European Journal of Obstetrics & Gynecology and Reproductive Biology 237 (2019) 100–105

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Full length article

Vaginal progesterone gel is non-inferior to intramuscular progesterone in efficacy with acceptable tolerability for luteal phase support: A prospective, randomized, multicenter study in China

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ARTICLE INFO

Article history:
Received 29 August 2018
Received in revised form 4 April 2019
Accepted 14 April 2019

Keywords:
Luteal phase support
Vaginal progesterone gel
In vitro fertilization
Ongoing pregnancy rate
Safety

ABSTRACT

Objectives: Research suggests the efficacy of progesterone for luteal phase support in assisted reproduction cycles using gonadotropin-releasing hormone analogues. Our study objective was to compare the efficacy of two available preparations of progesterone, vaginal gel and intramuscular injection, for luteal phase support in assisted reproduction cycles.

Study design: This study included data gathered from 18 reproductive centers in China. Subjects were randomly allocated to receive progesterone gel or intramuscular progesterone (IMP). The progesterone gel group received micronized progesterone in gel (8%, 90 mg) once daily; the IMP group received IMP (progesterone oil) once daily. The ongoing pregnancy rate was calculated (number of women with a viable pregnancy at 12 weeks divided by the number of women who had undergone an oocyte pickup cycle).

Results: A total of 1313 patients were enrolled in the study, 1248 of whom began treatment. The intention-to-treat set included 527 and 531 patients in the gel and IMP groups, respectively. The ongoing pregnancy rate in the progesterone gel group was non-inferior to that in the IMP group (48.4% [95% confidence interval (CI): 44.0, 52.8] vs. 46.3% [95% CI: 42.0, 50.7]); the between-group rate difference was 2.1% (−4.0, 8.1). There was no difference between the gel group and IMP group on most secondary endpoints, including implantation rate, biochemical pregnancy rate, clinical pregnancy rate, multiple pregnancy rate, early abortion rate, and vaginal bleeding rate, but there was a between-group difference in luteal phase bleeding

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https://doi.org/10.1016/j.ejogrb.2019.04.012

rate. The safety analysis showed no difference in the incidence of total adverse events.
Conclusions: Progesterone gel showed good efficacy and safety outcomes and therefore provides an alternative method of luteal support in Chinese in vitro fertilization patients.

Introduction

Normal luteal function in childbearing-age women is essential for embryo implantation and pregnancy maintenance. The corpus luteum supports these processes by secreting progesterone from ovulation to the establishment of placental function. Premature removal of the corpus luteum can lead to spontaneous abortion [1]. It is well established that spontaneous abortion is directly related to luteal phase shortening in in vitro fertilization (IVF). Insufficient preparation of the endometrium during embryo implantation can lead to lower pregnancy rates [2].

Intramuscular progesterone (IMP) is widely used for luteal phase support in Chinese IVF patients because of its stability, effectiveness, and lower price compared with other preparations. However, in one study that used injections of 60-mg progesterone in a 3-mL oil vehicle, difficulties in absorption necessitated frequent changes in injection location [3]. Pain, occasional sterile abscesses or allergic responses, and local abscesses from IMP are mostly associated with oil vehicle usage [3]. Additionally, IMP injections in China are administered by nurses, requiring patients to attend hospital daily, increasing burdens to health care practitioners and patients. An effective and convenient progesterone supplement preparation with fewer side effects is desirable. Progesterone vaginal gel, frequently used for luteal phase supplementation, is an alternative to IMP [4].

Progesterone vaginal gel is a bio-adhesive gel containing progesterone in a fine powder (micronized) form to facilitate absorption [5]. Many studies indicate the effectiveness of transvaginal administration of progesterone gel. Chantilis et al. showed that, compared with IMP, progesterone gel was associated with a lower rate of spontaneous abortion in women undergoing IVF and embryo transfer (ET) [6]. Silverberg et al. found that IVF patients receiving progesterone gel showed higher pregnancy and delivery rates than those receiving IMP [7]. Similarly, Chi et al. found a non-inferior effect of progesterone gel compared with IMP in women undergoing IVF/intracytoplasmic sperm injection (ICSI)-ET in China [8]. In postmenopausal women deprived of ovarian function taking estrogen, transvaginal administration of progesterone gel induced normal secretory endometrial transformation, despite low serum progesterone levels [9]. Yanushpolsky et al. found that progesterone gel and IMP were associated with similar pregnancy and failed pregnancy rates in women undergoing IVF; however, progesterone gel was better tolerated [10]. A recent meta-analysis of randomized controlled trials comparing different types of luteal phase support found a lack of high-quality trials and mixed results regarding route of progesterone administration and IVF outcomes [11].

To our knowledge, there are no well-designed, large-scale, randomized controlled trials to verify these findings in the Chinese population. This trial compared the efficacy of two forms of progesterone for luteal phase support in assisted reproduction cycles in Chinese patients.

Materials and methods

Study design

This was a prospective, randomized, open-label study that included patients from 18 centers in China. In this non-inferiority clinical trial, the primary endpoint was the ongoing pregnancy rate after using vaginal progesterone gel compared with that of progesterone in oil in patients undergoing IVF.

Population

Patients who had completed controlled ovarian stimulation and ready to receive fresh ETs were evaluated using the following inclusion/exclusion criteria before allocation. The inclusion criteria were 1) aged 20–40 years; 2) tubal or idiopathic infertility, or infertility caused by endometriosis or male factors; 3) treated by a standard long protocol; 4) normal uterus and at least one normal ovary; 5) serum follicle-stimulating hormone (FSH) levels < 12 IU/L and estradiol (E2) levels < 80 pg/mL; 6) body mass index (BMI) < 25 kg/m^2; 7) meeting the national family planning policy; 8) signed informed consent; and 9) willing to follow the study protocol and able to complete the study.

The exclusion criteria were 1) previous IVF/ICSI cycles ≥ 3 times; 2) poor ovary response (<5 oocytes expected); 3) severe pelvic adhesions and hydrosalpinx (>2 cm hydrosalpinx on ultrasound); 4) hypersensitivity to progesterone; 5) history of habitual abortion; 6) pathological cervical smear within 6 months; 7) liver/kidney dysfunction; 8) severe cardiovascular, pulmonary, liver, or kidney disease; 9) systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 90 mmHg; 10) any investigation result deviating > 25% from normal range; 11) uncontrolled vaginal inflammation; 12) pregnancy contraindications; and 13) alcoholism, drug abuse/addiction, or uncontrolled sexually transmitted disease.

Patients were randomly allocated on the day of oocyte retrieval in a 1:1 ratio to receive vaginal progesterone gel or IMP using the block permutation method, and stratified by center and age (20–35 or >35 years old). Allocation was according to computer randomization conducted at the main study site and subsequently provided to participating sites. Patients could voluntarily withdraw from the study at any stage or at the investigators' discretion if adverse events/serious adverse events (AEs/SAEs) occurred, or if the risks of participation were deemed to outweigh the benefits.

Administration

Vaginal progesterone gel (Crinone® [Merck Serono], manufactured by Fleet Laboratories Limited, Watford, UK) was administered vaginally at a once-daily 90-mg dose from the day of oocyte retrieval. IMP was obtained from local suppliers (same active ingredient) by each study site and administered by injection at a once-daily 60-mg dose from the day of oocyte retrieval. Drugs were administered at the same time each day. If pregnancy was confirmed on day 14 after ET, either treatment was continuously prescribed until 6 weeks after ET (or early termination of pregnancy), according to the random group allocation.

In this study, IVF/ET was recommended as follows. 1) A gonadotropin-releasing hormone agonist (GnRHa) down-regulation long protocol was used for treatment from the 21st day of the last menstrual cycle. GnRHa was administered daily by intramuscular injection until follicles developed (trigger for human chorionic gonadotropin [hCG] injection). 2) Recombinant FSH (Gonal-F) was used to stimulate multifollicular development. 3) The levels of E2, luteinizing hormone, and progesterone were

monitored and follicular maturation and endometrial status were observed using B-ultrasound. 4) hCG (Ovidrel®) was used for ovulation triggering. 5) All subjects completed ET (≤3 embryos/transfer, according to national and hospital policies).

All investigational drugs (vaginal progesterone gel and IMP) and pre-ovulation drugs (GnRH agonists, FSH, and hCG) were prescribed to subjects by investigators and subjects purchased these from the clinic pharmacy. During the study, subjects were permitted to take non-hormonal drugs but no additional progesterone or other ongoing vaginal medications.

Endpoints and assessment

Doses and dates of administration of concomitant medications were recorded. Follow-up was until pregnancy was confirmed or the study completed. Blood/urine tests and ultrasound examinations were performed throughout the study to monitor pregnancy. The primary endpoint (ongoing pregnancy rate) was calculated as the number of women with a viable pregnancy at 12 weeks divided by the number who had undergone an oocyte pickup cycle. Implantation, biochemical/clinical/multiple pregnancy, early abortion, luteal phase bleeding, and vaginal bleeding rates were compared as secondary endpoints. The formulae are shown in Supplementary Table 1.

Regarding safety, all AEs or SAEs during the study were recorded and relationship to the investigational drugs was assessed. Investigators evaluated if the patient could continue with the study.

This study was conducted under investigator supervision and all procedures were in accordance with the Declaration of Helsinki, the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice guideline, and the relevant Chinese health regulations. All subjects provided written informed consent. The study was approved by independent ethics committees at each study site.

Monitors from a contract research organization (CRO) monitored the study process and collected completed case report forms (CRFs). The CRO conducted central data input, analyzed data from the completed CRFs, and completed the statistical report. Monitors contacted the investigator to clarify any incomplete CRFs.

Statistical methods

The primary study objective was to demonstrate the non-inferiority of ongoing pregnancy rate in IVF/ICSI-ET patients using progesterone gel versus IMP for luteal phase support. The statistical analyses were based on two-sided 95% confidence interval (CI) differences in ongoing pregnancy rates in the progesterone gel and IMP groups. The 95% CIs were calculated following the Wilson score method without continuity correction, as described by Newcombe and colleagues. Non-inferiority was demonstrated if the lower limit of the 95% CI for the difference between the two proportions $P_{\text{progesterone gel}} - P_{\text{IMP}}$ was $\geq -10\%$. Percentages and corresponding CIs were reported for secondary endpoints.

Three analysis sets were used: intention-to-treat (ITT), per protocol (PP), and safety (SS). The ITT analysis included all subjects who received at least one dose of progesterone gel or IMP and finished the ET. The PP set included all subjects treated according to the protocol. The SS included all subjects who received at least one dose of vaginal progesterone gel or IMP. A supportive analysis was performed using the ITT population, as the PP population was <90% of the ITT population.

A required sample size of 1042 patients (521/group) was estimated, assuming a non-inferiority delta margin (clinically significant difference) of 10% between the gel and IMP groups (based on an ongoing pregnancy rate in both groups of 45% [data from Chinese IVF centers], alpha of 2.5% (one-sided test), and statistical power of 90%. After estimating a 10% dropout rate, a sample size of 1148 was selected.

Results

A total of 1313 patients were enrolled and randomly allocated to the vaginal progesterone gel or IMP groups from December 2014 to March 2016. A total of 1248 patients began treatment and were included in the SS; 1058 patients were included in the ITT (Fig. 1).

The size of the PP population was <90% of the ITT population, so the ITT population was used for a supportive analysis (following the study protocol). The mean (±standard deviation) ages of the progesterone gel and IMP groups were 30.2 ± 3.9 and 30.3 ± 3.8 years, respectively. There were no between-group differences in baseline characteristics of BMI, nationality, history of infertility, or reason for infertility (all $p > 0.05$, Table 1). A comparison of clinical/embryology characteristics of fresh cycles is shown in Table 2. Patients who received progesterone gel had small but significant increases in the number of oocytes retrieved (12.48 ± 4.99 vs. 11.66 ± 4.57; $p = 0.0055$) and the number of embryos on day 3 (7.17 ± 4.10 vs. 6.63 ± 3.75; $p = 0.0257$) vs. patients who received IMP.

The ongoing pregnancy rate was 48.4% [95% CI: 44.0, 52.8] and 46.3% [95% CI: 42.0, 50.7] in the gel and IMP groups, respectively. The lower limit of the 95% CIs for the between-group difference (progesterone vaginal gel−IMP group) was −4.0%, higher than the non-inferiority threshold of −10%, indicating that progesterone gel was non-inferior to IMP ($p < 0.0001$, Table 3).

There were no differences between the gel and IMP groups in most secondary endpoints: implantation rate (37.3% vs. 34.8%), biochemical pregnancy rate (57.5% vs. 56.5%), clinical pregnancy rate (52.2% vs. 50.7%), multiple pregnancy rate (38.6% vs. 34.0%), early abortion rate (8.0% vs. 8.9%), and vaginal bleeding rate (0.8% vs. 0.4%), but there was a between-group difference in luteal phase bleeding rate (12.1% vs. 6.2%, $p = 0.0008$) (Fig. 2).

In patients with biochemical pregnancies, the uterine bleeding rate during the luteal phase was only 4.3%; this rate was 15.6% in those without biochemical pregnancies (Table 4). Further analysis was conducted in the with/without luteal phase bleeding subgroup. Compared with the subjects without luteal phase bleeding, those with bleeding had a clinically significantly lower biochemical pregnancy rate (26/97, 26.8% vs. 577/961, 60.0%, Table 4). The biochemical pregnancy rates were higher in the progesterone gel vs. IMP group, both with (19/64, 29.69% vs. 7/33, 21.21%) and without luteal phase bleeding (284/463, 61.34% vs. 293/498, 58.84%), but this difference was not statistically significant.

No statistical difference in the incidence of AEs between the progesterone gel and IMP groups (11.6% vs. 9.0%) was found, but the incidence of drug-related AEs was higher in the progesterone gel group (3.9% vs. 1.4%, $p = 0.0061$). The most common drug-related AEs in the progesterone gel group were threatened abortion, vaginal bleeding, and abnormal liver function. There was no between-group difference in incidence of SAEs and drug-related SAEs (2.6% vs. 2.1% and 0.3% vs. 0.2%).

Discussion

Progesterone vaginal gel has been widely used in Western countries and has the advantages of less pain, inflammation, and other risks caused by injection or oil vehicle usage. However, vaginal gel is less popular in China because of cost and doctor/patient preconceptions about vaginal drugs. To our knowledge, this was the largest multicenter randomized controlled study conducted on a Chinese population.

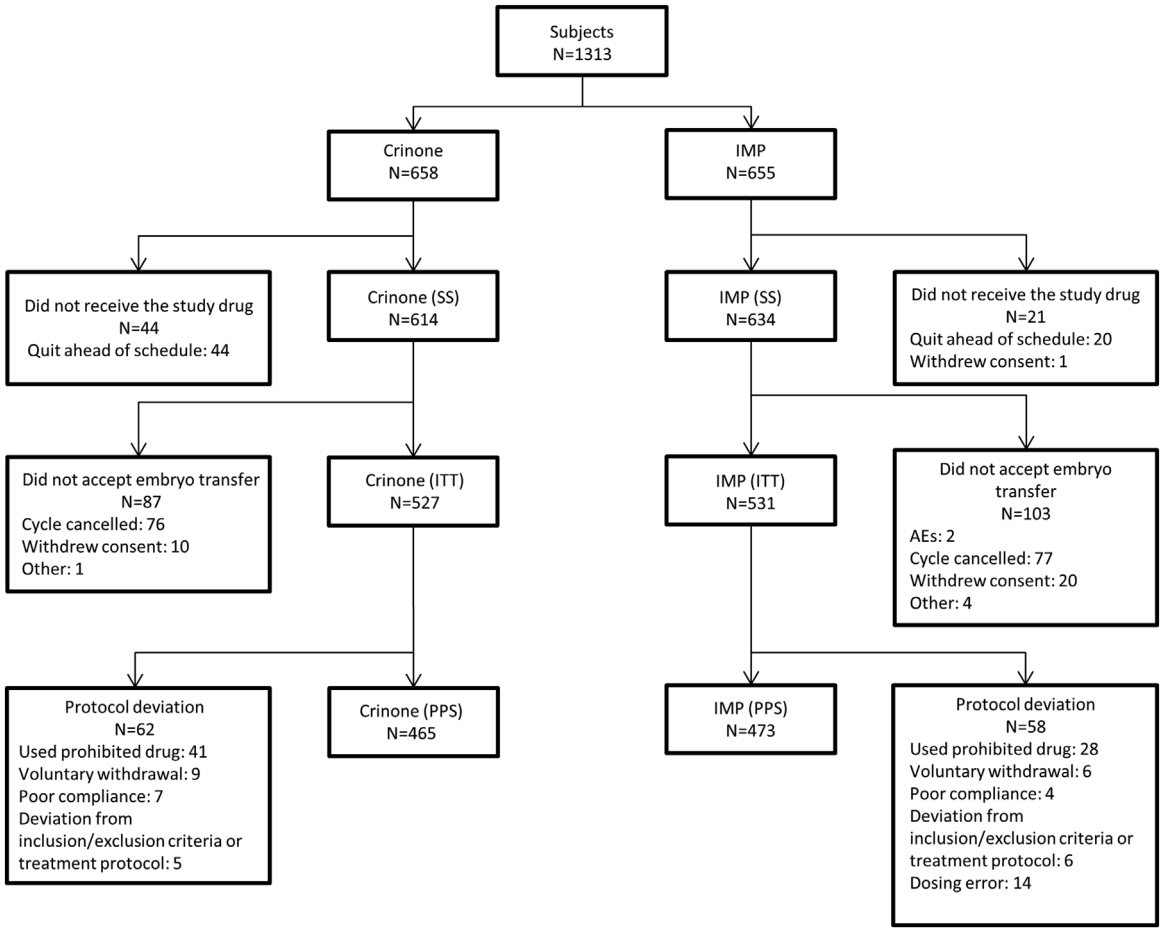

Fig. 1. Patient allocation and treatment.
SS, safety set; IMP, intramuscular progesterone; ITT, intention-to-treat; PPS, per protocol set; AEs, adverse events.

Table 1
Baseline characteristics.

	Progesterone gel (N = 527/1058)	IMP (N = 531/1058)
Age (years) (±SD)	30.2 ± 3.9	30.3 ± 3.8
Body mass index (kg/m^2)	21.4 ± 2.1	21.5 ± 2.1
Nationality (Han; n, %)	511 (97.0)	509 (95.9)
History of infertility (years) (± SD)	3.7 ± 2.6	3.8 ± 2.5
Reasons for infertility (n, %)		
Primary infertility	291 (55.2)	256 (48.3)
Fallopian tube factors	292 (55.4)	307 (57.9)
Endometriosis	12 (2.3)	20 (3.8)
Anovulation	17 (3.2)	19 (3.6)
Male factors	191 (36.2)	201 (37.9)
Other	145 (27.5)	152 (28.7)

IMP = intramuscular progesterone; SD = standard deviation.

Table 2
Comparison of clinical (stimulation) and embryology characteristics of fresh cycles between patients receiving progesterone gel or IMP.

	Progesterone gel N = 527	IMP N = 531	p-value
Duration of GnRHa down-regulation (days)	11.20 ± 2.12	11.28 ± 2.17	0.5443
Dose of rFSH (IU)	207.44 ± 101.54	211.96 ± 90.07	0.4438
Number of oocytes retrieved	12.48 ± 4.99	11.66 ± 4.57	0.0055
Number of mature metaphase II oocytes retrieved	10.15 ± 4.66	9.49 ± 4.14	0.0585
Number of zygotes	7.89 ± 3.94	7.45 ± 3.83	0.0663
Number of embryos on Day 3	7.17 ± 4.10	6.63 ± 3.75	0.0257
Number of embryos transferred	1.94 ± 0.31	1.93 ± 0.33	0.6116

Data are reported as mean ± standard deviation.
GnRHa = gonadotropin-releasing hormone agonist; IMP = intramuscular progesterone; rFSH = recombinant follicle-stimulating hormone.

In this study, ongoing pregnancy rate was assessed in IVF/ET patients using sustained-release progesterone vaginal gel compared with IMP in oil for luteal phase support. The ongoing pregnancy rate of the progesterone gel group was non-inferior to that of the IMP group, and patients administered progesterone gel had a slightly higher ongoing pregnancy rate.

The results support findings from a previous study, which showed a similar ongoing/delivery rate for patients using vaginal gel or IMP (45.2 vs. 42.2%) [10]. Another study found that women administered progesterone gel had a significantly higher live birth rate (51.7%) than those receiving IMP (45.4%) [7]. In that study, a subgroup analysis revealed that the difference was mainly in younger patients (aged <35 years). Subgroup analyses for age were not conducted in the present study, as most patients were <35 years old.

The positive results for progesterone gel reported here might be explained by the first uterine pass effect [10]. This could enhance the therapeutic effect by elevating the progesterone concentration in the endometrium to a considerably higher level than serum progesterone; steady-state level can be achieved 4–5 h after administration [9].

Table 3
Ongoing pregnancy rate outcomes.

	Progesterone gel	IMP	p-value	(Progesterone gel–IMP)
Ongoing pregnancy rate (case/total cases)	255/527	246/531		
Rate (95% confidence interval)	48.4 (44.0, 52.8)	46.3 (42.0, 50.7)	<0.0001	2.1 (−4.0, 8.1)

IMP = intramuscular progesterone.

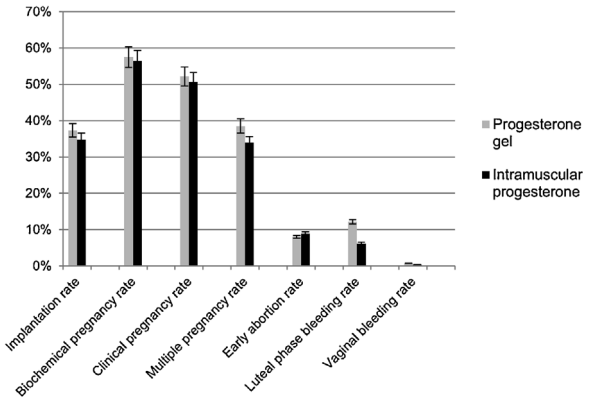

Fig. 2. Outcomes of the secondary endpoints.

Table 4
Analysis of the correlation between luteal phase bleeding and pregnancy rate.

		Uterine bleeding during the luteal phase		Rate of uterine bleeding
		Yes (n = 97)	No (n = 961)	
Biochemical pregnancy	Yes	26 (19/7)	577 (284/293)	4.3%
	No	71 (45/26)	384 (179/205)	15.6%

Data are reported as total (number in progesterone gel group/number in IMP group). IMP = intramuscular progesterone.

Although most studies have found that vaginal gel has good efficacy, some have not. For example, Kaser et al. reported that the IMP group had significantly higher clinical pregnancy (51.1% vs. 36.9%) and live birth (39.1% vs. 24.4%) rates [12]. Despite several studies indicating the efficacy of progesterone gel versus IMP—together with the efficacy results from our study—varied results across studies make it difficult to draw firm conclusions.

Regarding safety, the most common drug-associated AE was bleeding, including luteal phase bleeding. A previous study reported that a greater proportion of women receiving vaginal progesterone gel than IMP experienced bleeding before the first pregnancy test (42% vs. 27%) [13], similar to the present study. Our subgroup analysis of the relationship between bleeding and biochemical pregnancy found that a higher rate of luteal phase bleeding occurred among non-pregnant vs. pregnant patients (15.6% vs. 4.3%). This result is similar to findings from a previous study, which indicated that bleeding occurred more frequently in a subgroup of non-pregnant patients treated with gel vs. IMP (56.5% vs. 38.1%, respectively), but there was no difference in frequency of bleeding in pregnant patients in the gel and IMP groups (21.9% vs. 18.6%, respectively) [14]. The present study findings show that luteal phase bleeding does not affect ongoing pregnancy rates.

Study limitations included the following. Quality of life was not assessed; therefore, conclusions about patient preference cannot be drawn, although the easier administration of progesterone vaginal gel compared with intramuscular injection may be assumed. Owing to the small sample size, further observational studies are needed to confirm the safety of progesterone gel. Live birth rates were not reported, as collection of follow-up data after study completion is not permitted by Chinese health authorities unless prespecified in the study protocol. Finally, patients were almost exclusively of Han Chinese ethnicity, reducing the generalizability to other ethnic groups.

Conclusions

Progesterone gel shows good efficacy and safety outcomes and provides an alternative method of luteal support for Chinese IVF patients.

Conflict of interest

Jie Qiao received study funding from Merck Serono Co. Ltd. China (an affiliate of Merck KGaA Darmstadt, Germany). All other authors have no competing financial interests.

Acknowledgments

The authors would like to thank Diane Williams (Edanz Medical Writing) for editorial assistance, which was funded by Merck Serono Co. Ltd. China (an affiliate of Merck KGaA Darmstadt, Germany). This work was supported by Merck Serono Co. Ltd. China (an affiliate of Merck KGaA Darmstadt, Germany). The sponsor had no role in the collection, analysis and interpretation of the data and writing of the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejogrb.2019.04.012.

References

[1] Practice Committee of the American Society for Reproductive Medicine. Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. Fertil Steril 2008;90:S150–3.
[2] Casper RF, Yanushpolsky EH. Optimal endometrial preparation for frozen embryo transfer cycles: window of implantation and progesterone support. Fertil Steril 2016;105:867–72.
[3] Zhang P, Sun H, Niu Z. Analysis of 15 cases of artificial panniculitis induced by progesterone after intramuscular injection of progesterone. Chin J Pract Gynecol Obstet 2012;28:948–9.
[4] Kahraman S, Karagozoglu SH, Karlikaya G. The efficiency of progesterone vaginal gel versus intramuscular progesterone for luteal phase supplementation in gonadotropin-releasing hormone antagonist cycles: a prospective clinical trial. Fertil Steril 2010;94:761–3.
[5] Merck, Crinone 8% progesterone vaginal gel product information. Available from: https://www.medicines.org.uk/emc/product/1283, (Accessed 28 May 2018).
[6] Chantilis SJ, Zeitoun KM, Patel SI, Johns DA, Madziar VA, McIntire DD. Use of Crinone vaginal progesterone gel for luteal support in in vitro fertilization cycles. Fertil Steril 1999;72:823–9.
[7] Silverberg KM, Vaughn TC, Hansard LJ, Burger NZ, Minter T. Vaginal (Crinone 8%) gel vs. intramuscular progesterone in oil for luteal phase support in in vitro fertilization: a large prospective trial. Fertil Steril 2012;97:344–8.
[8] Chi H, Qiao J, Chen X, Wang X. Comparison of ongoing pregnancy rate of fresh embryo transfer cycles with crinone or intramuscular progesterone for luteal phase support in Chinese population. Fertil Steril 2017;108:e356.
[9] Fanchin R, De Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R. Transvaginal administration of progesterone. Obstet Gynecol 1997;90:396–401.
[10] Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M. Crinone vaginal gel is equally effective and better tolerated than intramuscular

progesterone for luteal phase support in in vitro fertilization–embryo transfer cycles: a prospective randomized study. Fertil Steril 2010;94:2596–9.
[11] van der Linden M, Buckingham K, Farquhar C, Kremer JA, Metwally M. Luteal phase support for assisted reproduction cycles. Cochrane Database Syst Rev 2015;7:CD009154.
[12] Kaser DJ, Ginsburg ES, Missmer SA, Correia KF, Racowsky C. Intramuscular progesterone versus 8% Crinone vaginal gel for luteal phase support for day 3 cryopreserved embryo transfer. Fertil Steril 2012;98:1464–9.
[13] Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein MD. Comparison of Crinone 8% intravaginal gel and intramuscular progesterone supplementation for in vitro fertilization/embryo transfer in women under age 40: interim analysis of a prospective randomized trial. Fertil Steril 2008;89:485–7.
[14] Yanushpolsky E, Hurwitz S, Greenberg L, Racowsky C, Hornstein M. Patterns of luteal phase bleeding in in vitro fertilization cycles supplemented with Crinone vaginal gel and with intramuscular progesterone—impact of luteal estrogen: prospective, randomized study and post hoc analysis. Fertil Steril 2011;95:617–20.