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ORIGINAL ARTICLE

Chlormadinone acetate in progestin-primed ovarian stimulation does not negatively affect clinical results

Sena Shibasaki[1,2] | Hiromitsu Hattori[1,2] | Masae Koizumi[1] | Satoko Nagaura[1] | Mayumi Toya[1] | Hideki Igarashi[1] | Koichi Kyono[1,2,3,4]

[1]Kyono ART Clinic Sendai, Sendai, Japan

[2]Kyono ART Clinic Shinagawa/ Japan Human Ovarian-tissue Preservation Enterprise (HOPE), Tokyo, Japan

[3]Kyono ART Clinic Takanawa, Tokyo, Japan

[4]Kyono ART Clinic Morioka, Iwate, Japan

Correspondence
Koichi Kyono, Kyono ART Clinic Takanawa, Takanawa 3-13-1 Takanawa COURT 5F, Minato-ku, Tokyo, 108-0074, Japan.
Email: info@ivf-kyono.or.jp

Abstract

Purpose: To investigate whether progestin-primed ovarian stimulation (PPOS) with chlormadinone acetate (CMA) adversely affects clinical results and neonatal outcomes, or causes congenital deformities.

Methods: This retrospective study was conducted at private IVF clinic from November 2018 to November 2021. Women underwent oocyte retrieval using gonadotropin-releasing hormone (GnRH) antagonist protocol ($n=835$) or PPOS protocol ($n=57$) were included. Eligible patients were normal ovarian responders (aged <40, AMH ≧1.0 ng/mL) with freeze-all cycle. Embryo developments, clinical results, or neonatal outcomes of singletons derived from transfer of frozen single blastocysts were compared within each group.

Results: Patient characteristics were similar in both groups. The median LH level (mIU/mL) at trigger in the GnRH antagonist group [2.0 (1.2–3.7)] was significantly higher than in the PPOS group [0.9 (0.3–1.7)]. There was no cycle with premature LH surge in the PPOS group. Fertilization and blastocyst formation rates did not differ significantly between groups. Furthermore, clinical outcomes were also similar in the two groups. Congenital abnormality rates did not differ significantly [0.9% (3/329), 0.0% (0/17)].

Conclusions: CMA using ovarian stimulation did not negatively affect clinical results. Our data suggest that PPOS with CMA is an appropriate ovarian stimulation method for normal ovarian responders.

KEYWORDS
chlormadinone acetate, congenital abnormality, cryopreservation, newborn infant, ovulation induction

1 | INTRODUCTION

Controlled-ovarian stimulation (COS) is widely used for patients undergoing assisted reproductive technology (ART) procedures. COS, using gonadotropin drugs, often causes ovarian hyper-stimulation syndrome (OHSS) or a premature luteinizing hormone (LH) surge to retrieve multiple oocytes. A gonadotropin releasing hormone (GnRH) antagonist is routinely used in order to collect multiple oocytes and to prevent OHSS and a premature LH surge. Its suppressive effect lasts for a short period without an initial flare-up effect.[1] On the

other hand, a new regimen for COS, progestin-primed ovarian stimulation (PPOS) was first reported in 2015. Kuang et al. found that administration of exogenous progesterone (P), medroxyprogesterone acetate (MPA) during the follicle phase prevents OHSS or a premature LH surge by negative feedback, by decreasing the frequency of GnRH pulses from the hypothalamus.[2]

There have been several reports on PPOS using exogenous synthetic progestin, such as MPA, dydrogesterone (DYG). Some studies have indicated that clinical outcomes, neonatal outcomes, and the incidence of congenital deformities are similar in PPOS using MPA and conventional ovarian stimulation protocols, such as the GnRH antagonist protocol, the short protocol or mild ovarian stimulation.[3–5] According to Yu et al., DYG could be an appropriate alternative progestin for PPOS.[6] It has been reported that the clinical and ongoing pregnancy rates in PPOS with dydrogesterone are comparable to those of a GnRH antagonist protocol.[7] One recent study reported that the rate of mature oocytes was higher with PPOS using dienogest (DNG) than with DYG, although the fertilization rate was similar.[8] In contrast, there are very few reports on PPOS with chlormadinone acetate (CMA), an oral progestin. The moderate antiandrogenic effect of CMA runs a risk of hypospadias for male newborns if taken orally during pregnancy.[9]

Takeshige et al. previously proposed that PPOS using CMA could be an appropriate alternative for COS.[10] To our knowledge, this is the first report on the impact of PPOS with CMA on neonates. We investigated clinical results, neonatal outcomes, and incidence of congenital deformities between protocols using a GnRH antagonist and using PPOS with CMA in freeze-all cycles.

2 | MATERIALS AND METHODS

2.1 | Study design

This retrospective study was conducted at a single center, Kyono ART Clinic Sendai, from November 2018 to November 2021. It included 835 cycles using a GnRH antagonist protocol (ANT) in 740 patients and 57 cycles with a PPOS protocol in 48 patients. We included normal responders, aged <40 years at oocyte pick up (OPU) and Anti-Müllerian Hormone (AMH) levels ≧1.0 ng/mL according to the Bologna criteria.[11] Patients who had performed pre-implantation genetic tests, in vitro maturation, or severe male factor, and poor ovarian responders were excluded from this study, which was approved by the Ladies Clinic Kyono Ethics Committee. All participants provided written informed consent.

2.2 | Study protocol

In our clinic, the antagonist protocol is the first choice for ovarian stimulation in the first oocyte retrieval; the second and subsequent ovarian stimulation methods is selected based on previous treatment result, basic patient characteristics and ovarian response. Ovarian stimulation was initiated using CMA (Lutoral, 2 mg: Fuji Pharma, Japan) and human menopausal gonadotropin (hMG) or follicle stimulation hormone (FSH) at follicle phase. The hMG or FSH dosage was selected depending on basic patient characteristics, such as age, antral follicle count, anti-Müllerian hormone, and body mass index, based on past treatment. Patients were triggered for final oocyte maturation with human chorionic gonadotropin (hCG) and GnRH agonist (Lucrin, 1 mg: Abbvie, Australia).

According to the GnRH antagonist protocol, GnRH antagonist (Relugolix, 40 mg: ASKA Pharmaceutical Corporation, Japan) was administered when several ovarian follicles had reached a diameter of ~14 mm or more. Human chorionic gonadotropin (hCG: Gonatropin: ASKA pharmaceutical, Japan; Ovidrel, 250 μg: Merck Serono, Switzerland) only, a GnRH agonist only, or a dual trigger (GnRH agonist and hCG) were administrated for final oocyte maturation.

Vaginal ultrasound-guided follicle puncture was conducted 36–37 h after the trigger. Retrieved oocytes were cultured for 2–3 h in sequential Fert™ (Cooper Surgical®, USA) at 37°C in an atmosphere of 5.0% O_2, 6.0% CO_2, 89.0% N_2. After in vitro fertilization or intracytoplasmic sperm injection (ICSI), all embryos were cultured in single-step medium, continuous single culture-NX (FULIFILM Wako Pure Chemical Corporation, Japan) or global® total® LP (Cooper Surgical®, USA) until day 6.

Blastocysts were cryopreserved at least 3BC< on day 4, 5, or 6. Blastocysts were scored according to Gardner's score.[12] Good-quality blastocysts were defined as 3BB≦ on day 5, 4BB≦ on day 6, and not including C. All embryos were cryopreserved for vitrification with an opened system using a CryoTop® (Kitazato, Japan) device. The protocol used was based on the Kitazato Vitrification Kit (Kitazato, Japan).

2.3 | Frozen–thawed embryo transfer

All embryos were thawed using a Kitazato Thawing Kit (Kitazato, Japan) on the day of transfer and were transferred after 3–4 h of recovery culture. Frozen-thawed blastocyst transfer was performed in a natural cycle or hormone replacement treatment (HRT) cycle on the fifth day after progesterone administration (Lutoral, 2 mg: Fuji Pharma, Lutinus, Ferring Pharmaceuticals, Switzerland, Duphanston, Mylan EPD, Japan) when endometrial thickness was >7 mm. Clinical pregnancy was defined as more than 50 mIU/mL of β-hCG at 4 weeks 0 day, and by an intrauterine gestational sac at the fifth week. If pregnancy was achieved, vaginal progesterone tablets (Lutinus, Ferring Pharmaceuticals, Switzerland) or/and oral dydrogesterone (Duphanston, Mylan EPD, Japan) were administered since 4 weeks 1 day.

2.4 | Statistical analysis

The Mann–Whitney *U*-test was used to compare patient characteristics or newborn status in each group. The chi-square test and

Fisher's exact test were used to compare percentages of embryo development or obstetric outcomes. For statistical analysis, we used the open-source software, EZR (Jichi Medical University, Saitama, Japan). $p < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient and ovarian stimulation characteristics

Patient characteristics are shown in Table 1. Patient age at oocyte retrieval, BMI value, AMH levels, and antral follicle counts (AFC) were similar between the ANT and PPOS groups. The two groups also had comparable means for basal serum LH, FSH, E2, and P levels.

Total gonadotropin dose in the PPOS group [2400 (2025–2700) IU] was higher than that in the ANT group [2025 (1650–2700) IU]. LH levels [0.3 (0.2–0.4) mIU/mL] or P levels [0.9 (0.3–1.7) pg/mL] in the PPOS protocol group at the time of trigger administration were lower than in the ANT protocol group [2.0 (1.2–3.7), 0.4 (0.2–0.6), respectively]. There were no cycles with premature LH surge rates in the PPOS group, although there was no significant difference [5.3% (44/835), 0.0% (0/57)]. Moreover, there was only one canceled cycle due to ovulation in the ANT protocol. Ovarian hyper-stimulation syndrome rates [ANT group: 7.7% (64/835), PPOS group: 12.3% (7/57)] did not differ significantly in the two groups. The median number of retrieved oocytes [ANT group: 9 (7–13), PPOS group: 9 (5–12)] was not significantly different (Table 2).

3.2 | Embryo developments

Embryo development is shown in Table 3. The oocyte maturation rate was also similar between the ANT and PPOS groups. Fertilization rates of conventional in vitro fertilization [ANT group: 71.4% (1829/2563), the PPOS group: 71.2% (79/111)] or intracytoplasmic sperm injection [81.7% (3337/4097), 80.1% (233/291)] were not significantly different in the two groups.

Similarly, blastocyst formation rates [66.1% (3366/5093), 63.5% (179/282)] and the good-quality blastocyst formation rate [33.2% (1693/5093), 32.3% (91/282)] were similar in both groups (Table 3).

3.3 | Clinical and neonatal outcomes

There were no significant differences in the clinical pregnancy rates of frozen-thawed embryo transfer [59.1% (638/1080), 50.0% (40/80)], abortion rates [18.8% (120/638), 12.5% (5/40)], or live-birth rates [30.6% (331/1080), 22.5% (18/80)] between the two groups (Table 4).

330 singletons and twins with the ANT protocol and 18 singletons in the PPOS group were live born. Neonatal outcomes of singletons delivered from frozen blastocyst transfer are shown Table 5. Birthweight and height are similar in both groups. Furthermore, the congenital abnormality rate in the ANT group [0.9% (3/329)] was similar to that in the PPOS group [0.0% (0/17)]. The three congenital deformities in the ANT group included dactylosymphysis, cryptorchidism, and congenital scalp and skull defect. The percentage of males in the PPOS group [82.4% (14/17)] was significantly higher

TABLE 1 Patient characteristics.

Group	ANT group	PPOS group	*p* value
Patients	740	48	—
Maternal age (year)[a]	35.0 (33.0–37.3)	36.0 (34.0–38.0)	0.37
Paternal age (year)[a]	36.0 (33.0–39.3)	36.0 (33.0–39.0)	0.84
BMI (kg/m^2)[a]	20.7 (19.3–22.6)	21.3 (20.0–23.1)	0.09
AMH level (ng/mL)[a]	2.5 (1.7–3.5)	2.4 (1.5–3.3)	0.20
Infertility reason			
Ovarian factor, *n* (%)	148/835 (17.7)	12/57 (21.1)	0.48
Uterine factor, *n* (%)	125/835 (15.0)	7/57 (12.3)	0.70
Male factor, *n* (%)	214/835 (25.6)	12/57 (21.1)	0.53
Tubal factor, *n* (%)	104/835 (12.5)	12/57 (21.1)	0.07
Unexplained, *n* (%)	186/835 (22.3)	10/57 (17.5)	0.51
Other, *n* (%)	58/835 (6.9)	4/57 (7.0)	1.00
Basal LH level (mIU/mL)[a]	5.7 (4.2–7.3)	5.1 (4.0–6.6)	0.13
Basal FSH level (mIU/mL)[a]	4.8 (6.5–9.6)	7.9 (6.2–9.2)	0.84
Basal E2 level (pg/mL)[a]	30.0 (19.3–41.8)	29.8 (21.6–40.1)	0.87
Basal P level (pg/mL)[a]	0.1 (0.1–0.2)	0.1 (0.1–0.2)	0.82

Abbreviations: AMH, Anti-Müllerian Hormone; BMI, body mass index; E2, estradiol; FSH, follicle stimulation hormone; LH, luteinizing hormone; P, progesterone.

[a]Values are median and interquartile range.

TABLE 2 Ovarian stimulation characteristics.

Group	ANT group	PPOS group	*p* value
Number of cycles (*n*)	835	57	—
AFC (*n*)[a]	2.5 (1.7–3.5)	2.4 (1.5–3.3)	0.20
Total gonadotropin dose (IU)[a]	2025.0 (1650.0–2700.0)	2400.0 (2025.0–2700.0)	<0.05
Triggered LH level (mIU/mL)[a]	2.0 (1.2–3.7)	0.9 (0.3–1.7)	<0.05
Triggered P level (pg/mL)[a]	0.4 (0.2–0.6)	0.3 (0.2–0.4)	<0.05
Triggered E2 level (pg/mL)[a]	1451.0 (1032.0–1954.3)	1288.0 (926.7–1851.0)	0.14
Triggered type			
Dual trigger, *n* (%)	799/835 (95.7)	57/57 (100.0%)	0.16
hCG only, *n* (%)	19/835 (2.3)	0/57 (0.0)	0.63
GnRH agonist, *n* (%)	17/835 (2.0)	0/57 (0.0)	0.62
Duration of stimulation (day)[a]	9 (8–10)	9 (8–10)	0.57
No. of oocytes retrieved[a]	9.0 (7.0–13.0)	9.0 (5.0–12.0)	0.14
Premature LH serge rate, *n* (%)	44 (5.3)	0 (0.0)	0.11
Moderate OHSS rate, *n* (%)	64 (7.7)	7 (12.3)	0.21

Abbreviations: AFC, Antral follicle count; E2, estradiol; LH, luteinizing hormone; OHSS, ovarian hyper stimulation syndrome; P, progesterone.

[a]Values are median and interquartile range.

TABLE 3 Embryo developments.

Group	ANT group	PPOS group	*p* value
Oocytes maturity rate, *n* (%)	6660/8419 (79.1)	402/527 (76.3)	0.14
Fertilization rate of IVF, *n* (%)	1829/2563 (71.4)	79/111 (71.2)	1.00
Abnormal fertilization of IVF (≧3PN) rate, *n* (%)	318/2563 (12.4)	8/111 (7.2)	0.13
Fertilization rate post- ICSI, *n* (%)	3337/4097 (81.7)	233/291 (80.1)	0.61
Degeneration rate post-ICSI, *n* (%)	162/4097 (4.0)	17/291 (5.8)	0.16
Day 3 good embryo formation rate, *n* (%)	1989/5104 (39.0)	122/285 (42.8)	0.22
Blastocyst formation rate, *n* (%)	3366/5093 (66.1)	179/282 (63.5)	0.40
Good blastocyst formation rate, *n* (%)	1693/5093 (33.2)	91/282 (32.3)	0.79

Abbreviations: ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization.

TABLE 4 Clinical results from transfers of single frozen blastocysts.

Group	ANT group	PPOS group	*p* value
Number of cycles (*n*)	1080	80	—
Clinical pregnancy rate, *n* (%)	638/1080 (59.1)	40/80 (50.0)	0.13
Miscarriage rate, *n* (%)	120/638 (18.8)	5/40 (12.5)	0.40
On-going pregnancy rate, *n* (%)	518/1080 (48.0)	35/80 (43.8)	0.49
Live-birth rate, *n* (%)	331[a]/1080 (30.6)	18/80 (22.5)	0.13

[a]Including twins.

than in the ANT group [54.9% (180/328)] ($p=0.04$). There was no hypospadias among male infants. Any neonate with missing data was excluded from the analysis.

4 | DISCUSSION

To the best of our knowledge, this is the first study to investigate pregnancy or neonatal outcomes after frozen blastocyst transfer following the PPOS protocol using CMA. The principle finding of this study is that pregnancy outcomes were comparable and the incidence of congenital deformities of singletons did not differ between the PPOS protocol using CMA and the GnRH antagonist protocol, in normal ovarian responders. These results were similar to those of previous reports using MPA or dydrogesterone. Zhang et al. showed that gestational age, birthweight, length, and incidence of congenital deformities were similar between hMG+MPA treatment and the GnRH short protocol or mild ovarian stimulation.[5] Iwami et al. argued that clinical pregnancy rates in PPOS using dydrogesterone were comparable to those with a GnRH antagonist.[7] Although the results showed a higher percentage of male infants in the PPOS

TABLE 5 Neonatal outcomes.

Group	ANT group	PPOS group	*p* value
Singletons (*n*)	330	18	—
Gestational age (week)[a]	39.4 (38.1–40.7)	39.1 (38.3–40.7)	0.80
Birthweight (g)[a]	3106.0 (2760.0–3366.0)	3219.0 (2925.0–3482.0)	0.18
Height (cm)[a]	49.9 (48.0–51.0)	49.0 (48.0–50.5)	0.57
Incidence of congenital malformations, *n* (%)	3/329[b] (0.9)	0/17[b] (0.0)	1.00
Percentage of males, *n* (%)	180/328[b] (54.9%)	14/17[b] (82.4%)	0.04

[a]Values are median and interquartile range.
[b]Excluding missing data.

group, there is no reason to believe that CMA affected embryo gender. Several reports have suggested that fertilization method or embryo and blastocyst transfer may influence the sex ratio, but we did not investigate this issue in this study.[13,14]

CMA shows moderate anti-androgenic properties by binding to androgen receptors. In 2008, the American Society for Reproductive Medicine (ASRM) expressly stated that although maternal exposure to exogenous progesterone that binds to androgen receptors during early pregnancy increased the risk of hypospadias, the risk appears to be limited.[15] However, it should be noted that this statement did not refer to CMA because it is not approved in the United States. Testosterone is involved in formation of male reproductive organs in early pregnancy. Androgen receptors are expressed in fetuses after 8 weeks of gestation. Inhibition of secretion of testicular testosterone by Leydig cells might cause hypospadias. There is only one report in Japan that administration of CMA in early pregnancy did not affect newborn infants. The incidence of hypospadias was only 0.03% and CMA consequently proved to be as safe and effective as virginal progestin tablets.[16] For this reason, at our clinic, we use vaginal progesterone tablets or oral progestins, such as dydrogesterone as progesterone replacement during pregnancy.

Similar numbers of oocytes were retrieved using the PPOS and GnRH antagonist protocols in this study. There was one canceled cycle because of ovulation with the GnRH antagonist protocol; however, no cycles were missed with PPOS. These results are consistent with previous reports for ovarian stimulation or oocyte donation cycles, compared to other ovarian stimulation protocols.[17,18] Several studies reported that the total cycle cancellation rate with the PPOS protocol did not increase compared with other ovarian stimulation protocols.[7,18] According to guidelines of the European Society of Human Reproduction and Embryology, oral progestin can prevent an LH surge without GnRH analogs in controlled ovarian stimulation.[19] Progesterone has a negative feedback function to suppress LH surging in natural menstrual cycles. Administration of progestins at early follicular phase under controlled ovarian stimulation provides hypothalamic suppression to decrease gonadotropin secretion.[20] Only a freeze-all cycle is applied since early exposure to exogenous progestin causes endometrial asynchrony. Overall, it is beneficial for patients not to experience cycle cancellation because ovulation occurs as a result of premature LH surge suppression in PPOS. Therefore, choosing PPOS for controlled ovarian stimulation has the advantage for patients of reducing the number of visits to the hospital and a reduced cycle cancellation rate.

Our finding that PPOS using CMA does not affect clinical outcomes offers support for the safety of CMA use in controlled ovarian stimulation; however, the study has some limitations. The first is that the sample size of the PPOS group was relatively small compared to the ANT group. This study was based on a retrospective analysis from a single center, including only normal ovarian responders. Further investigation is needed for poor responders. Second, the study included no neonates delivered from fresh embryo transfer. It is impossible to completely assess the impact of CMA in ovarian stimulation on newborn infants, because we can only evaluate newborn infants delivered from frozen embryo transfer. The effects of CMA in ovarian stimulation for infants derived from frozen-thawed blastocyst transfer could not be evaluated, because CMA was also used in HRT cycles. As mentioned above, there is only one report on the safety of CMA in HRT cycles. The safety of CMA in ART has not been adequately studied. Long-term follow-up of children born after undergoing ovarian stimulation using CMA in PPOS is needed.

In conclusion, our data show that limited use of CMA in ovarian stimulation procedures not only suppresses premature LH surges, but shows no negative effects on embryo development or clinical outcomes. PPOS with CMA could be an appropriate ovarian stimulation method for normal ovarian responders.

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CONFLICT OF INTEREST STATEMENT

The authors declare no Conflict of Interests for this article.

ETHICS STATEMENT

This study was approved by the Ladies Clinic Kyono Ethics Committee.

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.

ANIMAL STUDIES

This article does not contain any studies with animal subjects performed by the any of the authors.

CLINICAL TRIAL REGISTRY

Not applicable.

ORCID

Hideki Igarashi https://orcid.org/0000-0002-3478-497X
Koichi Kyono https://orcid.org/0000-0001-5211-7778

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