CASE REPORT

Nagoya J. Med. Sci. **86**. 333–340, 2024
doi:10.18999/nagjms.86.2.333

Pregnancy co-treated with oral gonadotropin-releasing hormone antagonist in a woman with premature ovarian insufficiency: a case report

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ABSTRACT

To the best of our knowledge, this is the first case of pregnancy with a healthy baby after treatment with an oral gonadotropin-releasing hormone (GnRH) antagonist in women with premature ovarian insufficiency. A 36-year-old female presented at our hospital after being diagnosed with premature ovarian insufficiency by a previous doctor. We administered clomiphene, human menopausal gonadotropin (hMG), and GnRH antagonist (injection) together with estrogen replacement for 11 cycles (27 months), but no follicular development was observed. When the oral GnRH antagonist (relugolix), which has recently become available, was used in the 12th cycle, follicular growth of 13 mm was confirmed on the 14th day of stimulation. After stimulation, the use of hMG and GnRH antagonist (injection) was continued, and a maturation trigger, human chorionic gonadotropin 10000 IU, was administered. Oocyte retrieval was performed successfully, intracytoplasmic sperm injection and frozen embryo transfer were performed, and fetal heartbeat was confirmed. The patient was admitted to the perinatal management facility. She delivered a healthy baby of 3,732 g via cesarean section at 41 weeks +2. This case shows the possibility of using an oral GnRH antagonist as an option for infertility treatment.

Keywords: clomiphene, pregnancy, premature ovarian insufficiency, relugolix, oral gonadotropin-releasing hormone antagonist

Abbreviations:
ERT: estrogen replacement therapy
FSH: follicle stimulating hormone
hMG: human menopausal gonadotropin
POI: premature ovarian insufficiency

BACKGROUND

The definition of premature ovarian insufficiency (POI) by the European Society of Human Reproduction and Embryology includes three criteria: the presence of primary or secondary

Received: June 27, 2023; accepted: August 2, 2023

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amenorrhea for >4 months, onset before the age of 40 years, and a follicle stimulating hormone (FSH) level of >25 mIU/mL (as determined by two measurements obtained at least 4 weeks apart).[1] Although the prevalence of POI is often unknown,[2] a prospective study by Coulam et al[3] reported that 0.9% of the total female population will have natural menopause by the age of 40.

The etiology of POI has been found to be genetic, chromosomal, autoimmune and iatrogenic due to surgery or cancer survivor. However considerably few patients of the outpatient visits are found a clear cause of POI. Since the inhibition of follicular development in these patients could be attributed to high gonadotropin levels, we decided to try a newly marketed oral antagonist.[4]

Infertility treatment in women with POI is intractable; such patients often do not respond to traditional infertility treatments and have no choice but to rely on methods such as adoption, spontaneous ovulation, and embryo and egg donation using IVF.[1,5] However, adoption and embryo and egg donation may not be acceptable to patients based on their place of residence, legal constraints, and religious and ethical points of view.

We report a case in which the oral gonadotropin-releasing hormone (GnRH) antagonist relugolix, which was newly approved and released in Japan, was used in the 12th cycle, which resulted in clinical pregnancy through egg collection, intracytoplasmic sperm injection (ICSI), and frozen embryo transfer. The patient was referred to a perinatal management facility and delivered a healthy baby via cesarean section.

CASE PRESENTATION

First consultation after diagnosed POI

A 36 year-old woman with 0 gravida 0 para desired to raise a child at the age of 35. There was no significant medical or of ovarian surgery history. She had secondary amenorrhea for >4 months; therefore, she visited a doctor for infertility treatment. She was diagnosed with POI due to an FSH level of 108 mIU/mL (defined as amenorrhea due to loss of ovarian function before 40 years of age).[6]

After 3 months of hormone replacement therapy, the patient did not ovulate and was admitted to our clinic for treatment. Tests after first consultation included body mass index 26.1 kg/m^2, prolactin 4.1 ng/mL, anti-Mullerian hormone 0.02 ng/mL, anti-nuclear antibody >×40, anticardiolipin antibody, cardiolipin antibody β2-glycoprotein-1 complex >1.2 U/mL, free-thyroxine 1.16 ng/dL, thyroid stimulating hormone 1.49 μIU/mL, and anti-thyroid peroxydase antibody 8 IU/mL.

Clinical course before follicle growth cycle

As the patient had amenorrhea at the time of the first visit, she was prescribed a conjugated estrogen tablet (PREMALIN, Pfizer, Japan) 0.625 mg × 2 Tab × 10 days and Norethisterone (Norluten, Fujipharma, Japan) 5 mg × 2 Tab × 10 days; from the 11th day, estradiol (Julina, Bayer, Japan) 0.5 mg × 6 Tab × 10 days was prescribed. The first treatment started with withdrawal bleeding on the 2nd day. Thereafter, clomiphene citrate (Clomid, Fujipharma, Japan) mainly via oral administration, estradiol (Estrana Tapes, 0.72 mg, Japan) as a transdermal estrogen patch, and human menopausal gonadotropin (hMG) (HMG "F," Fujipharma, Japan) as an injection were administered for 11 cycles, but no follicular development was observed. In every cycle, 19–94 days after the start of stimulation, treatment was discontinued because of the elevation of FSH and luteinizing hormone (LH).

Twelfth cycle of estrogen replacement + oral GnRH antagonist

The ethics committee of our hospital had approved the application of the oral GnRH antagonist

relugolix[7] for infertility treatment in March 2019; thus, this patient received oral GnRH antagonist treatment.

After canceling the 11th cycle, she was prescribed estrogen (PREMALIN) 0.625 mg × 2 Tab × 10 days and Norethisterone (Norluten) 5 mg × 2 Tab × 10 days; from the 11th day, she was prescribed estradiol (Julina) 0.5 mg × 6 Tab × 10 days. Treatment was started from withdrawal bleeding at 4th day. While continuing with six Julina tablets, ovarian stimulation was initiated with 2 Estrana Tapes (0.72 mg), 1 Relumina tablet (40 mg; relugolix, ASKA, Japan), and one clomid tablet (50 mg). Thereafter, the stimulation of the clomid was administered at an appropriate interval, and a 13-mm follicle was confirmed on the 14th day of the stimulation; further, hMG and GnRH antagonist injections were added for follicular development. After 2 days, follicular growth of 18 mm was observed, and as a final oocyte maturation trigger, human chorionic gonadotropin (hCG) 10,000 IU was administered 35 h before oocyte retrieval (Fig. 1, 2). Although the follicle had shrunk to 12 mm on the day of egg collection (Fig. 3), an egg was collected under intravenous general anesthesia, and the collected egg was at the meitosis-2 (M2) stage. Semen findings were 7.8 mL, motile sperm 2 × 10^6/mL, and fertilization was performed by intracytoplasmic sperm injection (ICSI). Fertilization was confirmed the next day, so it was cryopreserved in the state of two pronuclei.

																	trigger		OPU	
cycle day		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
stimulation		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
hMG																150	150			
cetrotide																A	A			
estradiol tape		2		2		2		2		2		2		2		2		2		
relugolix		1																		
clomiphene citrate		1					1								1					
estradiol		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6		
Rt	1	5 x 5						5 x 4							14 x 12		20 x 16			
	2																			
	3																			
	4																			
	f	1						1							1		1(1)			
Lt	1																			
	2																			
	3																			
	4																			
	f	0						0							0		0			
EM		7.5						7.6							10.6		9.9			
FSH		4.5						11.9							9.4		15.1			
LH		3.1						6.6							8.0		10.8			
E2		154						221							522		460			

Fig. 1 Clinical course during controlled ovarian stimulation

Administered agents (upper column): hMG, human menopausal gonadotropin (IU); cetrotide, 0.25 mg; estradiol tape, Estrana Tapes 0.72 mg; relugolix, RELUMINA 40 mg; climiphene citrate, clomid 50 mg; estradiol, Julina 0.5 mg.

Ultrasound measurement (middle column): diameter of maximum four follicles (mm); f, follicle count ≥ 5 mm, parentheses ≥ 14 mm; EM, thickness of the endometrium (mm).

Serum concentration of hormone (lower column): E2, serum estradiol (pg/mL).

A combination of estradiol tape, relugolix, clomiphene, and estradiol (oral) was used for follicle development while maintaining FSH and LH, and if the follicle grew to ≥10 mm, hMG and antagonist (injection) were used together.

OPU: ovum pick-up

FSH: follicle stimulating hormone

LH: luteinizing hormone

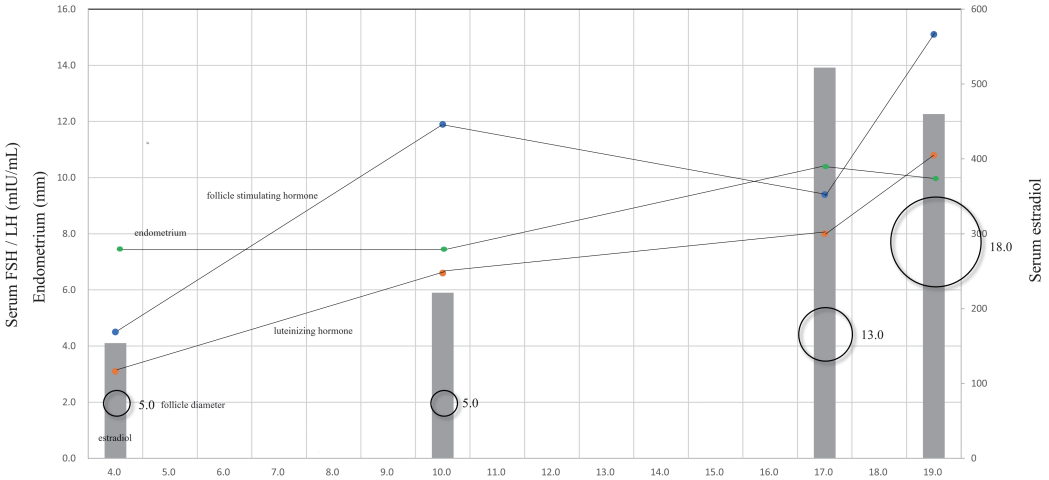

Fig. 2 Twelfth cycle of estrogen replacement + oral GnRH antagonist
Clinical course of serum hormone level (follicle stimulating hormone, luteinizing hormone, estradiol), thickness of endometrium and follicle diameter of the right ovary at cycle day 4, 10, 17 and 19.
GnRH: gonadotropin-releasing hormone
FSH: follicle stimulating hormone
LH: luteinizing hormone

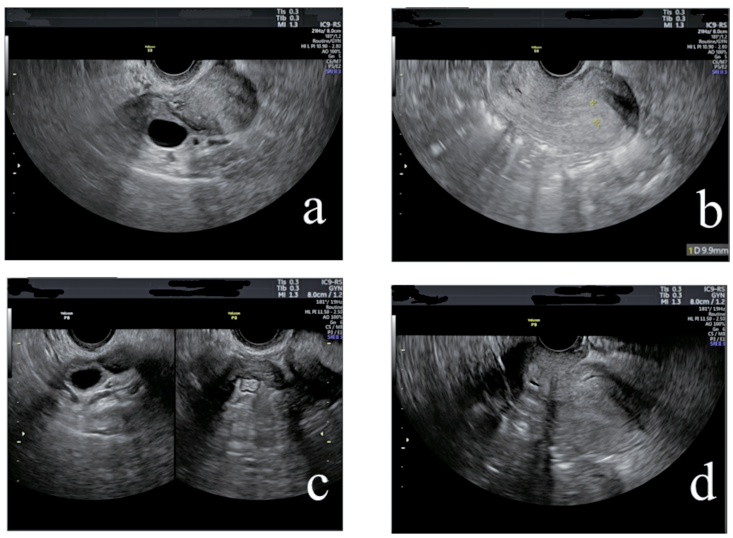

Fig. 3 Ultrasound image findings at the time of the egg retrieval decision and on the day of egg retrieval
Fig. 3a: Follicle of the right ovary (20×16 mm) on the egg retrieval decision.
Fig. 3b: Endometrium (9.9 mm) on the egg retrieval decision.
Fig. 3c: Follicle of the right ovary (12 mm) on the day of egg retrieval.
Fig. 3d: Endometrium (not measured) on the day of egg retrieval.

Frozen embryo transfer and clinical course

After oral administration of Premarin and Norluten for 10 days after egg collection and withdrawal bleeding on the 3rd day, hormone replacement was started with 2 Estrana Tapes (0.72 mg), and luteal replacement was performed with chlormadinone acetate (Lutoral, Fujipharma, Japan) 2 mg × 3 Tab × 3 days (Fig. 4). Frozen embryo transfer of day 2 embryos (4-cell) was performed, and after 17 days (4 weeks + 5), the pregnancy test was positive and serum hCG was 3692 mIU/mL.

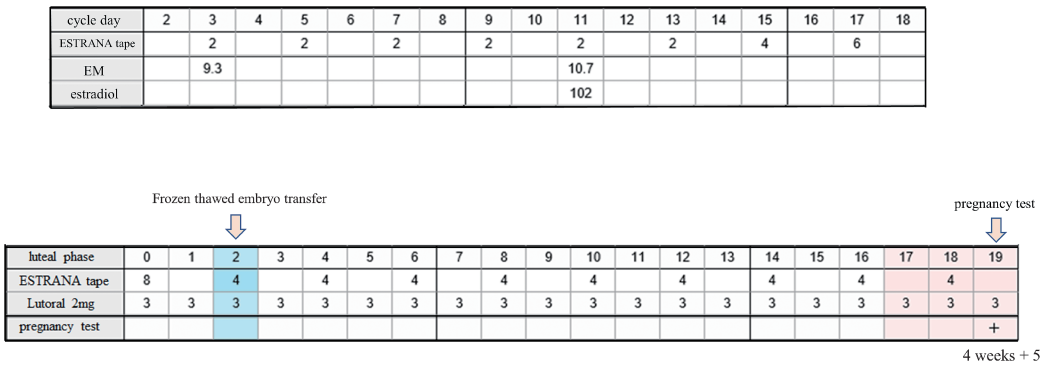

Fig. 4 Clinical course of frozen embryo transfer with hormone replacement therapy

Clinical course of hormone replacement for frozen embryo transfer (top): Estrana Tapes 0.72 mg; EM (measured as thickness of endometrium [mm]); estradiol (measured as serum concentration [pg/mL]). Clinical course after priming with progesterone (bottom).

Starting with 2 Estrana Tapes (0.72 mg) every other day and on day 11 of the cycle, the endometrium was 10.7 mm and serum estradiol was 102 pg/mL, so the day of transfer was decided 10 days later. Priming of progesterone was performed at CD 19 (luteal phase 0 day) and at 4 weeks + 5, and the pregnancy test was positive.

Subsequently, gestational sac (GS) and fetal heart beat (FHB) were confirmed in 6 weeks + 2, with GS diameter 49.5 mm, crown-rump length 22.5 mm, and FHB (+) in 8 weeks + 6; the formation of subchorionic hematoma and the like were not observed.

The patient was admitted to the perinatal management facility. She delivered a healthy baby of 3,732 g via cesarean section at 41 weeks + 2.

DISCUSSION AND CONCLUSION

Cases of pregnancy with POI are uncommon, and among these, pregnancy cases receiving no treatment are rare, as can be seen from the review of Eloise et al.[8] Therefore, some intervention is necessary when visiting the hospital in the hope of raising a child. Based on the report by Eloise et al, the treatments that have been performed in previous pregnancy cases with POI can be classified as therapies based mainly on 1) hormone replacement therapy (estrogen + progesterone), 2) oral contraceptives, 3) estrogen replacement therapy (ERT), and 4) others (such as recombinant FSH, Chinese herbal, azathioprine, antagonist, and in vitro maturation [IVM]). Our clinic prefers ERT in combination with clomiphene, hMG, and GnRH antagonists while measuring the hormone levels. The theoretical background of the treatment based on ERT is as follows: nearly three of four women with POI have residual follicles in their ovaries.[9] However, the steep rise in LH

levels causes premature luteinization, resulting in a loss of possibility for spontaneous ovulation and response to ovarian stimulation.[10] Therefore, supplementation with estradiol suppresses LH levels and prevents premature luteinization of follicles while promoting follicular development by endogenous or exogenous gonadotropins.[11] Moreover, patients with POI exhibit downregulated FSH receptors in granulosa cells owing to a constant high FSH level, which is suppressed by the use of estradiol. As a result, estradiol restores FSH receptor and enhances the response of the ovarian follicle pool to exogenous gonadotropins.[12] Furthermore, we added a small amount (50 mg/1–10 days) of clomiphene to promote the slow secretion of endogenous FSH.

According to the above idea, in this case, while controlling the excessive elevation of endogenous gonadotropin, clomiphene, hMG, and GnRH antagonist were used in combination to perform ovarian stimulation, but no follicular development was observed for a total of 29 months.

With regard to the application of GnRH antagonists in patients with POI, only a few cases of pregnancy with POI have been reported. One study showed that estrradiol was difficult to use because of Hodgkin's disease and breast cancer after chemotherapy and radiation[13]; therefore, a GnRH antagonist (injection) was selected for use.

For patients who feel the mental and physical strain by injection, there might be the advantage of using oral antagonist due to the following reasons: 1) oral administration has a longer half-life (45.42 ± 9.4669) h[14,15] than that of injection (5.0 [2.4–48.8] h, 0.25 mg single sub cutaneous),[16] 2) the adherence of the antagonist is better compared with the injection because it is administered orally, and 3) no flare-up phenomenon is reported.

This case was treated by suppressing endogenous gonadotropin using ERT and an oral GnRH antagonist with a long half-life and adjusting the balance using a small dose of clomiphene to prevent excessive decrease in endogenous FSH. This treatment also promoted follicular development and was considered to be successful. To our knowledge, this is the first reported case of follicular development, egg collection, embryo transfer, and pregnancy using ERT, clomiphene, and an oral GnRH antagonist in a patient with POI.

Regarding the limitations of this case, the cause of POI is often unknown, but genetic, autoimmune, iatrogenic, metabolic, infectious, or environmental factors are considered.[17] In this case, the POI diagnostic criteria were met at the first visit, but no chromosomal test was performed.

In addition, if an oral GnRH antagonist can be used without restrictions related to the place of residence in the near future, it can be a treatment option for patients with POI who desire infertility treatment, and the oral GnRH antagonist Elagolix[18] has also been shown to be applicable in infertility treatment.

In conclusion, when patients with POI wish to undergo infertility treatment, the appropriate combination treatment of clomiphene, oral GnRH antagonist (relugolix), hMG, and GnRH antagonist (injection) can help develop follicle growth with the suppression of gonadotropin by ERT.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This manuscript adheres to the Declaration of Helsinki, and the patient provided informed consent, and the study design was approved by the appropriate ethics review board.

CONSENT FOR PUBLICATION

The participant has consented to the submission of the case report to the journal.

AUTHOR CONTRIBUTIONS

All authors contributed to the preparation of this case report article. The authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare no competing interests to disclose.

FUNDING

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

ACKNOWLEDGMENTS

We would like to thank the medical staff at Asada Ladies Clinic for their support and assistance.

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