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Clinical efficacy of Crinone on pregnancy outcomes in frozen embryo transfer

A retrospective study in the Chinese population

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Abstract

Background: The aim of this study was to retrospectively investigate the effect of Crinone vaginal gel on pregnancy outcomes in women undergoing natural cycle (NC) frozen embryo transfer (FET) and to obtain the most suitable population for its routine application.

Methods: The 1613 women who underwent FET in the NC regimen [including the controlled ovulation stimulation protocol for the natural cycle, or the controlled ovulation stimulation protocol for the natural cycle (NC-COS)] from 2017 to 2021 were included. All patients were divided into 2 groups including Control group and Crinone group, which administered with or without Crinone vaginal gel. The key clinical information and between the 2 groups was recorded in detail.

Results: The results indicated that there were no statistical differences in blood β human chorionic gonadotropin (HCG) positive rate, clinical pregnancy, live birth, abortion (spontaneous and induced) and stillbirth between Control group and Crinone group. Moreover, Crinone could prevent spontaneous abortion. The spontaneous abortion rate in the Crinone group was 5.93% while this in control group was 8.32%. In the cohort exposed to Femoston, the preventive result was more significant (0/32 vs 5/15, $P = .001$). Furthermore, Crinone exhibited a significant protective effect on spontaneous abortion in 1520 patients who received no human menopausal gonadotropin (HMG) treatment.

Conclusion: This study demonstrated that the Crinone could protect women against spontaneous abortion, especially in patients who do not need HMG or in combination with Femoston.

Abbreviations: FET = frozen embryo transfer, HCG = human chorionic gonadotropin, HMG = human menopausal gonadotropin, LH = luteinizing hormone, NC = natural cycle, NC-COS = the controlled ovulation stimulation protocol for the natural cycle.

Keywords: Crinone, Femoston, frozen embryo transfer, natural cycle, spontaneous abortion

1. Introduction

It has been reported that up to 1 in 6 couples may experience fertility issues.[1,2] The use of assisted reproductive technology by couples seeking a healthy live birth is becoming increasingly common. Treatment cycles involving frozen (thawed) embryo transfer (FET) have been demonstrated to enhance cumulative pregnancy rates, reduce costs, and are relatively straightforward to perform.[3,4] Assisted reproduction has extensively utilized FET. It is primarily employed in cases where women do not conceive following fresh embryo transfer cycles, where the endometrium is unsuitable for fresh embryo transfer, or when there is a high risk of ovarian hyperstimulation syndrome. Typically, FET is conducted using various cycle regimens: spontaneous ovulatory cycles (natural cycle, NC); hormone therapy FET cycles, where the endometrium is artificially prepared using estrogen and progesterone; and cycles where ovulation is induced by medication (ovulation induction FET cycles).

FET success is influenced by the embryo, endometrial preparation, and luteal support. Both the oocyte/embryo and the maternal endometrium are crucial for achieving a successful birth. Since ovulation does not occur in the FET cycle, endogenous formation of the corpus luteum is absent. Thus, secretory transformation of the endometrium prior to embryo transfer and maintenance of normal embryonic development afterward relies entirely on exogenous progesterone supplementation. Progesterone is essential for establishing and maintaining early pregnancy until the luteal-placental transfer, offering numerous

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The informed consent was signed by each enrolled patient.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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benefits to FET outcomes.[3,5,6] Even, live birth rates are not negatively impacted by the premature initiation of luteal phase progesterone support in natural FET cycles.[7] Overall, enhancing endometrial tolerance is positively affected by exogenous progesterone support, making it a recommended strategy. The most common routes for luteal phase support are via vaginal capsule (the most convenient administration), gel, or tablet. A steady endometrial concentration can be achieved by vaginal progesterone administration, while a low serum level of progesterone is caused, potentially avoiding systemic adverse effects.

One of the most widely used vaginal progesterone medications in assisted reproductive technology programs is Crinone vaginal gel (8%).[8] Studies on the efficacy and safety of Crinone in FET, as well as the most suitable population, are found to be inadequate.[9] Currently, there is less consensus on whether the administration of progesterone support affects the clinical outcome of FET cycles.[10,11] The benefits and risks associated with the routine use of Crinone vaginal gel in FET have yet to be supported by sufficient data, as conflicting findings regarding its effect on pregnancy outcomes compared to intramuscular progesterone exist.

The aim of this study was to retrospectively investigate the effect of Crinone vaginal gel on pregnancy outcomes in women undergoing natural cycle (NC) frozen embryo transfer (FET) and to obtain the most suitable population for its routine application. The results were hoped to provide some references of the application of comprehensive utilization in clinical selection of luteal support regimens.

2. Methods

2.1. Study design and participants

The whole experiment was approved by Wuxi Maternal and Child Health Hospital Ethics Committee (No. 2024-06-0515-17). The files of medical ethics approval, medical ethics review and patient informed consent were attached in the submission files.

All 1613 women who underwent frozen embryo transfer (FET) for pregnancy in our Reproductive Center from 2017 to 2021 in the natural cycle (NC) regimen (including the controlled ovulation stimulation protocol for the natural cycle, or NC-COS) were retrospectively analyzed. The inclusion criteria were: patients aged between 20 and 48, and day 3 to 6 frozen embryos were used. Based on our purpose, all the enrolled patients were divided into 2 groups: the control group and the Crinone group. The Crinone group was administered to Crinone vaginal gel (Merck Serono, Switzerland, 90 mg/d), while the control group had not. The whole study was shown in Figure 1.

2.2. FET study

Embryos were frozen and thawed by vitrification according to the routine procedures of the center. Embryo evaluation was performed according to the literature criteria. Follicle growth was monitored by transvaginal ultrasound from the 10th to 12th day of menstruation. If the dominant follicle diameter was ≥ 14 mm and endometrial thickness ≤ 6 mm, Fenmortone (2 mg/d, Abbott, Netherlands) was added, vaginal medication was used, and the endometrial thickness reached 8 mm or the endometrial transformation day was changed to oral administration. If the dominant follicle diameter is ≥ 16 mm, luteinizing hormone (LH), estradiol (E2) and progesterone (*P*) levels are measured and LH support is given from the day of ovulation or 24 hours after the LH peak (labeled as ovulation day) until 14 days after embryo transfer. Under the guidance of abdominal ultrasound, the embryo at the cleavage stage was transferred on day 3 after ovulation, and the blastocyst on day 5 after ovulation.

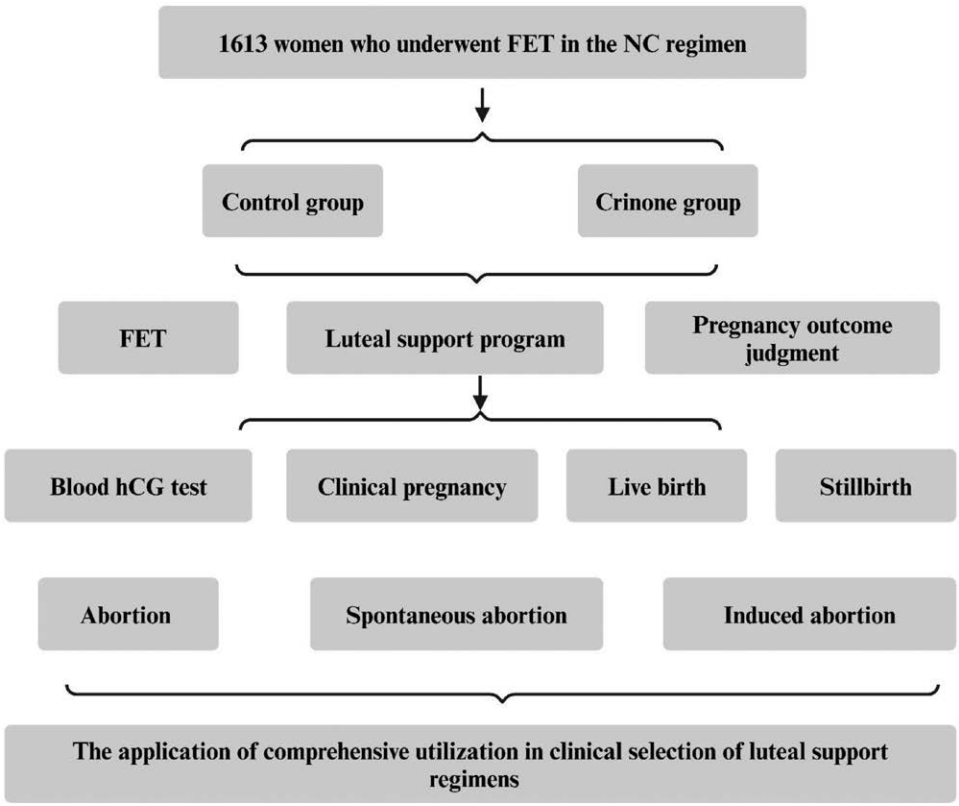

Figure 1. The brief experimental plan. FET = frozen embryo transfer, HCG = human chorionic gonadotropin, NC = natural cycle.

2.3. Luteal support program

From the day of ovulation, the control group was given progesterone injection 60 mg/d intramuscular injection, the seronotone group was given progesterone sustained-release gel 90 mg/d, vaginal medication combined with dydrogesterone tablet 20 mg/d orally, serum β-HCG was detected 12 to 14 days after transplantation, and the drug was stopped if there was no pregnancy, and continued to be used if pregnancy continued until 10 weeks of pregnancy. Discontinue medication if there are indications that pregnancy cannot continue.

2.4. Pregnancy outcome judgment

Serum β-HCG was measured 12 to 14 days after embryo transfer, and if β-HCG < 5 U/L was defined as no pregnancy; β-HCG ≥ 5 U/L was defined as HCG positive, and vaginal ultrasound was performed 25 to 30 days after transplantation. The pregnancy was biochemical if β-HCG was positive in blood or urine and there was no echo of pregnancy sac under vaginal ultrasound. Intrauterine pregnancy sac or fluid product and extrauterine tissue villi were clinically pregnant. If the gestational age is <28 weeks and the pregnancy is terminated, it is an abortion (including natural abortion and artificial abortion); Gestational age ≥ 28 weeks delivered with heartbeat, breathing is a live birth, vice versa for stillbirth.

The detailed arrangement between Control group and Crinone group was as follows: patient age, the husband's age, NC regimen (NC or NC-COS), medications used in addition to Crinone (including Progynova, Femoston, progesterone injection, dydrogesterone, HCG and HMG), the FET date, endometrial thickness, endometrial type, and the embryo grade. The following outcome indicators were used to analyze the differences between groups: biochemical pregnancy indicated by the blood HCG test result on day 12 post FET, clinical pregnancy (the vaginal ultrasound examination revealed a fetal sac in the uterus with a germ and primitive heartbeat) or not, live birth or not, abortion (including spontaneous abortion and induced abortion during the late pregnancy), and stillbirth or not.

2.5. Data measurement

The main outcome measures observed are blood HCG test, clinical pregnancy, live birth, abortion, spontaneous abortion, induced abortion and stillbirth.

Blood HCG test = number of HCG positive cycles/total number of transfer cycles × 100%

Clinical pregnancy = clinical pregnancy cycle/total number of transfer cycles × 100%

Abortion = number of abortion cycles within 28 weeks of pregnancy/total clinical pregnancy cycles × 100%

Spontaneous abortion = spontaneous abortion cycles/number of clinical pregnancy cycles × 100%

Stillbirth = stillbirth cycles/number of live birth cycles × 100%

2.6. Statistical methods

The data were analyzed by SPSS (version 25). Categorical data were described by percentages and compared by χ^2 test (double checked by Fisher's exact test when necessary); numeric variables were expressed as mean ± standard deviation (SD) and compared by *t* test (between 2 groups). A *P* value <.05 was regarded as statistically significant.

3. Results

3.1. General information of enrolled subjects

Together, this retrospective study analyzed the records of 1613 cases, including 685 ones in the control group and 928 ones in the Crinone group (Table 1). Between 2 groups, there were no differences in the age of the patient, the age of the husband, the pregnancy protocol, the endometrial thickness, and endometrial type. The average ages were both around 32 in 2 groups. In the control group, 5.98% cases received the NC-COS protocol, and 4.85% received the NC-COS protocol in the Crinone group (*P* > .05). The endometrial thickness was about 10 mm in both groups. Additionally, 93.4% (640/685) had the B type endometrium in the control group, and this ratio was 92.8% (861/928; *P* > .05).

3.2. Effect of Crinone on pregnancy outcomes

Overall, no statistical differences were observed between 2 groups in the blood HCG test, clinical pregnancy, live birth, abortion (spontaneous abortion and induced abortion), and stillbirth (Table 2). However, Crinone could prevent spontaneous abortion, that the spontaneous abortion percentage in the Crinone group was 5.93% in comparison with 8.32% in the control group (*P* = .061 by χ^2 test, and *P* = .039 by Fisher's exact test).

Moreover, the subgroups in the patients under NC and NC-COS regimens, respectively were analyzed. In the NC regimen (Table 3), the preventive effect of Crinone on spontaneous abortion was statistically significant (*P* = .045 by χ^2 test, and *P* = .0329 by Fisher's exact test), and no impacts on other outcomes were found. And this influence was not observed in patients under the NC-COS protocol (Table 4, *P* > .05 in all outcomes).

Further, whether Crinone still palyed a role in preventing spontaneous abortion in each treatment subgroup were analyzed. Patients were stratified according to different drugs and different embryonic grades, and no differences were detected in most stratification. However, in the cohort with Femoston treatment (Table 5), a dramatically strong effect was found (0/32 vs 5/15, *P* = .001). Moreover, 1520 patients among the 1613 cases had not received HMG treatment. In these patients, the protective effect of Crinone on spontaneous abortion was able to manifest (*P* = .040, Table 5).

4. Discussion

The use of Crinone vaginal gel for luteal support has been reported by scholars. Comparative studies used following

Table 1

Clinical characteristics of included women.

Variables		Control group	Crinone group	*P*
Number		685	928	
Age		32.16 ± 4.708	31.96 ± 4.308	.383
Age of husband		33.45 ± 5.331	33.36 ± 5.369	.741
Pregnancy regimen	NC	644 (94.0%)	883 (95.2%)	.315
	NC-COS	41 (6.0%)	45 (4.8%)	
Endometrial thickness (mm)		10.117 ± 1.8089	10.000 ± 1.6571	.181
Endometrial type	A	45 (6.6%)	67 (7.2%)	.611
	B	640 (93.4%)	861 (92.8%)	

NC = natural cycle, NC-COS = the controlled ovulation stimulation protocol for the natural cycle.

Table 2

Pregnancy outcomes of 2 groups.

Outcomes		Control group		Crinone group		*P*
Blood HCG test	Negative	236	35.2%	330	36.1%	.706
	Positive	434	64.8%	583	63.9%	
Clinical pregnancy	Fail	338	49.3%	454	48.9%	.867
	Success	347	50.7%	474	51.1%	
Live birth	No	405	59.1%	525	56.6%	.305
	Yes	280	40.9%	403	43.4%	
Abortion	No	626	91.4%	868	93.5%	.103
	Yes	59	8.6%	60	6.5%	
Spontaneous abortion	No	628	91.7%	873	94.1%	.061*
	Yes	57	8.3%	55	5.9%	
Induced abortion	No	683	99.7%	923	99.5%	.456
	Yes	2	0.3%	5	0.5%	
Stillbirth	No	683	99.7%	927	99.9%	.396
	Yes	2	0.3%	1	0.1%	

HCG = human chorionic gonadotophin.

* In Fisher's exact test, $P = .039$.

Table 3

Pregnancy outcomes of 2 groups in the NC regimen.

Outcomes		Control group		Crinone group		*P*
Blood HCG test	Negative	225	35.7%	314	36.2%	.854
	Positive	405	64.3%	554	63.8%	
Clinical pregnancy	Fail	317	49.2%	434	49.2%	.978
	Success	327	50.8%	449	50.8%	
Live birth	No	382	59.3%	502	56.9%	.335
	Yes	262	40.7%	381	43.1%	
Abortion	No	587	91.1%	826	93.5%	.079
	Yes	57	8.9%	57	6.5%	
Spontaneous abortion	No	589	91.5%	831	94.1%	.045*
	Yes	55	8.5%	52	5.9%	
Induced abortion	No	642	99.7%	878	99.4%	.465
	Yes	2	0.3%	5	0.6%	
Stillbirth	No	642	99.7%	882	99.9%	.390
	Yes	2	0.3%	1	0.1%	

NC = natural cycle.

* In Fisher's exact test, $P = .029$.

Table 4

Pregnancy outcomes of 2 groups in the NC-COS protocol.

Outcomes		Control group		Crinone group		*P*
Blood HCG test	Negative	11	27.5%	16	35.6%	.426
	Positive	29	72.5%	29	64.4%	
Clinical pregnancy	Fail	21	51.2%	20	44.4%	.530
	Success	20	48.8%	25	55.6%	
Live birth	No	23	56.1%	23	51.1%	.643
	Yes	18	43.9%	22	48.9%	
Abortion	No	39	95.1%	42	93.3%	.723
	Yes	2	4.9%	3	6.7%	
Spontaneous abortion	No	39	95.1%	42	93.3%	.723
	Yes	2	4.9%	3	6.7%	
Induced abortion	No	41	100%	45	100%	–
	Yes	0	0	0	0	
Stillbirth	No	41	100%	45	100%	–
	Yes	0	0	0	0	

HCG = human chorionic gonadotophin, NC-COS = the controlled ovulation stimulation protocol for the natural cycle.

controls: without usage, Utrogestan capsules, aqueous subcutaneous progesterone (Prolutex), or intramuscular progesterone injection.[12–17] Our results are similar to majority of conclusions, that Crinone gel results in comparable pregnant outcomes vs controls, such as biochemical pregnancy,[13] clinical pregnancy,[15,18] live birth,[13] spontaneous abortion, implantation, and miscarriage rates.[14] When acknowledging that Crinone vaginal gel is equally effective to intramuscular progesterone, some studies also implied that it is better tolerated for luteal phase support.[19] However, there are some studies that suggest its safety risks. A

Table 5

Crinone prevents spontaneous abortion for women with Femoston treatment and those without progesterone injection.

Cohort		Control group	Crinone group	*P*
Femoston treatment	No Spontaneous abortion	12 (70.6%)	32 (100%)	.001
	Spontaneous abortion	5 (29.4%)	0 (0%)	
Without HMG	No Spontaneous abortion	583 (91.4%)	830 (94.1%)	.040
	Spontaneous abortion	55 (8.6%)	52 (5.9%)	

HMG = human menopausal gonadotropin.

study has investigated Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer, and they reported that women supplemented with Crinone had significantly lower rates of clinical pregnancy (36.9% vs 51.1%) and live birth (24.4% vs 39.1%) compared with those on intramuscular progesterone.[20] In comparison with Prolutex, Crinone has fewer side effects, that patients receiving Prolutex complained of more local pain at the injection sites.[17]

Our study shows that Crinone has no effect on biochemical and clinical pregnancies, but slightly reduces the rate of spontaneous abortions, especially in the NC regimen, in patients who do not require HMG or in combination with Femoston. However, unlike previous studies, oral Utrogest capsules or intramuscular progesterone injection were not compared, but the use of vaginal gel with or without. Notably, Crinone also had no effect on pregnancy outcome in both subgroups that received progesterone injections and those that did not. This suggests that, although generally it is safe and perhaps available as a routine protocol, the additional administration of a vaginal gel does not provide more benefits from progesterone. Nevertheless, in Table 5, it was observed that Crinone prevents spontaneous abortion for women with Femoston treatment and those without HMG injection. These 2 populations may be the key contributors to the overall significant differences. Femoston is a hormone replacement therapy (HRT) preparation. Generally, it is used to relieve symptoms of the menopause, and it is the second-line option for preventing osteoporosis in postmenopausal women who are at high risk of fractures and cannot take other medicines licensed for preventing osteoporosis. Here, it is used in assisted reproduction for the preparation of the endometrium for FET and also for the prevention of early-pregnancy and preterm abortion. It is routinely administered orally but also can be used as a vaginal plug for endometrial preparation, which effectively increases the local estrogen level. A Chinese study showed that, for patients with thin endometrium, Femoston may be added vaginally if ideal endometrial thickness or E2 level is not achieved by Progynova alone.[21] In patients receiving Femoston treatment, Crinone exerted a highly significant protective effect against spontaneous abortion, which suggests that Crinone may act synergistically with Femoston locally and improve the endometrial receptivity. However, the above hypothesis has to be confirmed by further data accumulation. Besides, the protective role of Crinone is significant in patients without HMG treatment, and this effect was nor detected in the patients receiving HMG treatment. HMG (human menopausal gonadotropin) is a urinary sex hormone with components containing follicle-stimulating hormone and luteinizing hormone. Injection of HMG is aimed at the development of follicles and induction of secreting estrogen which drives the endometrial proliferation. HMG can promote the simultaneous development and maturation of follicles, which can result in a higher number of good quality eggs for embryos, therefore, it is commonly used by women with underdeveloped follicles.[22–24] In the late follicular phase, using HMG alone may be a feasible alternative for normal-ovulatory women undergoing FET.[25] The protective effect of Crinone against spontaneous abortion is more sufficient for patients without HMG treatment, and this finding suggests that in patients with normal follicular maturation function, improving the environment of the endometrium with Crinone can indeed bring benefits in assisted reproduction. In summary, on account of its mild protective effect against spontaneous abortion, as well as a high safety, Crinone may be a promising routine drug in FET, especially in patients who do not require HMG or in combination with Femoston.

Our study still has the following shortcomings. Firstly, as a retrospective study, its reliability remains to be verified by prospective experiments. Secondly, some positive statistical findings were on the margin of significance, and they were also validated post hoc by logistic regression, but the efficacy was found to be weak. Therefore, the previous consensus that the protective effect of Crinone was considered very limited remained unchallenged by the above findings.

5. Conclusions

Overall, Crinone showed good effect on pregnancy outcomes. But it protected woman from spontaneous abortion, especially in patients who did not require HMG or in combination with Femoston.

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