removed in a single operation, and all postoperative patients were evaluated with ultrasonography and, in some cases, with hysteroscopy, showing no residual mass. In the pathological examination, most patients were diagnosed with uterine fibroids, but one had adenomyosis in the nonhormonal group, and one had atypical polypoid adenomyoma in the GnRH agonist group.

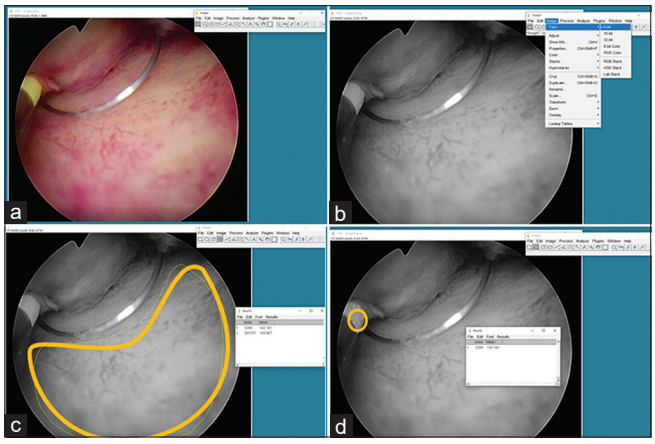

Figure 1: The assessment of endometrial color using image software. The part where the normal endometrium and the yellow part of the electrode of hysteroscopy are photo-captured from the surgical video. (a) The image is processed in black and white using Image software (Image J, Ver. 1.52a). This will make the red areas of the endometrium appear black and the white areas white. (b) The endometrial luminance in the areas without fibroid was measured with Image J. (c) The yellow part of the TCR electrode was also measured, (d) and the value obtained for the endometrium was divided by the value of the electrode to obtain the corrected value. TCR: Transcervical resection

Bleeding and the thickness of endometrium during surgery

In all cases, none of the patients presented with improper bleeding at the time of surgery. The endometrium of a normal lesion in the GnRH agonist, the GnRH antagonist, and the proliferative phase group did not exhibit prominence in all patients, contributing to produce a clear view when performing TCR-myomectomy, while 3 out of 7 cases in the secretory phase group exhibited prominence, a condition with endometrial thickness. There were no cases of uterine perforation, and no women required a blood transfusion.

The coloration of the endometrium

The color tone of the endometrium in the normal part was assessed by digital image evaluation. This method allows whiter substances to show higher values and redder substances to show lower values. As shown in Figure 2, endometrial coloration in the GnRH antagonist group averaged 0.85 ± 0.06 (mean ± SEM), which was not statistically different from that of the GnRH agonist group (0.76 ± 0.04, P = 0.19), and comparable to that of the secretory phase (0.76 ± 0.07). There was a statistically significant difference in the whiteness of endometrium between the GnRH antagonist and proliferative phase groups (0.55 ± 0.05, P = 0.01), while the GnRH agonist and proliferative groups tended to be different (P = 0.06).

Discussion

Before TCR surgery, many patients receive hormonal therapy with the aim of obtaining a better view by inducing a thinner

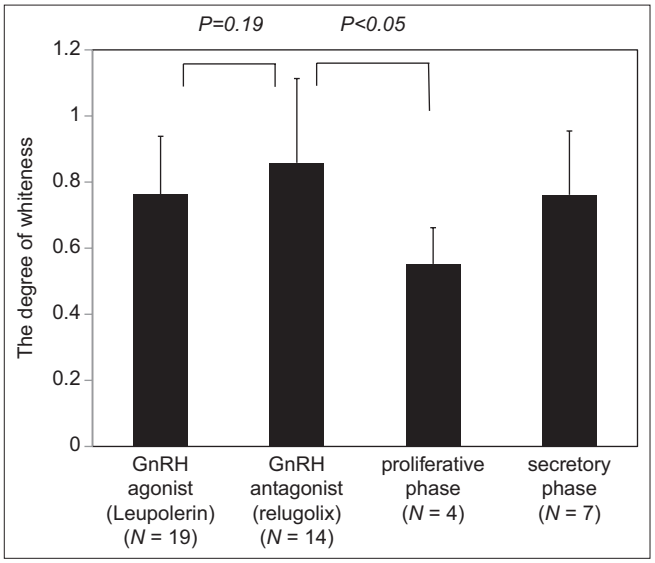

Figure 2: The color tone of the endometrium in the normal part of GnRH agonist (n = 19), GnRH antagonist (n = 14), proliferative phase (n = 4), and secretory phase (n = 7) was assessed by digital image evaluation (Image J, Ver. 1.52a). This method allows whiter substances to show higher values and redder substances to show lower values. The relative ratio of the color tone in the endometrium to the yellow part of the TCR electrode was shown. TCR: Transcervical resection, GnRH: Gonadotropin-releasing hormone

endometrium. As the oral contraceptive drug has the risk of thrombosis, the GnRH agonist has been often used so far. However due to the flare-up effect of GnRH agonist, it takes more than 2–3 weeks after the first dose of GnRH analog to induce a low estrogen state, and the estrogen level remains low for a long time after the last administration of GnRH agonist.[7] In the research of hormonal preparations used preoperatively in TCR, a significantly higher proportion of women receiving GnRH agonists experienced hot flushes, sweating, and headaches than those receiving placebo.[5] Recently, an oral GnRH antagonist has been marketed. This drug can induce a hypoestrogenic state in a short time (within 24 h) and, because it has a half-life of 25 h, allows rapid elimination of the hypo-estrogenic state after surgery by withdrawing the drugs.[7] In the present study, we mainly compared the preoperative use of GnRH agonists and oral GnRH antagonists in TCR-myomectomy retrospectively. Data from nonhormone-treated patients (proliferative phase $n = 4$, and secretory phase $n = 7$) were also added for reference. Because of the small number of cases and the fact that some cases did not require pharmacotherapy, we were not able to match the patient backgrounds with those of the hormone-treated group.

It is known that the endometrium turns thin after menopause. In this study, we attempted to express the degree of endometrial atrophy induced by low estrogen status as endometrial flatness (no prominence in the endometrium) and whiteness. To assess the state of the whiteness of the endometrium, we quantified the endometrial coloration of the normal part of the uterine cavity. We did not measure the thickness of the endometrium with ultrasonography due to the presence of uterine fibroid.

With hormonal therapy, the normal endometrium was flat in all cases, which is an ideal condition for TCR operation, while in cases where surgery was performed during the secretory phase, normal endometrium exhibited prominence in 3 out of 7 patients. As for the color of the endometrium, after GnRH agonist or antagonist therapy, the endometrium appeared white compared to the natural proliferating endometrium [Figure 2]. There was no difference in the coloration of the endometrium between the oral GnRH antagonist and the GnRH agonist group. There is no correlation between the duration of GnRH antagonist or agonist administration and the color tone of the endometrium (Pearson correlation analysis; $P = 0.6$ and 0.2, respectively), suggesting that once a low estrogen state is induced, the endometrial condition might be similar.

Collectively, although the median duration of relugolix administration was 18.5 days, the endometrium was atrophied in all cases, and the endometrial color of whiteness was similar to those of the group that received GnRH agonist of an average of 2.3 times, or 67 days. Oral GnRH antagonist might be useful to prepare endometrium in TCR-myomectomy from the point of healthcare economics. Since the half-life of relugolix is 25 h, it is assumed that postoperative estrogen secretion from the ovaries resumes earlier compared to subcutaneous GnRH agonist, which takes 65 days to resume the menstrual cycle.[7] In other words, the early resumption of estrogen secretion by relugolix may be useful in regenerating the damaged endometrium. Further study is needed to confirm this notion. Furthermore, as the present study was a retrospective comparison of GnRH agonists and antagonists, it should necessitate future studies with prospective comparison. Since we had a variety of cases with long-term and short-term hormonal treatments, we could not get data on either symptom improvement or size reduction of uterine fibroids. We would like to present that oral therapy, which took a shorter duration of administration than GnRH agonist, had a similar effect, at least with respect to endometrial coloration and prominence for the preparation for TCR operation.

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Conflicts of interest

There are no conflicts of interest.

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