Impact of an oral gonadotropin-releasing hormone antagonist on severe ovarian hyperstimulation syndrome in a patient with breast cancer who received a sustained-release gonadotropin-releasing hormone agonist: a case report

Tetsuro Hanada, Fuminori Kimura, Jun Kitazawa, Aina Morimune and Takashi Murakami

Department of Obstetrics and Gynecology, Shiga University of Medical Science, Otsu, Shiga, Japan

Correspondence:

Tetsuro Hanada

Department of Obstetrics and Gynecology, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan

Tel.: +81-77-548-2267; Fax: +81-77-548-2406

E-mail: thanada@belle.shiga-med.ac.jp

Running title: Relugolix for GnRH agonist-induced OHSS

Abstract

Postoperative hormone therapy for hormone-sensitive patients with breast cancer is important to prevent a recurrence. As hormone therapy does not induce infertility in patients, fertility-preserving therapy is not provided during treatment. Here, however, we performed controlled ovarian stimulation and embryo freezing for fertility preservation under the influence of a sustained-release gonadotropin-releasing hormone agonist in a patient with breast cancer whose postoperative treatment plan was changed from hormone therapy to chemotherapy. After oocyte retrieval, the patient developed treatment-resistant severe symptomatic ovarian hyperstimulation syndrome. Following treatment with oral gonadotropin-releasing hormone antagonist, her symptoms immediately improved, and she could receive chemotherapy on schedule.

Key words: breast cancer, gonadotropin-releasing hormone agonist, gonadotropin-releasing hormone antagonist, oncofertility, ovarian hyperstimulation syndrome

Introduction

Chemotherapy, particularly alkylating agents for patients with breast cancer, is highly toxic to the ovarian reserve, and it is important to give full consideration to fertility preservation for patients of reproductive age.[1] According to recent reports, fertility preservation such as embryo or oocyte banking does not delay the initiation of chemotherapy for breast cancer, nor does controlled ovarian stimulation (COS) increase the risk of cancer development and/or recurrence.[2,3] For patients with premenopausal hormone-sensitive breast cancer, adjuvant hormone therapy is considered as soon as possible after surgery if fertility preservation is not necessary.[4] Postoperative histopathological diagnosis sometimes reveals a more advanced cancer status than estimated preoperatively, and additional adjuvant chemotherapy including agents that diminish the ovarian reserve is needed depending on the situation. In such cases, information about fertility preservation therapy should be provided to patients prior to adjuvant chemotherapy, and its implementation should be considered. However, if hormone therapy has already been started, the effects cannot be ignored.

Here, we report a case in which there was a rapid improvement in severe symptomatic ovarian hyperstimulation syndrome (OHSS) after administration of an oral

gonadotropin-releasing hormone (GnRH) antagonist in a patient with breast cancer who received a sustained-release GnRH agonist prior to postoperative staging. Written informed consent was obtained from the patient for publication of this report. We report this case because with the growing momentum of fertility preservation, similar cases may be encountered in the future.

Case Description

A 24-year-old woman (gravida 0, para 0) had undergone surgery for left-breast cancer. The doctor who performed the surgery had administered 22.5 mg of leuprorelin acetate depot as a sustained-release GnRH agonist with an action lasting for 24 weeks and 20 mg of tamoxifen citrate a day starting from 2 weeks after the operation because in the preoperative assessment, the doctor had estimated that she had early-stage cancer and did not need fertility preservation. However, she was postoperatively diagnosed with stage IIA breast cancer (pT1N1M0, luminal A-like type, axillary lymph node metastasis), and she needed to be treated with adjuvant chemotherapy including cyclophosphamide. Therefore, she was referred to our oncofertility outpatient clinic at 1 week after hormone therapy induction.

The physical and laboratory findings at her first visit were as follows: a total of 16 small antral follicles with no observed corpus luteum were detected in her ovaries by transvaginal ultrasound, and the serum follicle-stimulating hormone, luteinizing hormone, and estradiol levels were 4.4 mIU/mL, 7.3 mIU/mL, and <20.0 pg/mL, respectively. Her body mass index (BMI) was 22.3 kg/m^2, and the duration of her menstrual cycle before the administration of leuprorelin acetate was mostly 29 days. At 6 days after suspending tamoxifen citrate medication, we started COS while the effect of sustained-release GnRH agonist remained active.

Human menopausal gonadotropin (hMG) (2700 IU) was administered for 10 days. From the 8th day of COS, aromatase inhibitor (letrozole, 2.5 mg/day) was administered for 3 days. Maturation was triggered by the administration of 10,000 IU of human chorionic gonadotrophin (hCG) on day 10, when the estradiol level reached 2105.1 pg/mL and ten follicles grew to over 15 mm in diameter. Oocyte pick-up (OPU) was undertaken at 35 h after hCG injection, and 12 oocytes were retrieved using vaginal ultrasound-guided follicle aspiration. Although the husband’s semen findings were normal, spermatozoa were injected into 12 metaphase II oocytes to avoid the risk of unexpected fertilization failure via conventional insemination. Of these, seven oocytes

fertilized and cleaved; five of these were frozen at the 8-cell stage, and one was frozen at the early blastocyte stage. A dopamine receptor agonist (cabergoline, 0.5 mg/day) and an aromatase inhibitor (letrozole, 5.0 mg/day) were administered for 8 days from the day of oocyte retrieval to prevent OHSS.

At 3 days after OPU, the patient developed abdominal distention and visited the outpatient clinic. As vaginal ultrasonography revealed swelling of both ovaries and mild ascites, we decided to keep her on follow-up as an outpatient. However, when she was seen 4 days later, she had severe abdominal distention, nausea, dyspnea, and oliguria. Abdominal ultrasonography revealed ascites reaching the level of Morrison's fossa in the supine position, with the right and left ovaries swelling up to 12 and 9 cm in diameter, respectively. Chest X-ray showed no pleural effusion. Laboratory findings were as follows: hematocrit, 49.4%; white blood cells, 17,500/μL; total protein, 5.9 g/dL; albumin, 3.2 g/dL; and creatinine, 0.97 mg/dL. She was diagnosed with severe OHSS according to both the Golan classification system and the classification system of the Committee on Reproduction and Endocrinology of the Japan Society of Obstetrics and Gynecology.[5,6] She was admitted to the hospital for continuous monitoring and treatment. The treatment after surgery and the COS are shown in Fig. 1.

After admission, Ringer's lactate solution 2000 mL/day, unfractionated heparin sodium (10,000 IU/day), and dopamine hydrochloride (3 μg/kg/min) were infused. This treatment was continued for 3 days; however, the symptoms worsened, and abdominal ultrasonography revealed ascites reaching the upper abdomen, with a continuous increase in body weight. Therefore, we removed 1400 mL ascites by abdominal paracentesis. As we speculated that the leuprorelin acetate depot given before COS promoted OHSS development, the administration of GnRH antagonist was considered in order to improve her condition. The use of relugolix (Relumina; ASKA Pharmaceutical Co., Ltd., Tokyo, Japan, and Takeda Pharmaceutical Co., Ltd., Osaka, Japan), a GnRH antagonist, as an oral tablet was approved by the Clinical Ethics Committee of our hospital (approval number: R2-3). The patient was fully briefed on the purpose, content, and start date of the treatment as well as the side effects and right to self-determination of drug use, and she agreed in writing to take 40 mg of relugolix a day.

On the next day, ultrasound findings showed that ovarian swelling persisted, but ascites decreased and fluid was detected only inside the pelvic cavity; the patient's urine volume increased to more than 5000 mL/day. After 2 days of relugolix administration,

we discontinued all infusions, and she left the hospital on the next day. The improvements in laboratory tests and physical examination during hospitalization are shown in Figs. 2 and 3. She was able to receive chemotherapy at 10 days after discharge from the hospital without any delay in her adjuvant treatment schedule.

Discussion

In the present study, we reported a case of a patient with breast cancer whose COS was performed for fertility preservation while she was under the effect of sustained-release GnRH agonist. Considering her BMI, the number of retrieved oocytes, the level of serum estradiol when hCG was administered, and the prophylactic administration of cabergoline and letrozole, the development of such severe OHSS was unusual and unexpected. We suspected that what differentiated the clinical course of this case from other such cases was the use of sustained-release GnRH agonist prior to COS, and we consequently decided to administer an oral GnRH antagonist; in the present case, this treatment rapidly improved the severity of OHSS. These clinical findings suggested that administration of sustained-release GnRH agonist aggravated OHSS.

Overproduction of vascular endothelial growth factor (VEGF) in a large number

of luteal cells stimulated by hCG has been implicated as a key causative factor in the development of OHSS.[7] Targeting decreased VEGF production has been developed to treat OHSS. Dopamine agonists reduce vascular permeability by inhibiting both VEGF receptor 2 phosphorylation and VEGF production.[8] Aromatase inhibitor also reduces VEGF production as well as estrogen synthesis in the luteal cells, although the underlying mechanism is not clearly understood.[9] Moreover, GnRH antagonists have been reported to suppress the VEGF production and be effective in the treatment and prevention of OHSS.[10–12]

GnRH agonists have the potential to stimulate sex steroidogenesis not only indirectly by gonadotropins via the pituitary gland, but also by acting directly on GnRH receptors expressed in granulosa-luteal cells in some conditions.[13] Estrogen induces the production of VEGF and contributes to the exacerbation of OHSS. The GnRH agonist used for this patient had a sustained-release depot formulation, which was released at a functionally constant and stable daily dose over approximately 24 weeks.[14] Although there have been reports that have shown a suppressive effect of GnRH agonist on the development of OHSS[15], the type of GnRH and the duration of administration used for this patient was different from that used in those reports. We believe that

153 sustained-release GnRH agonist promoted a sustained stimulation of the luteinized
154 granulosa cells, caused the development of OHSS, and possibly caused the regulation of
155 symptoms by administering a GnRH antagonist.

156 In this case, we used the hMG instead of the follicle-stimulating hormone, and no
157 aromatase inhibitor was used for COS initially because the pituitary function was
158 thought to be already suppressed, and there was a possibility of down-regulation of the
159 gonadotropin receptor in the ovaries. After confirming the development of follicles, we
160 introduced an aromatase inhibitor to suppress serum E_2. In addition, COS was started
161 while the effects of TAM had not completely worn off, and hCG was administered at a
162 high dose, which may have exacerbated the OHSS. The improvement of the OHSS
163 might have occurred naturally, and it is unclear whether the GnRH antagonist actually
164 inhibited the GnRH agonist in vivo. The difference in affinity between GnRH agonist
165 and antagonist in the luteal cells is also unclear. These points need to be further
166 investigated in the future.

167 This case suggests that COS after the administration of sustained-release GnRH
168 antagonist in a patient with breast cancer led to severe symptomatic OHSS despite
169 adequate prophylaxis. With growing awareness of oncofertility, we may experience

similar cases in the future. In such cases, the administration of GnRH antagonist is one of the options to be considered for treating and preventing OHSS.

Disclosure

None declared.

Funding Information

No funding was received for this article.

References

1. Thomas-Teinturier C, Allodji RS, Svetlova E *et al*. Ovarian reserve after treatment with alkylating agents during childhood. *Hum Reprod* 2015; 30: 1437-1446.

2. Vuković P, Kasum M, Raguž J *et al*. Fertility preservation in young women with early-stage breast cancer. *Acta Clin Croat* 2019; 58: 147-156.

3. Carneiro MM, Cota AM, Amaral MC *et al*. Motherhood after breast cancer: can we balance fertility preservation and cancer treatment? A narrative review of the

literature. *JBRA Assist Reprod* 2018; 22: 244-252.

4. Francis PA, Pagani O, Fleming GF *et al*. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med* 2018; 379: 122-137.

5. Golan A, Weissman A. Symposium: Update on prediction and management of OHSS. A modern classification of OHSS. *Reprod Biomed Online* 2009; 19: 28-32.

6. Irahara M, Yano T, Fukaya T *et al*. Management and prevention of ovarian hyperstimulation syndrome. *Acta Obstet Gynaecol Jpn* 2009; 61: 1138-1145. (in Japanese)

7. Elchalal U, Schenker JG. The pathophysiology of ovarian hyperstimulation syndrome--views and ideas. *Hum Reprod* 1997; 12: 1129-1137.

8. Soares SR. Etiology of OHSS and use of dopamine agonists. *Fertil Steril* 2012; 97: 517-522.

9. Mai Q, Hu X, Yang G *et al*. Effect of letrozole on moderate and severe early-onset ovarian hyperstimulation syndrome in high-risk women: a prospective randomized trial. *Am J Obstet Gynecol* 2017; 216: 42.e1-10.

10. Asimakopoulos B, Nikolettos N, Nehls B *et al*. Gonadotropin-releasing hormone

antagonists do not influence the secretion of steroid hormones but affect the secretion of vascular endothelial growth factor from human granulosa luteinized cell cultures. *Fertil Steril* 2006; 86: 636-641.

11. Lee D, Kim SJ, Hong YH *et al*. Gonadotropin releasing hormone antagonist administration for treatment of early type severe ovarian hyperstimulation syndrome: a case series. *Obstet Gynecol Sci* 2017; 60: 449-454.

12. Lainas GT, Kolibianakis EM, Sfontouris IA *et al*. Serum vascular endothelial growth factor levels following luteal gonadotrophin-releasing hormone antagonist administration in women with severe early ovarian hyperstimulation syndrome. *BJOG* 2014; 121: 848-855.

13. Tarlatzis BC, Kolibianakis EM. Direct ovarian effects and safety aspects of GnRH agonists and antagonists. *Reprod Biomed Online* 2002; 5 Suppl 1: 8-13.

14. Periti P, Mazzei T, Mini E. Clinical pharmacokinetics of depot leuprorelin. *Clin Pharmacokinet* 2002; 41: 485-504.

15. Endo T, Honnma H, Hayashi T *et al*. Continuation of GnRH agonist administration for 1 week, after hCG injection, prevents ovarian hyperstimulation syndrome following elective cryopreservation of all pronucleate embryos. *Hum*

221 *Reprod* 2002; 17: 2548-2551.

222

223 **Figure Legends**

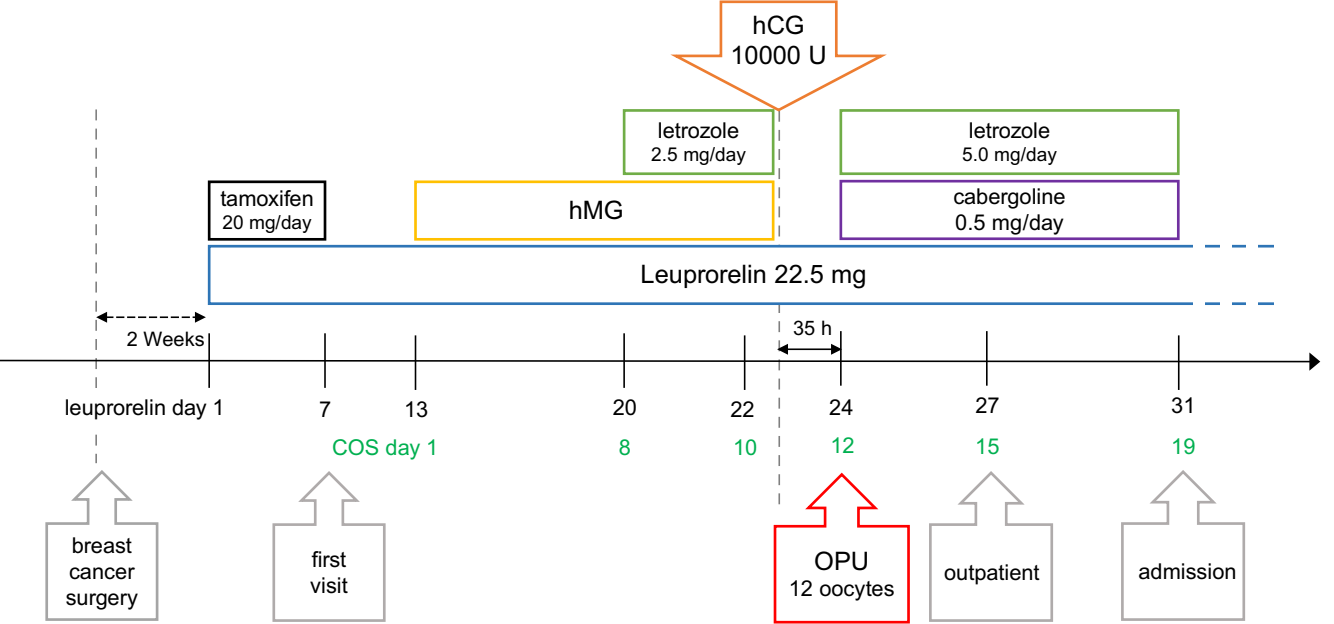
224 **FIGURE 1.** Details of the treatment after surgery and the controlled ovarian stimulation
225 (COS).

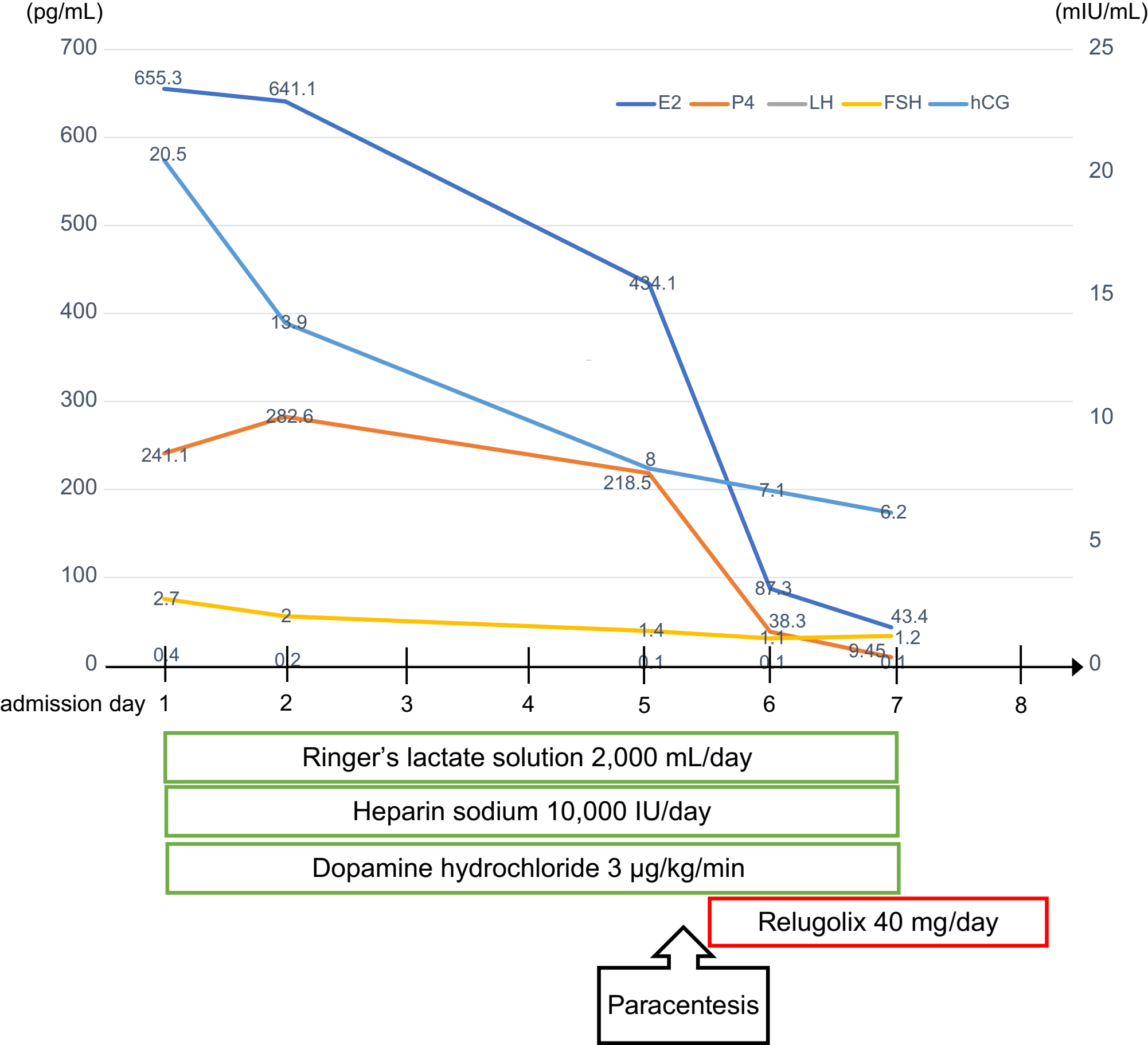
226

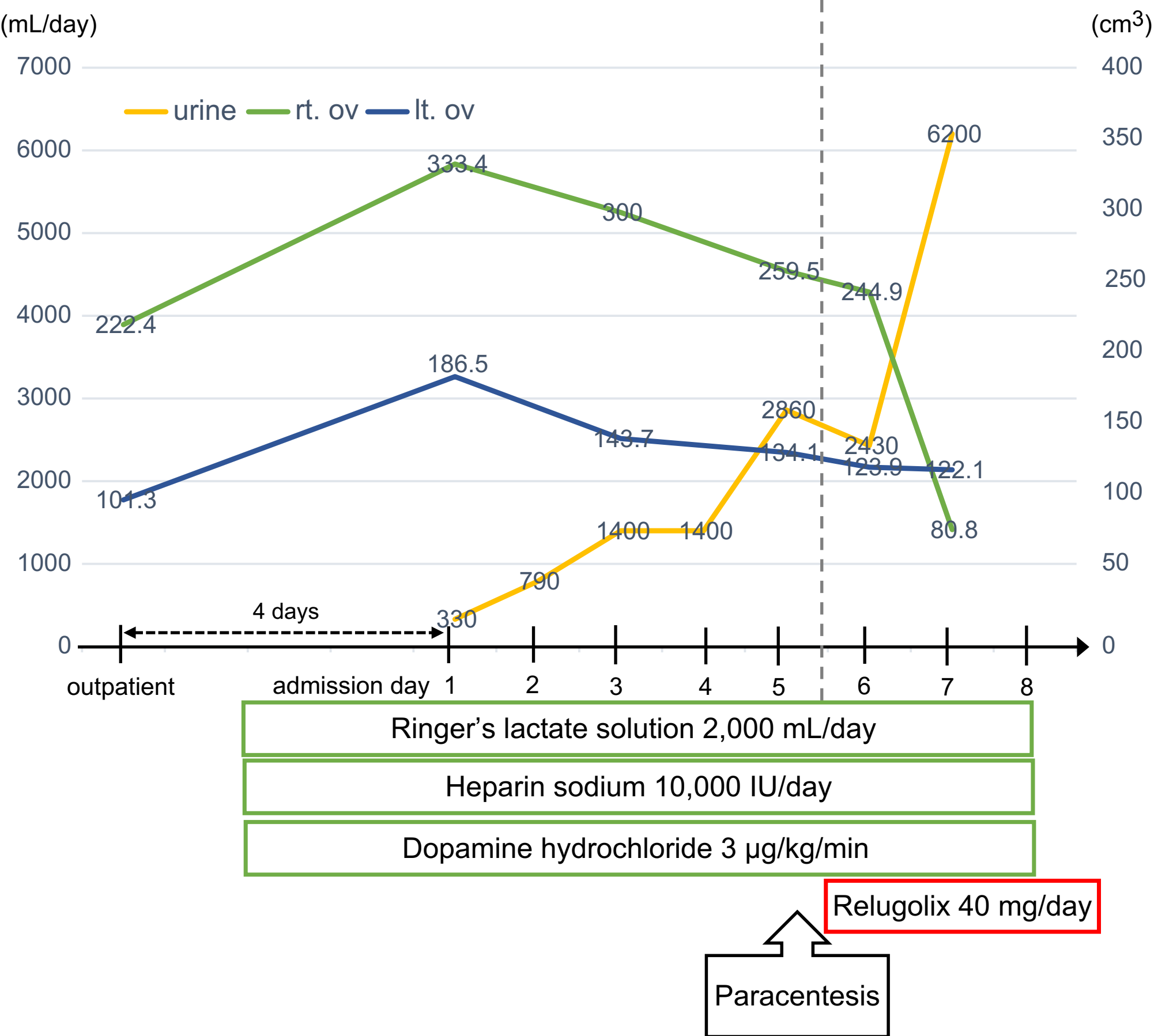
227 **FIGURE 2.** Serum estradiol (E_2), progesterone (P_4), follicular stimulation hormone
228 (FSH), luteinizing hormone (LH), and hCG levels during hospitalization.

229

230 **FIGURE 3.** Urine and bilateral ovary volume during hospitalization. The ovarian
231 volume was calculated from the radius of the three axes, assuming the ovary to
232 be ellipsoidal ($\pi = 3.14$ was used).


hCG
10000 U
letrozole
2.5 mg/day
letrozole
5.0 mg/day
tamoxifen
20 mg/day
hMG
cabergoline
0.5 mg/day
Leuprorelin 22.5 mg
2 Weeks
35 h
leuprorelin day 1
7
13
20
22
24
27
31
COS day 1
8
10
12
15
19
breast cancer surgery
first visit
OPU
12 oocytes
outpatient
admission


(pg/mL)
(mIU/mL)
700
600
500
400
300
200
100
0
25
20
15
10
5
0
E2
P4
LH
FSH
hCG
655.3
641.1
434.1
87.3
43.4
20.5
13.9
8
7.1
6.2
241.1
282.6
218.5
38.3
9.45
2.7
2
1.4
1.1
1.2
0.4
0.2
0.1
0.1
0.1
admission day
1
2
3
4
5
6
7
8
Ringer's lactate solution 2,000 mL/day
Heparin sodium 10,000 IU/day
Dopamine hydrochloride 3 μg/kg/min
Relugolix 40 mg/day
Paracentesis


(mL/day)
(cm3)
7000
6000
5000
4000
3000
2000
1000
0
400
350
300
250
200
150
100
50
0
urine
rt. ov
lt. ov
222.4
333.4
300
259.5
244.9
80.8
101.3
186.5
143.7
134.1
123.9
122.1
330
790
1400
1400
2860
2430
6200
4 days
outpatient
admission day
1
2
3
4
5
6
7
8
Ringer's lactate solution 2,000 mL/day
Heparin sodium 10,000 IU/day
Dopamine hydrochloride 3 μg/kg/min
Relugolix 40 mg/day
Paracentesis