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Research Article

The Early Coasting Method during Ovarian Stimulation in Antagonist Protocols with Combined Use of Cabergoline is Useful in Patients with Polycystic Ovary Syndrome

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Abstract

Purpose: This study aimed to investigate the efficacy of withholding gonadotropins (coasting) and early administration of cabergoline in a flexible Gonadotropin-Releasing Hormone (GnRH) antagonist protocol for patients with Polycystic Ovarian Syndrome (PCOS).

Methods: From November 2014 to April 2019, we studied 30 patients with PCOS aged <40 years who received their first assisted reproductive technology treatment on the basis of a flexible GnRH antagonist protocol. Sixteen patients received 1-4 days of coasting after the follicle size reached 13-15 mm, and cabergoline 250 mg per day was started simultaneously. Fourteen patients received the conventional antagonist protocol. Clinical outcomes were compared between the two groups.

Results: Coasting was performed for 1.65±1.08 days and it significantly reduced the amount of gonadotropin and GnRH antagonist used. The numbers of retrieved oocytes and morphologically good quality blastocysts were significantly higher in patients who received coasting and cabergoline than in those who received the conventional antagonist protocol (both P<0.05). The live birth rate was similar by thawed-embryo transfer cycles between the groups (92.9% vs 78.6%, p=0.298).

Conclusion: The combined use of coasting and cabergoline during ovarian stimulation in the GnRH antagonist protocol is effective for assisted reproductive technology treatment in patients with PCOS.

Keywords: Assisted reproductive technology; Cabergoline; Coasting; Gonadotropin-releasing hormone antagonist; Polycystic ovarian syndrome

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Introduction

Polycystic Ovarian Syndrome (PCOS) has been reported in 6.1%-19.9% of infertile patients [1,2]. PCOS contains more than 10 follicles in the unilateral ovary and is characterized by an irregular menstrual cycle for more than 40 days, anovulation and hyperandrogenism [3]. In the criteria of the Japan Society of Obstetrics and Gynecology, PCOS is also diagnosed if there are high serum Luteinizing Hormone (LH) concentrations or a high LH/Follicle-Stimulating Hormone (FSH) ratio >1 [4].

Ovarian stimulation using clomiphene or an aromatase inhibitor is effective for these patients in the timing of intercourse and artificial insemination treatment [5]. A gonadotropin injection is required in patients with resistance to these oral medicines [6,7]. However, there is a risk of multiple pregnancies and Ovarian Hyperstimulation Syndrome (OHSS) owing to multiple follicular growth, and ovarian stimulation should be carefully performed [7,8]. In the treatment of Assisted Reproductive Technology (ART), which prevents the occurrence of severe OHSS in high responders, is also an important issue [9-12]. A Gonadotropin-Releasing Hormone (GnRH) antagonist protocol combined with a GnRH agonist trigger [10,12,13], coasting of gonadotropin injection [14-16], and administration of cabergoline after oocyte retrieval [15-21] is recommended to reduce the risk of OHSS in ovarian stimulation in patients with PCOS. Additionally, avoiding fresh embryo transfer and freezing all embryos greatly reduce the risk of the occurrence of late-onset OHSS [22-24].

In recent years, obtaining a large number of oocytes by controlled ovulation stimulation has been a goal to obtain multiple live births using only one time of oocyte retrieval [25-28]. Furthermore, making as many blastocysts as possible for preimplantation genetic screening has been attempted [29,30]. However, development of numerous follicles in the early follicular phase increases the potential of the occurrence of early-onset severe OHSS, even if the freeze-all strategy is considered [31]. Therefore, many physicians hesitate in continuing injection of gonadotropins because of early discomfort, abdominal pain, and accumulation of ascites when they observe a large number of follicles growing.

The early coasting method (withholding gonadotropins) controls follicular development during the mid to late follicular phase and has led to appropriate clinical outcomes in the GnRH agonist long protocol [14,32]. There have been a few reports on the early coasting method based on the GnRH antagonist protocol [16,33,34]. However, the cumulative pregnancy rate and clinical outcomes after thawed embryo transfer are unknown. Therefore, this study aimed to investigate the efficiency of early coasting in the GnRH antagonist protocol in patients with PCOS.

Materials and Methods

Patients

This study included women aged ≤40 years with a high ovarian reserve due to PCOS who received their first ART session at our clinic from November 2014 to April 2019. Patients with PCOS who matched the Japanese criteria were recruited in this study.

Ovarian stimulation

Ovarian stimulation was performed with daily subcutaneous gonadotropin injections of 225-300 IU (Gonal-F; Merck Biopharma, Tokyo, Japan/FOLYRMON-P; Fuji, Toyama, Japan/HMG-F; Fuji, Toyama, Japan/HMG-Ferring; Ferring Pharmaceuticals, Tokyo, Japan) without pituitary suppression by GnRH agonists. Measurement of serum LH and estradiol levels was started when the leading follicles reached approximately 14 mm, and a GnRH antagonist (Cetrotide; Merck Biopharma) was flexibly administered according to serum LH concentrations or follicular growth. Early coasting was performed when the leading follicles reached 13-15 mm in high responder patients with >15 developing follicles to prevent OHSS. At the same time, daily intake of cabergoline 250 mg (Sawai Pharmaceutical Co., Ltd., Osaka, Japan) was administered to prevent production of ascites.

Daily measurement of the size of these follicles and monitoring of serum estradiol, progesterone, and LH levels were continued during coasting. The duration of coasting days was adjusted depending on follicular development. Gonadotropin injection was added according to follicular development. After the leading follicles exceeded 18 mm in diameter, ovulation was triggered by any of the following methods: two times of 300 μg GnRH agonist nasal spray (Buserecure; Fuji, Toyama, Japan), human chorionic gonadotropin 3000-5000 IU (HCG Fuji; Fuji, Toyama, Japan) injection, or a combination of GnRH agonist nasal spray with human chorionic gonadotropin 1500-3000 IU injection.

Women who received the usual antagonist protocol without coasting between November 2014 and September 2019 were retrospectively compared as a control group with women who had coasting and cabergoline (CS group).

Oocyte retrieval, insemination, embryo culture and cryopreservation

Oocytes were picked up 36-37 hours after the trigger using a 20 G needle under cervical block with 1% xylocaine injection (xylocaine injection 1%; Aspen, Tokyo, Japan), a diclofenac sodium suppository (Voltaren; Novartis, Tokyo, Japan), and intravenous anesthesia with propofol (propofol intravenous injection 1%, 20 ml, Maruisi; Maruishi Phramaceutical, Osaka, Japan). *In Vitro* Fertilization (IVF), Intracytoplasmic Sperm Injection (ICSI), or split-ICSI (IVF+ICSI) were performed 1-3 hours after collection of oocytes. Fertilization was confirmed 20 hours after insemination and embryos were cultured until the blastocyst stage. The embryo quality was evaluated morphologically at day 3 and days 5-6. One or two good quality embryos were cryopreserved using a vitrification procedure on day 3 and blastocysts with much better quality than CC grade (Gardner's classification) were additionally cryopreserved.

Cabergoline 250-500 mg and low-dose aspirin (Bayaspirin 100 mg; Bayer, Osaka, Japan) were used for preventing ascites production and thrombosis after oocyte retrieval. The severity of OHSS was evaluated by abdominal pain, discomfort and the estimated ascites volume. The necessity of hospitalization was assessed by each physician in each case.

Embryo transfer

Single frozen-thawed embryo transfers were conducted with a hormone replacement cycle or ovulation cycle after one or more menstruation cycles from oocyte retrieval. Hormone replacement cycles consisted of estrogen replacement using a transdermal estrogen patch (Estrana® Tapes 0.72 mg; Hisamitsu, Saga, Japan) or conjugated estrogen tablets (PREMARIN®; Pfizer, Tokyo, Japan) from days 3-5, and a sequential progestin vaginal suppository (lutinus; Ferring Pharmaceuticals, Tokyo, Japan). Ovulation cycle embryo transfers were conducted in spontaneous ovulation cycles or in ovarian stimulation cycles with an aromatase inhibitor. A urinary test was performed 2 weeks after embryo transfer to determine pregnancy. Clinical pregnancy was determined according to the appearance of a gestational sac, and hormone replacement therapy was continued until 10 weeks of gestational age.

Statistical analysis

The CS group was compared with the control group. Differences in the patients' characteristics and clinical outcomes were compared using the Mann-Whitney U test and chi-square test. All statistical comparisons were performed with Ekuseru - Toukei (Ekuseru - Toukei 2012; Social Survey Research Information Co., Ltd., Tokyo, Japan). P values <0.05 were considered significant.

Results

Thirty patients were diagnosed with PCOS according to the Japanese diagnostic criteria. Sixteen patients were in the CS group and 14 were in the control group. The clinical outcomes in each group are shown in tables 1 and 2.

	CS group	Control group	P*
N	16	14	
Age (years)	33.6±3.6	35.1±3.4	0.276
AMH (ng/ml)	11.4±5.0	8.9±2.9	0.124
Gravidity	0.75±1.18	0.57±1.09	0.717
Parity	0.31±1.01	0.07±0.27	0.604
Body mass index (kg/m2)	23.2±4.30	23.5±4.12	0.803
Day 3 FSH (mIU/ml)	6.17±1.37	6.38±1.58	0.618
Day 3 LH (mIU/ml)	7.74±3.64	8.02±3.68	0.708
DHEA-s (μg/dl)	209.1±156.8	221.7±89.5	0.800
Testosterone (ng/ml)	0.38±0.18	0.52±0.24	0.203
Total amount of Gn (IU)	1331.3±242.6	1682.1±345.2	0.004
Duration of Gn injection (days)	7.25±1.06	9.14±1.29	<0.001
Total amount of GnRH antagonist (mg)	0.132±0.155	0.58±0.29	<0.001
Duration of GnRH antagonist injection (days)	0.69±0.79	2.43±1.02	<0.001
Duration of Gn coasting (days)	1.69±1.08	0	<0.001
Number of follicles >14 mm	14.63±5.08	11.21±3.02	0.036
Estradiol (pg/ml) on the day of ovulation induction	10103.0±5132.9	4602.4±3436.1	0.001
LH (mIU/ml) on the day of ovulation induction	3.52±1.78	4.07±5.58	0.114

Progesterone (ng/ml) on the day of ovulation induction	1.24±0.69	0.68±0.29	0.012

Table 1: Characteristics of patients with polycystic ovarian syndrome in both groups.

Values are mean ± standard deviation. *Mann-Whitney U test.

Abbreviations: AMH, Anti-Müllerian Hormone; DHEA-s, Dehydroepiandrosterone Sulfate; FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; Gn, Gonadotropin; GnRH, Gonadotropin-Releasing Hormone; CS, patients with polycystic ovarian syndrome who received coasting.

	CS group	Control group	P*
Number of retrieved oocytes	22.75±8.93	15.23±3.83	0.011
Number of oocytes for IVF	10.25±8.99	8.36±5.52	0.079
Number of 2PN in IVF	6.25±6.40	6.8±3.85	0.619
Number of oocytes for ICSI	12.88±10.91	8.71±4.78	0.419
Number of MII oocytes in ICSI	11.56±9.02	6.79±3.96	0.091
Number of 2PN in ICSI	8.43±7.24	4.86±3.21	0.054
Total number of 2PN	14.69±6.36	9.71±3.83	0.067
Number of good quality embryos at day 3	9.44±5.60	5.93±3.65	0.208
Number of cryopreserved embryos at day 3	1.63±0.5	1.93±0.27	0.054
Number of prolonged culture embryos	13.06	7.78	0.055
Number of good quality expanded blastocysts (≥3BB)	4.13±3.32	1.36±1.34	0.012
Number of expanded blastocysts (>3CC)	6.63±4.91	2.36±2.53	0.016
Total number of blastocysts	9.31±6.23	5.29±3.24	0.084
Number of cryopreserved blastocysts	7.25±5.05	3.71±2.97	0.053
Total number of cryopreserved embryos	8.38±4.86	5.14±2.77	0.082
Number of patients hospitalized due to severe OHSS	0	0	1.000
Cumulative pregnancy rate, % (n)†	92.9 (13/14)	78.6 (11/14)	0.298
Live birth rate, %(n)‡	92.9 (13/14)	78.6 (11/14)	0.298

Table 2: Clinical outcomes of assisted reproductive technology treatment in both groups.

Values are mean ± standard deviation. *Mann-Whitney U test.

Abbreviations: CS, patients with polycystic ovarian syndrome who received coasting; IVF, In Vitro Fertilization; 2PN, two Pronuclei; ICSI, Intracytoplasmic Sperm Injection; MII, Metaphase II; OHSS, Ovarian Hyperstimulation Syndrome. BB and CC indicate Gardner classification grades.

†The cumulative pregnancy rate per patient who underwent thawed embryo transfer. Two patients did not undergo embryo transfer for private reasons in the CS group. ‡The live birth rate per patient who underwent thawed embryo transfer.

Comparison between the groups using the Japanese diagnostic criteria

There were no significant differences in the women's age, anti-Müllerian hormone levels, gravidity, parity, body mass index, and basal hormone levels between the CS and control groups. The mean (SD) coasting duration in the CS group was 1.69 (1.08) days. The dose of gonadotropin, the number of days of gonadotropin injection, the dose of the antagonist, and the number of days of GnRH antagonist injection were significantly lower in the CS group than in the control group (p=0.004, <0.001, <0.001, <0.001). The number of follicles >14 mm, and serum estradiol and progesterone concentrations at the day of the ovulation trigger were significantly higher in the CS group than in the control group.

Figure 1 shows the changes in serum estrogen and LH concentrations at the start and end of coasting according to the duration of coasting. No patients showed a decrease in estradiol values after coasting. Additionally, LH concentrations after coasting in all patients were maintained at >1.0 mIU/ml, which were considered sufficient for the GnRH agonist trigger.

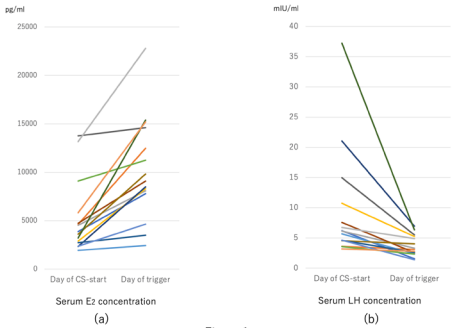

Figure 1: (a) Changes in serum estradiol concentrations in each patient in the coasting group from the day of starting coasting to the day of the ovulation trigger. None of the patients' estradiol values decreased after 1-4 days of coasting. (b) Changes in serum LH concentrations in each patient in the coasting group from the day of starting coasting to the day of the ovulation trigger. All patients' LH values decreased after coasting, but they were >1.0 mIU/ml in each patient on the day of the ovulation trigger.

CS, patients with polycystic ovarian syndrome who received coasting; E2, Estradiol; LH, Luteinizing Hormone.

The number of retrieved oocytes was significantly higher in the CS group than in the control group, but the total number of normal fertilized embryos by IVF or ICSI was comparable between the two groups. The number of good quality blastocysts of ≥3BB (Gardner classification) was significantly higher in the CS group than in the control group. The blastocyst formation rate per embryos cultured additionally after day 3 and the rate of high-quality blastocyst formation (≥3BB) were significantly higher in the CS group than in the control group. There was no significant difference in the cumulative pregnancy rate per patient who received subsequent frozen-thawed embryo transfer or the live birth rate between the two groups. No patients required hospitalization for severe OHSS.

Discussion

In this study, we retrospectively investigated ovarian stimulation using a GnRH antagonist protocol with the early coasting method and cabergoline in patients who were hyper-responders and diagnosed with PCOS by the Japanese criteria. This protocol was useful in these women who had an extremely high ovarian reserve and it improved clinical outcomes without the occurrence of severe OHSS. The early coasting protocol reduced the amount and duration of using gonadotropin and a GnRH antagonist, increased the number of retrieved

oocytes, and increased the number of high-quality blastocysts compared with the conventional GnRH antagonist protocol. This protocol might improve the cumulative pregnancy rate following embryo transfer cycles in patients with PCOS owing to the large number of good quality embryos.

In the GnRH agonist long protocol, even when coasting is performed in the mid to late follicular phase, the pregnancy and live birth rates are comparable with the conventional long protocol [14,35-38]. However, the rate of OHSS is decreased in the GnRH agonist long protocol, even in pregnant women [35-38]. There have been several controversial reports about the clinical effectiveness of coasting in the GnRH antagonist protocol [33,34]. In the antagonist protocol, serum estrogen concentrations decrease during coasting, but there is little effect on the embryo quality [33]. Benadiva et al., reported that serum gonadotropin concentrations had a sufficient effect on follicular development and serum estrogen level for 1.9±0.9 days (mean±SD), even after the injection was stopped in GnRH agonist protocol [39]. In our method, we started early coasting for 1-4 days in patients who had a relatively high number of large follicles when the leading follicle grew up to 13-15 mm in diameter. In this study, prolonged coasting for 3-4 days did not decrease serum estrogen concentrations. These patients had a sufficient number of oocytes and good quality embryos available for cryopreservation.

In this study, the rate of blastocyst formation per additional cultured embryos was increased in the CS group, especially the rate of high-quality blastocyst formation. Observing large numbers of follicles with ultrasound during ovarian stimulation may strongly indicate a risk of severe OHSS and may lead to premature trigger use without waiting for sufficient follicular development. Insufficient follicular development reportedly leads to oocyte immaturity and a low potential of blastocyst formation [40]. However, coasting may improve embryo quality due to waiting for oocyte maturation during withholding of additional gonadotropin and GnRH antagonist injection without the concern of early-onset severe OHSS occurring.

Cabergoline is usually used to suppress prolactin secretion from the pituitary gland in patients with hyperprolactinemia. Cabergoline also suppresses the Vascular Endothelial Growth Factor (VEGF)/vascular endothelial growth factor receptor pathway by inhibiting vascular endothelial growth factor receptor phosphorylation and reducing ascites retention after ovarian stimulation in the ART cycle [41]. The use of cabergoline is recommended to prevent severe OHSS with significantly reducing the production of ascites after oocyte retrieval [19,20]. Gaafar et al., reported that early administration of cabergoline in the middle follicular phase was useful for preventing the incidence of severe OHSS [18]. In our study, cabergoline was used from the day of coasting for 5-8 days. The use of cabergoline before oocyte retrieval did not adversely affect the embryo quality after oocyte retrieval. As a result, this method resulted in good clinical outcomes in patients without hospitalization for severe OHSS.

This was a retrospective case-control study with a small number of PCOS cases. A randomized, prospective study with a larger sample size is required to show the effectiveness of the coasting method in patients with PCOS with or without the combined use of cabergoline.

Conclusion

In controlled ovarian stimulation of patients with a high ovarian reserve, such as those with PCOS, the early coasting method may be useful in a GnRH antagonist protocol. This protocol may improve embryo quality and clinical outcomes without the occurrence of severe OHSS requiring hospitalization by the early combined use of cabergoline.

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Disclosure

Human rights statements and informed consent: All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and its later amendments. Informed consent was obtained from all patients for being included in the study.

Approval By Ethics Committee

This retrospective study was approved by our institutional review board (No. 2019-01).

Conflict of Interest

The authors declare no conflict of interest.

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