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Clinical utility of chlormadinone acetate (Lutoral™) in frozen-thawed embryo transfer with hormone replacement

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Abstract

Purpose: The clinical utility of chlormadinone acetate tablets (Lutoral™), an orally active progestin which has been available since June 2007, was compared to an in-house vaginal suppository formulation of progesterone used between 2006 and 2007 for assisted reproductive technology (ART).

Methods: We retrospectively evaluated the efficacy and safety of chlormadinone acetate by comparing the pregnancy rates and the incidences of birth defects and hypospadias in frozen-thawed embryo transfer cycles using the in-house vaginal progesterone and those using chlormadinone acetate for luteal phase support.

Results: The pregnancy rates in the frozen-thawed embryo transfer cycles were 31.2% (259/831) with vaginal progesterone for luteal phase support and 31.6% (4228/13381) with chlormadinone acetate (no significant difference). In the cycles resulting in live birth following administration of chlormadinone acetate between July 2007 and December 2015, the incidence of birth defects was 2.8% (80/2893), and the incidence of hypospadias was 0.03% (1/2893).

Conclusions: These results indicate that the pregnancy rate following frozen-thawed embryo transfer using chlormadinone acetate for luteal phase support was comparable with that using vaginal progesterone, with no increased risk of birth defects, including hypospadias, which has been a concern following the use of progestins.

KEYWORDS

assisted reproductive technology, endometrial preparation, frozen-thawed embryo transfer, luteal phase support, orally active progestin

1 | INTRODUCTION

With the successive introduction of various techniques such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and embryo cryopreservation using vitrification, assisted reproductive technology (ART) has made remarkable progress.

The application of vitrification as a cryopreservation method has dramatically improved the outcome of frozen-thawed embryo transfer, and it is contributing to an acceleration of the shift toward the "freeze-all" strategy, the cryopreservation of all embryos and the transfer of a thawed embryo in subsequent cycles.[1] However, some of the elements of frozen-thawed embryo transfer remain

controversial. Particularly regarding exogenous luteal phase support for endometrial preparation and support, there being no clear agreement and controversy exists as to whether natural progestogens (progesterone) or synthetic progestogens (progestins) should be used. It is undeniable that progestins have harmful effects on the fetus; however, American Society for Reproductive Medicine (ASRM) summarized that although maternal exposure to exogenous progestogens during early pregnancy has been associated with an increased risk of hypospadias in their infants, the risk appears to be limited to treatment with progestins that bind to the androgen receptor.[2] Nevertheless, the use of progestins for luteal phase support appears to be less preferable than that of progesterone.

Lutoral (Fuji Pharma Co., Ltd) is an orally active progestin containing chlormadinone acetate as the active ingredient. In Japan, chlormadinone acetate was approved for the treatment of amenorrhea, menstrual cycle disorder (oligomenorrhea, polymenorrhea), menstrual flow abnormality (hypomenorrhea, hypermenorrhea), dysmenorrhea, functional uterine bleeding, ovarian failure, and infertility due to luteal insufficiency, commercially introduced in April 1965 and reevaluated in June 1975.[3] Chlormadinone acetate is believed to induce no fetal virilization based on the results of a nonclinical study in rats,[4] neither virilization nor feminization of fetuses in castrated and intact rabbits.[5] Therefore, there are no precautionary statements for use during pregnancy, delivery, or lactation in Japanese prescribing information, as with another oral luteal hormone, dydrogesterone.

Many progestins have a vague action of fetal virilization, but chlormadinone acetate is a progestin that has pregnane structure without estrogenic action like progesterone, a natural progestogen. It has also been clarified that chlormadinone acetate has no estrane structure like norethisterone and therefore has neither androgenic action nor follicle hormone action other than luteinizing hormone action. However, as mentioned above, since many progestins have vague androgenic actions, there is a common opinion that the administration of progestins in large amounts after the 8th week of pregnancy has been associated with an increased risk of virilization of external genitalia for female infants. In contrast, there is a report that a high dose of maternal exposure with progestogen at the early pregnancy period for the prevention of miscarriage may induce virilization of female infants; however, it does not seem to occur by a short period of exposure with normal dosage of progestogen.[6] In addition, another report indicated that the maternal exposure with progestogen at or after the week 8 of gestation is associated with a dose-dependent risk of virilization of female infants, but it will not occur by the exposure before week 8 of gestation.[7] These reports suggest that there is little effect on fetuses by the administration of 6 mg/day of chlormadinone acetate for luteal phase support in frozen-thawed embryo transfer, and it is deniable that this dosage induces fetal virilization because the administration period for this purpose will be completed by week 9 of gestation.

In our clinic, though an in-house vaginal suppository formulation of progesterone had been used for luteal phase support in frozen-thawed embryo transfer, progesterone bulk powder became unavailable in 2007, and therefore, it was replaced by chlormadinone acetate in June 2007.

Here, we retrospectively evaluated the clinical utility of chlormadinone acetate for luteal phase support in frozen-thawed embryo transfer in cleavage or blastocyst stage by comparing the clinical pregnancy rates and live birth rates for efficacy analysis and the incidences of birth defects and hypospadias for safety analysis in cycles using vaginal progesterone and those using chlormadinone acetate.

2 | MATERIALS AND METHODS

This is a retrospective cohort study to evaluate the clinical utility of chlormadinone acetate in Asada Ladies Kachigawa Clinic conducted from January 2006 to December 2015.

The clinical results were obtained using in-house vaginal progesterone before May 2007 and chlormadinone acetate after July 2007, as two preparations were used at completely different period by switching agents for the luteal phase support.

The efficacy was evaluated by comparing the clinical pregnancy rates and live birth rates with in-house vaginal suppository formulation containing 400 mg progesterone administered twice daily or one 2-mg tablet of chlormadinone acetate administered three times daily.

As for the embryo freezing methods, it was gradually shifted from slow freezing to vitrification, and therefore, both methods were included in the results.

Endometrial preparation was performed according to the protocol established in house, based on the method proposed by Muasher et al.[8] For estradiol supplementation, transdermal estradiol patches (Estrana™ Tape; Hisamitsu Pharmaceutical Co., Inc) were started using two patches every other day from day 2 of the menstrual cycle. On cycle days 9-11, endometrial thickness was measured, and if the endometrium was ≥7 mm, the estradiol patches were increased by two patches per every other day up to a maximum of eight patches and the following day was designated as the assumed ovulation day. If the endometrium was <7 mm, the administration of estradiol patches was extended for another 1 week or so, and endometrial thickness was measured again. When the endometrium was prepared, luteal phase support was started (day 17) and the date of frozen-thawed embryo transfer was scheduled. The frozen-thawed embryo in cleavage stage (3 days after fertilization) or blastocyst stage (5 days after fertilization) was transferred. The estradiol patches were then decreased to four patches and continued every other day. Seventeen days after the assumed ovulation day, pregnancy was assessed by urinary hCG measurement. If the pregnancy test was positive, transvaginal ultrasound scan was performed 1 week later to confirm the presence of an intrauterine gestational sac. Clinical pregnancy was defined as the presence of intrauterine gestation sac on transvaginal ultrasound. Luteal phase support was performed with an in-house vaginal suppository formulation containing 400 mg progesterone twice daily or one 2-mg tablet of chlormadinone acetate three times

daily. The estradiol supplementation and luteal phase support were continued until the end of week 9 of gestation.

The data regarding the pregnancy outcomes of perinatal period including hypospadias or birth defect were obtained from reports by the patients or their doctors. The incidence of hypospadias and birth defects was evaluated in the frozen-thawed embryo transfer cycles resulting in live birth following administration of chlormadinone acetate.

3 | RESULTS

3.1 | Duration of treatment

The periods from ovum collection to embryo transfer ranged between 1 and 8 months for in-house vaginal progesterone and between 1 month and 4 years for chlormadinone acetate. The difference was due to the timing of transfer which varied greatly among patients, because frozen-thawed embryo transfer was performed from the subsequent cycle of ovum collection and this operation was continued until a pregnancy was achieved. In particular, the frozen-thawed embryos fertilized from the first ovum collection may be used for the second and third infants as well, which caused the extension of period of time up to 4 years.

3.2 | Pregnancy outcome of chlormadinone acetate compared to vaginal progesterone

The pregnancy rate in 831 frozen-thawed embryo transfer cycles conducted using vaginal progesterone between January 2006 and May 2007 was 31.2% and 31.6% in 13381 cycles conducted using chlormadinone acetate between July 2007 and December 2015. The mean age of patients was 34.4 years in the vaginal progesterone group and 36.9 years in the chlormadinone acetate group, and the mean numbers of embryos transferred per cycle were 2.2 and 1.4, respectively. In the chlormadinone acetate group, as compared with the vaginal progesterone group, the pregnancy rate per embryo transfer cycle was similar, though the mean age was 2.5 years higher and the mean number of embryos transferred was 0.8 less (Table 1).

3.3 | Birth data regarding safety concerns

In the cycles resulting in live birth following administration of chlormadinone acetate between July 2007 and December 2015, the incidence of birth defects was 2.8% (80 of 2893 cycles) and the incidence of hypospadias was 0.03% (1 of 2893 cycles; Table 2).

"Stillbirth" is defined as a miscarriage occurred at or after 22 weeks of pregnancy. In the cycles of clinical pregnancy following administration of chlormadinone acetate, stillbirth rate was 0.4% (15 of 4228 cycles). "Multiple pregnancy" is defined as a case where more than one gestational sac or heartbeat was identified, or final number of fetuses was two or more among the cycles in which clinical pregnancy was confirmed. In the cycles of clinical pregnancy following administration of chlormadinone acetate, multiple pregnancy rate was 7.3% (308 of 4228 cycles) and most of them were twin pregnancy. "Premature birth" is defined as a live birth case delivered at or before 36 weeks of pregnancy. In the cycles resulting in live births following administration of chlormadinone acetate, premature birth rate was 11.9% (345 of 2893 cycles; Table 2).

4 | DISCUSSION

There had been no drugs for luteal phase support to treat infertility for ART, until Ferring Pharmaceutical launched progesterone vaginal suppository in 2014. For this reason, in-house vaginal progesterone or synthetic oral progestins such as dydrogesterone or chlormadinone acetate had been used as a substitute for luteinizing hormone for a long time. The package insert and the interview form

TABLE 1 Pregnancy outcome of chlormadinone acetate compared to vaginal progesterone

	Vaginal progesterone (January 2006-May 2007)	Chlormadinone acetate (July 2007-December 2015)	*P* value[d]
Number of embryo transfer cycles	831	13381	-
Mean age at embryo transfer (y)	34.4	36.9	$P < 0.001$[e]
Mean number of embryos transferred per cycle	2.2	1.4	$P < 0.001$[e]
Number of cycles of clinical pregnancies	259	4228	0.7959[f]
(clinical pregnancy rate[a])	(31.2%)	(31.6%)	
Number of cycles resulting in abortions	71	1320	0.1984[f]
(abortion rate[b])	(27.4%)	(31.2%)	
Number of cycles resulting in births	188	2908	
(birth rate[c])	(72.6%)	(68.8%)	

[a]Clinical pregnancy rate (%) = Number of clinical pregnancies/Number of embryo transfer cycles × 100.
[b]Abortion rate (%) = Number of cycles resulting in abortions/Number of cycles of clinical pregnancies × 100 ("Abortion" is defined as a miscarriage occurred before 22 weeks of pregnancy).
[c]Birth rate (%) = Number of cycles resulting in births/Number of cycles of clinical pregnancies × 100.
[d]*P* values were determined by Mann-Whitney *U* test (e) or chi-square test (f).

TABLE 2 Birth outcome regarding safety concerns of chlormadinone acetate

Birth outcome	Number of cycles (%)
Clinical pregnancies	4228
Multiple pregnancies (multiple pregnancy rate[a])	308 (7.3%)
Births (birth rate[b])	2908 (68.8%)
Stillbirths (stillbirth rate[c])	15 (0.4%)
Live births (live birth rate[d])	2893 (68.4%)
Premature births (premature birth rate[e])	345 (11.9%)
Birth defects (incidence of Birth defect[f])	80 (2.8%)
Hypospadias (incidence of hypospadias[g])	1 (0.03%)

Note: The data were obtained between July 2007 and December 2015.
[a]Multiple pregnancy rate (%) = Number of cycles resulting in multiple pregnancies/Number of cycles of clinical pregnancies × 100. ("Multiple pregnancy" is defined as a case where more than one numbers of gestational sac or heartbeat was identified, or final number of fetuses was two or more among the cycles in which clinical pregnancy was confirmed).
[b]Birth rate (%) = Number of cycles resulting in births/Number of cycles of clinical pregnancies × 100.
[c]Stillbirth rate (%) = Number of cycles resulting in stillbirths/Number of cycles of clinical pregnancies × 100. ("Stillbirth" is defined as a miscarriage occurred at or after 22 weeks of pregnancy. Cycles with multiple pregnancy providing one or more live births were excluded from the estimation of stillbirths).
[d]Live birth rate (%) = Number of cycles resulting in live births/Number of cycles of clinical pregnancies × 100.
[e]Premature birth rate (%) = Number of cycles resulting in premature births/Number of cycles resulting in live births × 100. ("Premature birth" is defined as a live birth case delivered at or before 36 weeks of pregnancy).
[f]Incidence of birth defect (%) = Number of birth defects/Number of cycles resulting in live births × 100.
[g]Incidence of hypospadias (%) = Number of hypospadias/Number of cycles resulting in live births × 100.

of dydrogesterone or chlormadinone acetate describe that both of them do not have estrogenic or androgenic actions based on the results of nonclinical studies. In addition, dydrogesterone induces no fetal virilization in pregnant rats, and chlormadinone acetate has neither virilization nor feminization of fetuses in castrated and intact rabbits.

The indications and usage of both dydrogesterone and chlormadinone acetate include "to treat infertility due to luteal insufficiency"; however, with regard to the usage for luteal phase support in ART, cleft palate and others were reported in mice (ddS) regardless of gestation period or dosage, and carpal joint contractures or peritoneal defects were frequently reported in rabbits following administration at or more than 10 mg/kg in nonclinical studies of chlormadinone acetate,[9] while no teratogenicity was observed following administration of dydrogesterone. This makes the big difference between these two drugs as to the assessment for luteal phase support usage in ART. However, in terms of the dosages of chlormadinone acetate at which teratogenicity was observed, 10 or 50 mg/kg/day was administered from days 8 to 15 of gestation (n = 2) and days 14-17 of gestation (n = 2), and 1 or 3 mg/kg/day was administered from days 8 to 17 of gestation (n = 2) in mice. In rabbits (Japanese white species), 1, 3, or 10 mg/kg/day was orally administered from days 8 to 20 of gestation (n = 3). Thus, the dosages at which teratogenicity in both mice and rabbits was observed were much higher than those in clinical dosages.

Luteal phase support is indispensable; however, the oral dose of chlormadinone acetate required for the maintenance of pregnancy in an artificial hormone replacement cycle is 6 mg/day, which is surprisingly lower compared to the dose of vaginal progesterone.

Meanwhile, vaginal progesterone preparations are thought to be easily controlled by the measurement of serum progesterone concentrations. However, serum progesterone concentrations show mild diurnal variations and fluctuate in response to the pulsatile secretion of luteinizing hormone, a pituitary gonadotropin; consequently, a single serum progesterone measurement may not provide a truly accurate value, which has little diagnostic significance.[10-12]

Debates on which luteal phase support to utilize are largely based on serum progesterone concentrations. Since chlormadinone acetate can maintain pregnancy with a dose as low as 6 mg/day, it may be meaningless to discuss luteal phase support with chlormadinone acetate based on the measurements of serum progesterone concentration. It is noteworthy that the abundant clinical data from reported here demonstrated the equivalence of the efficacy of the frozen-thawed embryo transfer cycles incorporating luteal phase support with a long-acting, low-dose progestin, chlormadinone acetate, and those using high-dose vaginal progesterone.

The ASRM has stated that "Although maternal exposure to exogenous progestogens during early pregnancy has been associated with an increased risk of hypospadias in their infants, the risk appears to be limited to the treatment with progestins that bind to the androgen receptor."[2] This statement is reasonable in view of the fact that chlormadinone acetate is an antiandrogen drug that competes with 5-DHT at the androgen receptor and it is approved as a therapeutic agent at high-dose administration for prostatic hypertrophy (50 mg/day) and for prostate cancer (100 mg/day). However, there have been no reports on the association between the increased risk of hypospadias and the usage of chlormadinone acetate from the clinical findings on the potential risk in developing birth defects in male reproductive organs of infants despite the fact that chlormadinone acetate has been used for more than 50 years since the product was released in Japan. It might be because the usage for luteal phase support in ART is non-approved indication. The results of the present study revealed that in embryo transfer cycles resulting in live birth following administration of chlormadinone acetate between July 2007 and December 2015, the incidence of hypospadias in the cycles was 0.03% (1 of 2893 of live births) and the incidence of birth defects was 2.8% (80 of 2893 of live births; Table 2).

Meanwhile, the Japan Society of Pediatric Surgeons (JSPS) has stated that "The incidence of hypospadias has been reported to be about 1 in 300 male births in the articles in Europe and the US, and it is thought to be increasing due to environmental hormones in recent

years"; however, it has not been suggested that synthetic progestins such as chlormadinone acetate are contributory factors in their opinions on the incidence and factors for hypospadias.[13]

Progestogens used for endometrial preparation have been selected with a biased view of placing too much emphasis on the possible risks of progestins. Apart from the possible risks of progestins, however, physical, mental, and financial burdens on patients, as well as the long-term prognosis of offspring, should be highly contemplated.

Progesterone is commonly administered intravaginally, and chlormadinone acetate is given orally. Intravaginal administration, as compared with oral administration, imposes heavy mental and physical burdens on patients. The dosage of progesterone required for luteal phase support is 200-400 mg two or three times daily, while the dosage of chlormadinone acetate used here was 2 mg three times daily. In patients receiving vaginal progesterone, the vaginal mucosa is directly exposed to a high concentration of progesterone, frequently resulting in vulvovaginal pruritus as a vaginal-specific adverse reaction.

In our clinic, chlormadinone acetate is to be administered for 18 days from assumed ovulation day until pregnancy was assessed. When pregnancy was confirmed, administration of chlormadinone acetate was continued until around week 9 of gestation.

Testosterone is elevated in male fetus from about weeks 6-24 of gestation, which is called androgen shower. In our clinic, chlormadinone acetate is administered for luteal phase support at 6 mg/day until around 9th week of gestation as described above; thus, the chlormadinone acetate administration period is not completely overlapped with the androgen shower. Therefore, it is presumed that administration of chlormadinone acetate in this early stage of pregnancy does not completely disrupt the activity of testosterone, and if any, it is inferred that the effect is not significant.

It was in 2016 when a vaginal progesterone was launched in Japan, and eventually, all the formulation which had been on the overseas market became available in Japan. This is probably the reason why the present situation, in which dydrogesterone or chlormadinone acetate have been widely used as a substitute for luteinizing hormone, has been maintained during the period of the absence of vaginal progesterone. In this situation, we started using chlormadinone acetate for luteal phase support in 2007 and have accumulated vast clinical experiences. We compiled the results from 2007 to 2015 and retrospectively evaluated the efficacy and safety of chlormadinone acetate. As a result, the pregnancy rate and the live birth rate following administration of chlormadinone acetate were comparable with those following in-house vaginal progesterone. As for the safety concern, the incidence of hypospadias observed in our clinic was almost one tenth of what JSPS stated (1 in 300 male births) according to the reports in Europe and the United States. The incidence of birth defects was comparable with what the Center of Disease Control and Prevention (CDC) showed, that is, each year in the United States, 3% of live births have an identifiable structural birth defect.[14] Since we cannot see the perinatal period of the patients in our fertility clinic, there is no way to investigate the onset of birth defects other than the reports from patients or their obstetricians, and hence, there might be a possibility to miss some events occurred during perinatal period. However, even taking this into consideration, it seems that the incidence of birth defects due to chlormadinone acetate is not a concerning matter to be noted in particular as compared with that caused by natural pregnancy.

There was no significant difference in the pregnancy rate and incidence of birth defects including hypospadias of infants between the administration of vaginal progesterone and chlormadinone acetate for luteal phase support in the frozen-thawed embryo transfer in our clinic. This result would not bring to any opposite conclusion regarding teratogenicity observed in nonclinical studies. However, the dosages in the nonclinical studies to investigate teratogenicity of progestogens were much higher than those in the clinical dosages; therefore, it does not directly indicate that progestogens will cause teratogenicity for humans at clinical dosage. As the result of the safety review of our experience seemed to afford collateral evidence, we released our data here.

Although the fact that vaginal progesterone has obtained approval for the indication of luteal phase support for ART is very meaningful for those involved in reproductive medicine, it cannot be said that every problem has been solved due to its high price and poor usability for patients because of the administration route. Under such circumstances, it is unfortunate that highly reliable reports of clinical results of other formulations which have been widely used in medical settings, including chlormadinone acetate, have not been published. We hope the significance of using these drugs will be vigorously studied and discussed in the future.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

HUMAN RIGHTS STATEMENTS AND INFORMED CONSENT

This study was approved by the institutional review board of Asada Ladies Kachigawa Clinic and conducted in accordance with the principles of the Helsinki Declaration of 1964. Informed consent was obtained from all patients for being included in the study.

ANIMAL STUDIES

This article does not contain any study with animal participants that have been performed by any of the authors.

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