Efficacy and tolerability of vaginal progesterone capsules (Utrogest™ 200) compared with progesterone gel (Crinone™ 8%) for luteal phase support during assisted reproduction

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Objective: To demonstrate the comparative efficacy and tolerability of capsules containing 200 mg of P (Utrogest™ 200) or Crinone™ 8% gel for luteal phase and early pregnancy support during assisted reproduction techniques (ART).
Design: Prospective, multicenter, randomized, controlled, open, parallel-group Phase III trial.
Setting: Seventeen German IVF centers.
Patient(s): Four hundred thirty women who underwent their first IVF or intracytoplasmic sperm injection cycle were randomized after successful transfer of two or three embryos from July 1999 through September 2001.
Intervention(s): Patients vaginally applied capsules containing 200 mg of P (Utrogest™ 200) three times per day or containing Crinone™ 8% gel twice per day. Therapy was started in the evening of the ET day and continued up to 10 weeks in pregnant women. If the pregnancy test proved to be negative, application was stopped.
Main Outcome Measure(s): Ongoing pregnancy rate at the end of the study (12th week of gestation). Secondary outcomes were rate of implantation and abortion, number and reasons of withdrawals, as well as adverse events, assessment of tolerability, and acceptance.
Result(s): There were no relevant differences in demographic and other characteristics between the two groups. Ongoing pregnancy rates were 25.2% in the Utrogest™ 200 group and 22.2% in the Crinone™ 8% group when patients were analyzed who normally completed the trial. In the Utrogest™ 200 vs. the Crinone™ 8% group, the implantation rate (14.7% vs. 11.9%) and abortion rate (18.2% vs. 19.1%) were not statistically different. The rate of withdrawals at the individual visits also did not differ between treatment groups. Tolerability of both drugs was good, and very few study drug–related adverse events were observed in both groups.
Conclusion(s): The luteal phase support in ART cycles with Utrogest™ 200 capsules (three times per day) or Crinone™ 8% gel (two times per day) by the vaginal route resulted in similar outcomes with respect to implantation, ongoing pregnancy, and abortion rates. The two recommended regimens of P supplementation in ART proved to be equivalent and safe. (Fertil Steril® 2005;83:1641–9. ©2005 by American Society for Reproductive Medicine.)

Key Words: Assisted reproduction techniques, luteal phase support, vaginal progesterone, pregnancy rate, tolerability

There exist differences in progesterone (P) secretion in natural and stimulated cycles (1). In natural-conception cycles, the steady increase of P is superimposed by the embryonal hCG–induced stimulation of large luteal cells. Stimulated cycles are characterized by an unphysiological high, external hCG–induced P secretion in the early luteal phase that falls until it is sustained by the embryonal hCG production.

A defective luteal phase was particularly demonstrated in assisted reproduction technique (ART) cycles using long protocol pituitary desensitization with GnRH agonists. In such cases, a considerable fall in the P and E_2 concentration beginning from the 8th day of the luteal phase was observed (2), resulting in reduced overall success of ART treatment with lowered implantation and pregnancy rates (3, 4). However, immediate GnRH suppression caused by GnRH receptor blockage with subsequent luteal insufficiency appears to occur in ART cycles employing GnRH antagonists, too, despite a shorter half life of the compounds and a reduced time of application during ovarian stimulation (5, 6). These findings require the use of luteal support in both the GnRH agonist– as well as GnRH antagonist-controlled ART cycle.

Progesterone has become the agent of choice for luteal phase supplementation because hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS), particularly in younger women, good responders, and women with polycystic ovary syndrome. Progesterone may be administered by oral, IM, or vaginal routes. The vaginal

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route gained attraction because it circumvents the variable absorption and high first-pass hepatic metabolism after oral ingestion and also prevents the uncomfortable and sometimes painful IM injection. Moreover, experimental (7) as well as clinical (8, 9) data propose a *first uterine pass effect* after vaginal administration of P with high uterine concentrations despite low systemic exposure.

In addition to pharmacist-formulated suppositories, the well-standardized P preparations Utrogest/Utrogestan (Besins-Iscovesco, Paris, France) and Crinone™ 8% (Serono, Unterschleißheim, Germany) are suitable for vaginal use. In a randomized study using a cross-over design, the vaginal bioavailability of Utrogest™ 200 (200 mg of P) was evaluated in 23 healthy women in comparison to the case with one applicator dose of the 8% P gel (90 mg of P) after a single vaginal administration (10). Both formulations did not differ with respect to the measured peak serum concentrations; however, they clearly were different in regard to the duration of peak levels, which was longer with Utrogest™ 200 in comparison with Crinone™ 8%. The area under the concentration–time curve for P was almost 50% higher after administration of Utrogest™ 200 than after the reference preparation. There were no relevant differences in safety profiles and tolerability between the two investigated preparations.

The aim of the present study was to demonstrate the comparative efficacy and tolerability of capsules containing 200 mg of P (Utrogest™ 200) and a gel (Crinone™ 8%) containing 90 mg of P per applicator dose for luteal phase and early pregnancy support after ART. Women undergoing IVF–intracytoplasmic sperm injection (ICSI) were randomized to treatment with Utrogest™ 200 (three times per day intravaginally) or Crinone™ 8% (two times per day intravaginally) beginning from evening of the day of ET up to the 12th week of gestation, in case of pregnancy.

MATERIALS AND METHODS

Patient Selection

During a 2-year period, from July 1999 through September 2001, 430 women undergoing IVF or ICSI were consented for treatment and were randomized after successful ET to receive P. To achieve this, 583 women presenting for ART had to be screened by the 26 investigators in 17 German IVF centers. Finally, each center randomized 10 to 40 patients.

Patients were enrolled in the study if they fulfilled the following criteria: indication for IVF-ICSI given, successful transfer of two or three embryos, presentation for the first ART treatment cycle, age $\geq$18 years and $\leq$35 years, normal cervical cytological smear within the past 12 months, and legally valid declaration of consent from the patient. Patients were not eligible for the study if P therapy was contraindicated (presence of severe acute and chronic liver disease, Rotor or Dubin-Johnson syndrome, hepatocellular tumors, or known allergic reaction to one of the active constituents or inactive ingredients contained in the investigational medication).

Before the start of the study, the trial protocol was approved by the ethics committee of the Medical Faculty of the Otto-von-Guericke-University, Magdeburg, Germany, with jurisdiction over the principal investigator and by the ethics committees of the other participating investigators.

Study Design

The trial was performed as a multicenter, randomized, controlled, open, parallel-group Phase III study according to German legislation and Good Clinical Practice-European Union (GCP-EU) guidelines. In the study, a reference preparation (Crinone™ 8%) already on the market served as control (active control).

Visits in the study centers were scheduled at 2 and 4 weeks after ET and in the 8th week of gestation if a pregnancy was the ART outcome.

The primary end point was the ongoing pregnancy rate at the end of the 12th week of gestation. The implantation and abortion rates and the rate of withdrawals, overall or at the respective visits, were considered secondary study end points.

Treatment Protocol

There were no strict instructions as to the performance of multifollicular stimulation before oocyte retrieval and ET. Preceding therapy comprised pituitary down-regulation with a GnRH agonist in a long protocol and ovarian stimulation with hMG or FSH. Final follicle maturation was induced by injection of 10,000 IU hCG, followed by ultrasound (US)-guided vaginal oocyte retrieval. In vitro fertilization was performed conventionally or by ICSI technique.

There existed also no strict criteria for the transfer of two or three embryos; this decision was part of the treatment strategy of the center. Because patients' average age was between 30 and 31 years and it was their first ART cycle, in 75% of the cases, only two embryos were transferred to reduce the risk of multiple pregnancies.

After successful transfer of two or three embryos at day 3 after oocyte pickup, the patients were randomly assigned to one of the treatments with the aid of a randomization code. The trial investigators received consecutively numbered envelopes corresponding to the envisaged number to be recruited. An envelope was allowed to be opened in chronological sequence to assign treatment group only after successful transfer. Both the randomization number and the treatment group had to be transferred immediately to the case report form. The randomization code (Blocking-Factor 10) was generated by a computer program (Rancode-Plus, Report Version 6.4, Testimate Version 6.0, IDV, Gauting, Germany).

The trial started in the evening of the ET day, with the first dose of the test or comparative medication as sole form for luteal support. Patients were not permitted to receive any

additional treatment with steroid hormones or hCG during the trial phase.

Measures to prevent and treat OHSS had to be accepted. There were no restrictions on additional medication with electrolytes, albumin, vitamins and trace elements, iron, and folic acid.

If concurrent diseases occurred, necessary therapy had to be provided. In these cases, patients remained in the study if the therapy did not interfere with the study objectives. Any concomitant medication and therapy had to be documented in the case report form, including its dosage and duration.

Luteal Support

All patients started treatment with either Utrogest™ 200 or Crinone™ 8% as the unique form of luteal supplementation. Utrogest™ 200 are soft gelatin capsules containing P suspended in oil.

Pharmacokinetic investigations supported the vaginal use, demonstrating that maximum P serum concentration of about 7 ng/mL could be achieved after single vaginal application of an Utrogest™ capsule containing 200 mg of P (10). However, consistent P levels above those of the normal luteal phase required three daily applications of 200 mg of P vaginally (11). With this regimen, endometrial development was never out of phase if endometrial histology has been taken into consideration (12). Consequently, the three-times-per-day dosage of 200 mg of P (Utrogest™ 200) vaginally during the luteal phase and early pregnancy was suggested as optimal.

Crinone™ is a small-volume, polycarbophil-based P gel that attaches to the vaginal epithelium with proposed advantages such as facilitated diffusion of P across the vaginal wall and sustained release. One dose of 1.125 g of Crinone™ 8% delivers 90 mg of P. Women were advised to follow the application instructions on the patient leaflet for Crinone™ 8% gel. The daily dosage was adjusted to two applicator doses of Crinone™ 8% gel, one in the morning, the other in the evening.

Treatment was stopped if the pregnancy test was negative. In case of pregnancy, treatment continued up to the end of the trial, the 12th week of gestation.

Laboratory Determinations

Beside usual ART cycle monitoring, P, E_2, and β-hCG were exclusively measured at two visits that were scheduled 12–14 days and 27–29 days after ET. The determination and report of values were left at the discretion of the individual study center. Because the hormone values were not confirmed by a central laboratory, they are not reported. Biochemical pregnancies were not a defined study end point and therefore are not analyzed separately. Nevertheless, the pregnancy test results served as the relevant criterion for attesting pregnancy failure in many instances.

Clinical chemistry, hematology, and urine analysis were performed before enrollment and at conclusion of the study.

Determination of Pregnancy Status and Respective End Points

Pregnancy status was determined by US examination in the 6th and 10th week after ET. Only clinical pregnancies with increasing β-hCG levels and valid US evidence of an amniotic sac were recorded. The main outcome measure for confirmatory analysis was the ongoing pregnancy rate. This was the percentage of intact clinical pregnancies in the 12th week of gestation, that is, the percentage of pregnancies with fetal heart activity at US.

Safety and Patient Acceptability

Occurrence of adverse events (AEs) was examined at each visit. If the responsible investigators of the study centers indicated an AE in a patient, they were to describe it in their own words. Additionally, the case report form provided categories for intensity (mild, moderate, severe), clinical course (disappeared without therapy, required therapy, caused withdrawal), and causality with study drugs (certainly unrelated, questionable relation, certainly related). Furthermore, a categorical assessment of local tolerability by the responsible investigators had to be performed. So gynecologic investigation was required to identify intravaginal erythema or infection. Vaginal itching and burning had to be inquired about. Intensity and causality of symptoms had to be rated. At the end of the study, overall tolerability of the study drugs was rated by the patient, and overall acceptance of therapy with the study drug was judged by the physician on a scale including the points *very good, good, moderate*, and *bad.*

Statistical Analysis

Point estimates and confidence intervals were calculated for the primary end point. A difference in percentage of ongoing pregnancy rates of 10% was judged as being clinically acceptable because this corresponds to the variability between IVF centers. There was no attempt to differentiate between IVF and ICSI treatment, because there were comparable outcome figures for both of these treatment modalities with respect to pregnancy rate during the trial period in the national registry (13).

Accordingly, the lower limit of the 90% confidence interval of the difference in ongoing pregnancy rates between the two study groups, calculated by accepted methods, had to exceed -0.1 to attest noninferiority of Utrogest™ 200 relative to Crinone™ 8%. The exact number of patients required to confirm the test hypothesis with an α of 5% and a power of 80% was calculated to 444. Originally, it was intended that 450 women undergoing IVF-ICSI would be enrolled in the trial. Actually, only 430 women could be randomized within an acceptable time frame.

Secondary parameters were evaluated descriptively or using exploratory statistics, such as the Wilcoxon Mann-Whitney test or Fisher's exact test. Exploratory statistics also were applied to tolerability ratings by patients and physicians.

RESULTS

Patient Demographic Characteristics

Demographic data for the women randomized to each of the two treatment groups, 218 women in the Utrogest™ 200 group and 212 in the Crinone™ 8% group, are shown in Table 1. Although the figures for body mass index, the duration of infertility, and the distribution of infertility causes were very similar in the two groups, the women of the Utrogest™ 200 group were significantly ($P=.0431$) older than the women of the Crinone™ 8% group. Similarity existed also for the respective quota of transferred embryos (two or three) as well as for the relative frequencies of conventional IVF or ICSI treatments.

The portion of smokers and the number of patients with concurrent diseases were similar in the two groups. For 24 patients (11.0%) in the Utrogest™ 200 group and 26 patients (12.3%) in the Crinone™ 8% group, concurrent diseases were present. Thyroid dysfunction represented a third of all given concomitant diseases and were most frequent in both groups.

As case history details, allergic diseases occurred more often in the Utrogest™ 200 group (29.2%). The concurrent diseases and the concomitant medications used did not represent contraindications for IVF-ICSI treatment and were not considered to have detrimental influences on ART procedures and outcomes.

In the case of concomitant medication, folic acid preparations were used in 71.4% and 81.5% of cases in the Utrogest™ 200 and Crinone™ 8% group, respectively. Iodide, acetyl salicylic acid, and iron preparations occasionally were used alone or in combination with folic acid. In two women receiving Utrogest™ 200, antibiotics had to be administered, and two women of the Crinone™ 8% group received additional vaginal therapy with clotrimazole or lactobacilli. There were also single cases of concomitant enoxaparin and bromocriptine treatment.

As a measure of compliance, patients were instructed to return their unused study medication. An explicit evaluation of compliance was part of the case report forms. In the Utrogest™ 200 group, information about three patients was lacking. A divergent dosage was detected only once in one patient (four instead of three capsules in 1 day). On the other hand, in 12 women (5.7%) of the Crinone™ 8% group, the dosage was reduced to one applicator dose daily. These patients still were regarded as evaluable and remained in the analysis.

Comparable numbers of withdrawals were observed in both treatment groups. Overall, 163 (74.8%) of 218 women in the Utrogest™ 200 group withdrew prematurely, compared with 165 (77.8%) of 212 women in the Crinone™ 8% group. The rate difference amounted to −0.0306 ($P=.4839$). The reasons for withdrawal are given in Table 2. Most

TABLE 1

Demographic data, infertility, and ART-specific characteristics of patients.

Variable	Utrogest™ 200	Crinone™ 8%
Randomized patients (n)	218	212
Age in y, mean ± SD (range)	30.7 ± 2.9[a] (22–35)	30.1 ± 3.0 (23–35)
Body mass index in $[kg/m^2]$,[a] mean ± SD (range)	22.7 ± 3.8 (16.7–41.9)	22.8 ± 3.9 (16.2–38.7)
Duration of infertility in y, mean ± SD (range)	3.8 ± 2.2 (1–15)	3.7 ± 2.3 (1–15)
Cause of infertility, n (%)		
Tubal factor	66 (30.3)	48 (22.6)
Male factor	104 (47.7)	117 (55.2)
Endometriosis	12 (5.5)	16 (7.6)
Other	36 (16.5)	31 (14.6)
No. of transferred embryos		
2	165 (75.7)	155 (73.1)
3	53 (24.3)	57 (26.9)
Mode of fertilization		
Conventional IVF	143 (65.6)	140 (66.0)
ICSI	75 (34.4)	72 (34.0)

[a] $P<.05$ vs. Crinone™.

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TABLE 2

Reasons for discontinuation.

Withdrawal reason	Utrogest™ 200 No.	Utrogest™ 200 % of study group	Crinone™ 8% No.	Crinone™ 8% % of study group
Pregnancy failure	153	70.2	150	70.8
Lack of β-hCG increase or start of menstrual bleeding	143	65.6	141	66.5
Abortion	3	1.4	6	2.8
Missed abortion	7	3.2	3	1.4
Other reasons for withdrawal	10	4.6	15	7.1
Adverse event	1	0.5	2	0.9
Local intolerance	1	0.5	3	1.4
Unallowed hormone therapy	4	1.8	3	1.4
Withdrawal of consent			2	0.9
Patient did not return	3	1.4	2	0.9
Other	1	0.5	3	1.4
Total	163	74.8	165	77.8

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withdrawals occurred up to 14 days after ET and were caused by lack of β-hCG increase and/or beginning of menstrual bleeding that pertained to about two thirds of the study population.

The onset and heaviness of vaginal bleeding were not explicitly recorded. Therefore, the number of women who bled during P therapy or before β-hCG testing could not be exactly declared. However, this number may equate to the number of women who did not become pregnant and for whom no laboratory determinations, including β-hCG, were recorded. This happened in 30 (14.2%) of the 212 patients in the Crinone™ 8% group and in 24 (11.0%) of the 218 patients in the Utrogest™ 200 group.

Pregnancy failure was accountable for 93.9% and 90.9% of discontinuations in the Utrogest™ 200 and Crinone™ 8% groups, respectively. Concomitant hormone therapy was administered to 4 women of the Utrogest™ 200 group and to 2 women of the Crinone™ 8% group. This led to exclusion from the trial.

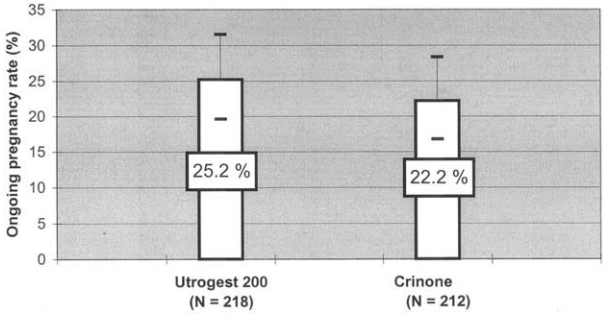
Efficacy

Fifty-five patients in the Utrogest™ 200 group and 47 patients in the Crinone™ 8% group completed the study regularly. These were all women with ongoing pregnancies at or beyond the 12th week of gestation and who were not withdrawing prematurely. Ongoing pregnancy rates of 25.2% (95% confidence interval [CI]: 19.6%–31.5%) for the Utrogest™ 200 group and of 22.2% (95% CI: 16.8%–28.4%) for the Crinone™ 8% group were calculated (Fig. 1). The odds ratio (calculated on the per-protocol population) for an intact pregnancy at the end of 12th week of gestation was 1.185 (90% CI: 0.733–1.833) when the Utrogest™ 200 group was compared with the Crinone™ 8% group. According to the prespecified criteria, the pregnancy rate in the Utrogest™ 200 group was thus demonstrated to be noninferior to that in the Crinone™ 8% group (lower limit of the 90% confidence interval > -0.1).

In consideration of the somewhat lower than planned sample size and using the same criteria and methods, noninferiority was retained under conservative assumptions for

FIGURE 1

Point estimate and 95% confidence limits of pregnancy rates in patients regularly completing the study with an ongoing pregnancy at or later than the 12th week of gestation in the per protocol population. The odds ratio for an intact pregnancy was 1.185 (90% CI, 0.733–1.833) when the Utrogest™ 200 group was compared with the Crinone™ 8% group.



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the remaining women who would have been included, that is, if only one pregnancy in seven additional users of Utrogest™ 200 (pregnancy rate 14%) had happened and also 12 pregnancies had occurred in 13 additional users of Crinone™ 8% (pregnancy rate, 92%).

The pregnancy rate ratios of the individual study centers and their 95% confidence intervals were calculated, too. Because of the low number of ETs in two centers, results from those two were combined for analysis. As expected, the confidence limits were wide. In seven centers, the pregnancy rates in the Utrogest™ 200 group were higher than those in the Crinone™ 8% group, and in eight centers, the reverse occurred. In the remaining center, identical rates were achieved in both groups. In only one center was a significant difference of the pregnancy rate ratio observed in favor of the Utrogest™ 200 group. This distribution is compatible with the assumption of equivalence.

Multiple gestation was recorded in the 8th week and 12th week of gestation. At this time, 71% in the Utrogest™ group and 79% in the Crinone™ 8% group were singleton pregnancies. The remainder were twin gestations. Only one case of triplets was observed. That woman was in the Utrogest™ 200 group.

Thus, 83 and 72 embryos were detected in the 8th and 12th week of gestation, respectively, in the 218 women of the Utrogest™ 200 group, and 64 and 58 embryos, respectively, were detected in the 212 women of the Crinone™ 8% group. The Mann-Whitney statistics were 0.5468 (0.4622–0.6313) in the 8th week (P=.3268) and 0.5432 (0.4600–0.6263) in the 12th week (P=.3268). This indicated a similar number of implantations or embryos with heart activity in both treatment groups. Only nonsignificant differences were found for the rate of abortions and missed abortions in both treatment groups. In the Utrogest™ 200 group, 10/218 (4.6%) experienced an abortion or missed abortion. The frequency in the Crinone™ 8% group was 9 of 212 women (4.2%; Table 2). The rate difference was 0.0034 (P=.990).

In summary, thrice-daily vaginal Utrogest™ 200 for luteal phase support in ART cycles was associated with equivalent implantation, clinical pregnancy, and abortion rates when compared with vaginal Crinone™ 8% twice daily (Table 3).

TABLE 3

Summary of outcomes.

Variable	Utrogest 200	Crinone 8%
No. of transfers	218	212
No. of embryos transferred	489	481
No. of implantations (% per transferred embryos)	72 (14.7)	57 (11.9)
No. of clinical pregnancies (% per transfer)	55 (25.2)	47 (22.2)
No. of abortions/missed abortions (% of clinical pregnancies)	10 (18.2)	9 (19.1)

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Safety

Only very few patients left the study because of AEs or local intolerance. In the Utrogest™ 200 group, one woman each (0.5% each) discontinued because of an AE and local intolerance, respectively, whereas in the Crinone™ 8% group, two women (0.9%) left because of an AE, and three women (1.4%), because of local intolerance. Overall, 24 AEs in 21 patients (9.6%) of the Utrogest™ 200 group and 26 AEs in 21 patients (9.9%) of the Crinone™ 8% group were reported.

Analysis of causality assessment reveals that only 3 of 24 AEs (one case each of severe local discomfort, bloating, vaginal discharge) were considered to be definitely related to the use of P capsules (Utrogest™ 200). All 7 AEs that were considered definitely related to P gel (Crinone™ 8%) use concerned local irritation or discomfort because of cloddy disposal or discharge of drug material. There was only one serious AE, a case of jugular vein thrombosis, which was rated as questionable and not certainly related to Utrogest™ 200 medication. The rate differences of AEs between the two groups was −0.0023 (P=1.000). Thus the frequency of AEs was not different between the two groups.

The frequency and severity of local intolerance did not raise particular concerns. In the Utrogest™ 200 group, 28 local intolerance events occurred in 15 women (6.9%); in the Crinone™ 8% group, the number was 31 local events in 15 women (7.1%; Table 4). Erythema accounted for half of local reactions in both groups. Burning and itching together constituted about 40% of the remaining local events, whereas vaginal discharge was observed in rare instances only.

Overall, 22 of 28 local events in the Utrogest™ 200 group and 28 of 31 events in the Crinone™ 8% group remained as study drug–related local intolerance. Even if intensity was indicated as severe, not any case of local intolerance fulfilled the criteria of a serious AE. The rate differences of local intolerance between the two groups amounted to −0.0019 (P=1.000). Thus, their frequency was not different between the two groups.

Clinical chemistry, hematology, and urine analysis did not detect clinically relevant abnormalities related to P treatment (data not shown). Increases in transaminases in individual women were generally marginal, and they were not associated with clinical symptoms of disease. Although mean hematology parameters also were within the normal range, mild anemia developed or became aggravated in some women; the majority of these women became pregnant through the trial. Thus, the observed slight deteriorations in red blood cell parameters evidently were caused by preg-

TABLE 4

Local adverse events detected by interview and gynecologic investigation.

Event	Mild		Moderate		Severe		Total		Total
	Related	NR[a]	Related	NR	Related	NR	Related	NR	All
Utrogest™ 200 group (n = 218)									
Erythema	10	3	1				11	3	14
Burning	4		1	1			5	1	6
Vaginal discharge	1	2	2				3	2	5
Itching	1				2		3		3
Total	16	5	4	1	2		22	6	28
Crinone™ 8% group (n = 212)									
Erythema	8	2	3		2		14	2	16
Itching	5		1				7		7
Burning	5						6		6
Vaginal discharge	1			1			1	1	2
Total	19	2	4	1	2		28	3	31

Note: NR = not related.

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nancy and were not related to treatment with study drugs. Hence, treatment with neither Utrogest™ 200 nor the comparator Crinone™ 8% induced abnormalities of laboratory parameters.

More than 90% of women rated overall tolerability of the study drugs as "very good" or "good." Similarly, acceptance of either treatment was positively assessed in >90% of women by the physicians. Nevertheless, both items indicated an overall significant difference ($P<.0001$) of the effect index, as calculated from rank sums, in favor of Utrogest™ 200.

DISCUSSION

Luteal-phase support is routinely prescribed after oocyte retrieval in ART cycles. According to the German national registry (Deutsches IVF-Register), luteal support is administered in 90% of the cycles (13). In about half of the cases, P alone is used for that purpose. There is an increasing tendency to use P alone as sole luteal phase supplementation for two reasons. On the one hand, hCG alone or in combination with P increases the risk of OHSS, sometimes with development of anuria, dyspnea, and thromboembolic phenomena as life-threatening complications (14). On the other hand, there is growing evidence of no significant benefit, in terms of (ongoing) pregnancy rate, if hCG is used as an alternative or even if it is added to P (15).

Progesterone can be applied orally, IM, or vaginally. Systemic availability of micronized P is lower after oral than after vaginal administration (16), and evidence indicates a less favorable ART outcome using oral application compared with either the IM or vaginal route (12). Because achievement of placental autonomy is considered to take up to 10–12 weeks, IM injections are unfavorable because they can lead to patient discomfort, inflammatory reactions, and even abscesses. Thus, vaginal P remains as the optimal choice for supplementation.

Capsules containing micronized P (Utrogestan) were successfully used vaginally at doses from 200 to 600 mg daily to perform secretory transformation of the estrogen-primed endometrium in women with ovarian failure (17). In ART cycles, particularly when GnRH agonist was part of the protocol, supplementation of the luteal phase and early pregnancy with 600 mg of micronized P daily by the vaginal route resulted in an adequate maturation of the endometrium (18) and in favorable pregnancy outcomes (19, 20).

In designing the presented trial, twice-daily dosing of Crinone™ 8% was chosen because study results demonstrated equivalence of this dosage with 100 mg of IM P daily in women with premature ovarian failure or diminished ovarian reserve accepted for oocyte donation (21). Later reports argued for the recommendation of once-daily Crinone™ 8% for complete luteal supplementation in a donor egg program (22) as well as in a conventional IVF program (23, 24). However, this was called into question by the demonstration of lower implantation and pregnancy rates and of higher rates of early-onset vaginal bleeding during once-daily use of Crinone™ 8% gel in comparison with 50 mg of IM P daily (25–27). Thus, recent discussion justifies the use of Crinone™ 8% twice daily in the present trial.

Published data are in good conformity with the results of the multicenter Phase III study comparing Utrogest™ 200 capsules (three times a day) with Crinone™ 8% gel (twice a day). With respect to achieved pregnancy rates, the restrictions of the German embryo protection law have to be taken

into consideration. In this context, it is worth mentioning that only a maximum of three embryos is allowed to develop in vitro and to be transferred. After insemination or fertilization of all collected mature oocytes, selection is restricted only to pronuclear stage oocytes and not to cleavage-stage embryos, and therefore no other embryos are available for later transfer than those selected at the pronuclear stage. At the pronuclear stage, it has to be decided which cells are cultured and used for ET and which are cryopreserved or discarded (28).

Under these conditions, Utrogest™ 200 was associated with similar implantation, ongoing pregnancy, and abortion rates as those of Crinone™ 8% gel. By prespecified criteria, noninferiority of Utrogest™ 200 relative to Crinone™ 8% could be attested. Thus, the investigated and recommended regimen of Utrogest™ 200 is considered therapeutically equivalent to the P supplementation with Crinone™ 8%.

Equivalence between Utrogest™ and Crinone™ was also confirmed in a recent prospective, randomized monocentric study using Utrogest™ 100 capsules (three capsules, twice per day) and Crinone™ 8% gel (one time daily) for luteal phase support (29).

Concerning the beginning of vaginal P support, consensus exists that it should start early. A recent study confirmed that an early onset of vaginal P supplementation at the day of ET led to significantly higher implantation and clinical pregnancy rates than the later initiation of the support, 3 days after the transfer. This was particularly true for patients treated with a GnRH-agonist long protocol (30).

Tolerability of either approach was good. Only very few patients left the study because of AEs or local intolerance to the study drugs. To date, long-term experience from use of micronized P has given no indication of any serious adverse reaction. The single possible exception is a reported hepatic toxicity after high oral-P doses in the second and third trimester of pregnancy (31, 32). Drowsiness and dizziness (33), bloating, and abdominal pain are the systemic side effects most frequently reported by P-treated women. Their incidence is lower if P is given by the vaginal instead of the oral route.

Only single cases of severe local discomfort, bloating, and vaginal discharge were considered to be definitely related to the use of Utrogest™ 200. Occasionally observed local irritation or discomfort caused by (cloddy) disposal or discharge of drug material may have contributed to the comparatively worse rating of Crinone™ 8% gel overall tolerability and acceptance by patients and physicians.

One of the most carefully observed AEs in both treatment groups was OHSS. A third-grade OHSS is considered a serious AE because it is characterized by significant though reversible disability. Hospitalization, intensive care, and therapy are necessary to manage this life-threatening complication. Although hCG for luteal support is seen as a risk factor for OHSS, P is not considered to be involved in the development and course of OHSS. Avoidance of exogenous hCG in the luteal phase is one of the main precautionary measures to prevent OHSS. The low number of severe OHSS in the presented study, one case of severe OHSS in the Utrogest™ 200 group and three cases in the Crinone™ 8% group, accounts for the OHSS-preventive effect of vaginally applied P.

Only two other cases of AEs that could be classified as serious were registered in the Utrogest™ 200 group. One case of cervical dysplasia (Pap III D) was evidently not related to study drug use. The other already-mentioned case of jugular vein thrombosis was rated as questionable by the responsible investigator. In contrast to elevated estrogens, there is no substantial evidence that P is a risk factor for venous thromboembolism. Hence, this case of jugular vein thrombosis may be a consequence of high estrogen levels during ART and early pregnancy.

In conclusion, this multicenter, randomized, controlled, open, parallel-group study in 430 women demonstrated the noninferiority of three one-capsule dosages of Utrogest™ 200 (600 mg of P) when compared with two one-applicator dosages of Crinone™ 8% (180 mg of P) daily vaginally. In detail, Utrogest™ 200 was associated with similar implantation, ongoing pregnancy, and abortion rates in comparison to Crinone™ 8%. The preparations were generally well tolerated both systemically and locally. Overall, the recommended regimen of P support in the luteal phase of ART cycles is considered equivalent and safe. It poses no risk for women in the first trimester of pregnancy.

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REFERENCES

1. Penzias AS. Luteal phase support. Semin Reprod Endocrinol 1995;13:32–8.
2. Smitz J, Devroey P, Braeckmans P, Camus M, Khan I, Staessen C, et al. Management of failed cycles in an IVF/GIFT program with the combination of a GnRH analogue and hMG. Hum Reprod 1987;2:309–12.
3. Van Steirteghem AC, Smitz J, Camus M, Van Waesberghe L, Deschacht J, Khan I, et al. The luteal phase after in-vitro fertilization and related procedures. Hum Reprod 1988;3:161–4.
4. Soliman S, Daya S, Collins J, Hughes EG. The role of luteal phase support in infertility treatment: a meta-analysis of randomized trials. Fertil Steril 1994;61:1068–76.
5. The European and Middle East Orgalutran Study Group. Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH

surges in women undergoing ovarian stimulation. Hum Reprod 2001;16:644–51.
6. Beckers NGM, Macklon NS, Eijkemans MJ, Ludwig M, Felberbaum R, Diedrich K, et al. Nonsupplemented luteal phase characteristics after the administration of recombinant human chorionic gonadotropin, recombinant luteinizing hormone, or gonadotropin-releasing hormone (GnRH) agonist to induce final oocyte maturation in in vitro fertilization patients after ovarian stimulation with recombinant follicle-stimulating hormone and GnRH antagonist cotreatment. J Clin Endocrinol Metab 2003;88:4186–92.
7. Buletti C, de Ziegler D, Flamigni C, Giacomucci F, Polli V, Bolelli G, et al. Targeted drug delivery in gynecology: the first uterine pass effect. Hum Reprod 1997;12:1073–9.
8. Cicinelli E, de Ziegler D, Buletti C, Matteo MG, Schonauer LM, Galantino P. Direct transport of progesterone from vagina to uterus. Obstet Gynecol 2000;95:403–6.
9. Miles R, Paulson R, Lobo R, Press M, Dahmoush L, Sauer M. Pharmacokinetics and endometrial tissue levels of progesterone after administration by intramuscular and vaginal routes: a comparative study. Fertil Steril 1994;62:485–90.
10. Kleinstein J, Schlegelmilch R, Mazur D, Vens-Cappell B. Vergleichende Pharmakokinetik von Progesteron-Kapseln und einem Progesteron-Gel nach vaginaler Anwendung. Arzneimittelforschung Drug Res 2002;52:615–21.
11. Devroey P, Palermo G, Bourgain C, Van Waesberghe L, et al. Progesterone administration in patients with absent ovaries. Int J Fertil 1989; 34:188–93.
12. Toner JP. The luteal phase: luteal support protocols. In: Gardner DK, Weissmann A, Howles CM, Shohan Z, eds. Textbook of assisted reproductive techniques. London: Martin Dunitz, 2001:515–25.
13. Deutsches IVF-Register. Jahrbuch 2001. DIR Bundesgeschäftsstelle Ärztekammer Schleswig-Holstein, Bismarckallee 8–12, D-23793 Bad Segeberg, Germany.
14. Navot D. Severe ovarian hyperstimulation syndrome. In: Gardner DK, Weissmann A, Howles CM, Shohan Z, eds. Textbook of assisted reproductive techniques. London: Martin Dunitz, 2001:645–54.
15. Ludwig M, Finas A, Katalinic A, Strick D, Kowalcek I, Schwartz P, et al. Prospective, randomized study to evaluate the success rates using hCG, vaginal progesterone or a combination of both for luteal phase support. Acta Obstet Gynecol Scand 2001;80:574–82.
16. Levine H, Watson N. Comparison of the pharmakinetics of Crinone™ 8% administered vaginally versus Prometrium administered orally in postmenopausal women. Fertil Steril 2000;73:516–21.
17. Salat-Baroux J, Carnet D, Alvarez S, Antoine JM, Tibi C, Mandelbaum J, et al. Pregnancies after replacement of frozen thawed embryos in a donation program. Fertil Steril 1988;49:817–21.
18. Bourgain C, Smitz J, Camus M, Erard P, Devroy P, Van Steirteghem AC, et al. Human endometrial maturation is markedly improved after luteal supplementation of gonadotrophin-releasing hormone analogue/human menopausal gonadotrophin stimulated cycles. Hum Reprod 1994;9:32–40.
19. Smitz J, Devroey P, Faguer B, Bourgain C, Camus M, Van Steirteghem AC. A prospective randomized comparison on intramuscular or intravaginal natural progesterone as a luteal phase and early pregnancy supplement. Hum Reprod 1992;7:168–75.
20. Devroey P, Smitz J, Bourgain C, Van Steirteghem AC. Only micronized progesterone is needed to substitute the luteal phase in stimulated cycles. Contracept Fertil Sex 1992;20:7–8.
21. Gibbons WE, Toner JP, Hamacher P, Kolm P. Experience with a novel vaginal progesterone preparation in a donor oocyte program. Fertil Steril 1998;69:96–101.
22. Jobanputra K, Toner JP, Denoncourt R, Gibbons WE. Crinone 8% (90 mg) given once daily for progesterone replacement therapy in donor egg cycles. Fertil Steril 1999;72:980–4.
23. Chantilis SJ, Zeitoun KM, Patel SI, John 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.
24. Schoolcraft WB, Hesla JS, Gee MJ. Experience with progesterone gel for luteal support in a highly successful IVF program. Hum Reprod 2000;15:1284–8.
25. Damario MA, Goudas VT, Session DR, Hammitt DG, Dumesic DA. Crinone 8% vaginal progesterone gel results in lower embryonic implantation efficiency after in vitro fertilization-embryo transfer. Fertil Steril 1999;72:830–6.
26. Licciardi FL, Sanghi A, Lawson G, Krey LC. Crinone vaginal gel vs. intramuscular progesterone for luteal support in oocyte donation cycles: clinical and endocrinologic differences [abstract]. 57th Annual Meeting of the ASRM, Orlando, FL, October 20–25, 2001, P-170. Fertil Steril 2001;76 (Suppl 3):168.
27. Probst AM, Hill JA, Ginsburg ES, Hurwitz S, Pollitch J, Yanushpolsky EH. A randomized study comparing Crinone 8% and intramuscular progesterone supplementation in in vitro fertilization—embryo transfer cycles. Fertil Steril 2001;79:1144–9.
28. Montag M, van der Ven H, on behalf of the German Pronuclear Morphology Study Group. Evaluation of pronuclear morphology as the only selection criterion for further embryo culture and transfer: results of a prospective multicentre study. Hum Reprod 2001;16:2384–9.
29. Ludwig M, Schwartz P, Babahan B, Katalinic A, Weiss JM, Felberbaum R, et al. Luteal phase support using either Crinone 8% or Utrogest: results of a prospective randomized study. Eur J Obstet Gynecol Reprod Biol 2002;103:48–52.
30. Williams SC, Oehninger S, Gibbons WE, Van Cleave WC, Muasher SJ. Delaying the initiation of progesterone supplementation results in decreased pregnancy rates after in vitro fertilization: a randomized, prospective study. Fertil Steril 2001;76:1140–3.
31. Magnin G, de Meeus JB, Sarfati R, Chaochi O, Paillat A. Hepatitis caused by micronized natural progesterone given for preterm labor. Presse Med 1996;25:102–5.
32. Bacq Y, Sapey T, Brechot MC, Pierre F, Fignon A, Dubois F. Intrahepatic cholestasis of pregnancy: a French prospective study. Hepatology 1997;26:358–64.
33. Arafat ES, Hargrove JT, Maxson WS, Desiderio DM, Wentz AC, Andersen RN. Sedative and hypnotic effects of oral administration of micronized progesterone may be mediated through its metabolites. Am J Obstet Gynecol 1988;159:1203–9.