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Endometrin for luteal phase support in a randomized, controlled, open-label, prospective in-vitro fertilization trial using a combination of Menopur and Bravelle for controlled ovarian hyperstimulation

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Objective: To assess the efficacy and safety of a vaginal progesterone (P_4) insert (Endometrin) for luteal support for assisted reproductive technology (ART).
Design: Multicenter, randomized, open-label (assessor-blinded) phase III clinical trial.
Setting: Twenty-five U.S. ART centers.
Patient(s): A total of 1,211 ART patients randomized to three groups: Endometrin 100 mg twice daily (n = 404), Endometrin 100 mg three times daily (n = 404), and P_4 90 mg 8% gel daily (n = 403).
Intervention(s): In vitro fertilization and ET were performed according to site-specific protocols. The day after oocyte retrieval, Endometrin or vaginal P_4 gel was begun for luteal support and continued for up to 10 weeks of pregnancy.
Main Outcome Measure(s): Biochemical, clinical, and ongoing pregnancy and live birth rates.
Result(s): Pregnancy rates were high and similar in all treatment groups, with biochemical rates exceeding 50%, clinical and ongoing rates ≥40%, and live birth rates at 35%–38%. The adverse event profiles were similar across groups.
Conclusion(s): Pregnancy rates and live birth rates for Endometrin (twice daily and three times daily) were high and similar to those for P_4 gel. The adverse event profiles for both were similar to that for P_4 gel and primarily due to IVF stimulation and oocyte retrieval. Endometrin was safe and well tolerated. (Fertil Steril® 2009;91: 1012–7. ©2009 by American Society for Reproductive Medicine.)

Key Words: IVF, ART, luteal phase support, progesterone, progesterone supplementation, pregnancy, human

In vitro fertilization and other assisted reproductive technology (ART) treatments often involve disruption of normal ovarian function. Progesterone (P_4) supplementation during the luteal phase of IVF cycles has become standard practice (1, 2) for supplementing endogenous contributions that may have been compromised during the treatment protocols. Progesterone supplementation has been shown to improve pregnancy rates during IVF (3).

Exogenous P_4 can be administered orally, vaginally, and by IM injection. To compensate for the first-pass liver effect, oral administration requires high doses that can result in progestational side effects. Intramuscular injections are not approved by the U.S. Food and Drug Administration and are painful, but they are used extensively. Vaginal formulations are more comfortable and convenient to administer and may permit targeted drug delivery to the uterus (4); it has been theorized that absorption through the vaginal walls could deliver high levels of medication directly to the uterine circulation, thereby providing high levels of P_4 to the endometrial tissue. However, pharmacy-compounded P_4 suppositories provide variable and unreliable levels of P_4 (5). In contrast, Endometrin vaginal inserts (Ferring Pharmaceuticals, Parsippany, NJ) provide reproducible levels and show less variability than vaginal P_4 gel in pharmacokinetic studies measuring serum concentrations over time (6).

The objective of this study was to compare the safety and efficacy of a micronized, naturally derived P_4 vaginal insert, Endometrin, with a vaginal P_4 gel in maintaining pregnancy in women undergoing IVF using a combination of Menopur and Bravelle (both from Ferring Pharmaceuticals) for ovarian stimulation. Endometrin 100 mg was administered two or three times daily (7) with an applicator; both regimens were compared with daily vaginal P_4 gel.

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Endometrin, Menopur, Bravelle: Ferring Pharmaceuticals, Parsippany, NJ.
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MATERIALS AND METHODS

This multicenter, randomized, open-label (assessor-blinded), parallel-group, phase III study in women undergoing IVF (using a combination of Menopur and Bravelle) was conducted to compare pregnancy rates after luteal phase support with micronized, naturally derived P_4 vaginal inserts (Endometrin two times or three times daily) or vaginal P_4 gel daily per the instructions in the package insert. The study was conducted at 25 sites in the United States between July 2005 and April 2006.

Institutional review board approval was obtained from all sites before initiation of the trial. Before any study-specific procedures were performed, written informed consent was obtained from all patients. Each study center followed the IVF protocol guidelines in practice at that site. All patients received at least 2 weeks of study drug, and those patients who conceived continued taking the study drug for approximately 10 weeks.

Patient Selection

Healthy, premenopausal women between 18 and 42 years of age, with a body mass index ≤ 34 kg/m^2, a baseline FSH level ≤ 15 IU/mL, with a history of infertility, and requiring IVF were eligible to enroll in the study if they had a normal uterine cavity, uterus, and adnexa adequate for ART by transvaginal ultrasound, and a male partner or donor sperm with semen analysis results adequate for IVF. Patients who had a history of recurrent pregnancy loss (defined as three or more spontaneous abortions), abnormal uterine bleeding of undetermined origin, or a history of either poor response to gonadotropins (two or fewer mature follicles) or two previous cancelled cycles were excluded. Patients who had clinically relevant systemic disease or male partners with obvious leukospermia or signs of infection in a recent semen sample were also excluded from the study. Any patient who failed to produce at least three oocytes for retrieval in the study cycle was not randomized and did not continue into the luteal support trial.

Study Procedures

The study was divided into two phases, pretreatment and randomization/treatment. The pretreatment phase included screening, GnRH agonist down-regulation, ovarian stimulation, hCG administration, and oocyte retrieval.

Screening procedures included medical and infertility history, physical and gynecological examination, transvaginal ultrasound examination, hormone evaluations, and semen analysis. Upon successful completion of the screening procedures, pituitary/ovarian down-regulation was performed with an injectable GnRH agonist (not antagonist), using a long protocol with luteal phase initiation and daily injections (not depot formulations), according to the usual protocol of that center. Documentation of down-regulation, indicated by a serum E_2 level of <50 pg/mL, endometrial lining of <7 mm, and no evidence of ovarian activity on transvaginal ultrasound was required before the start of gonadotropin treatment. Gonadotropin therapy was performed in accordance with the usual IVF protocol at each center, with the only requirement being that a minimum of 1 vial of hMG (Menopur) be used daily in conjunction with FSH (Bravelle) to ensure adequate LH activity in all subjects. In addition, the centers had the option of combining the Bravelle and Menopur in the syringe and administering it as one single daily injection. Single daily administration of the combined hMG/FSH was performed for approximately two thirds of the patients ($n = 777$), with others having twice-daily injections. Bravelle and Menopur stimulation was stopped when the lead follicle mean diameter was ≥ 18 mm, and a single IM injection of hCG (Novarel, Ferring Pharmaceuticals) was administered to trigger follicular maturation. Oocytes were retrieved within approximately 36 hours after hCG administration, according to site-specific procedures.

After the pretreatment procedures were completed, patients were randomly assigned to one of three treatment regimens: Endometrin 100 mg twice daily, Endometrin 100 mg three times daily, or the comparator, P_4 vaginal gel 8% (Crinone; Serono Pharmaceuticals, Rockland, MA). Given the impact of age and ovarian reserve on the response to hormonal treatment, the study was randomized and stratified a priori for age according to the Society for Assisted Reproductive Technology (SART) categories (<35, 35–37, 38–40, and 41–42 years) and for ovarian reserve as reflected in baseline FSH level (<10 and 10–15 IU/L). Allocation to treatment group was performed by a telephone-based electronic interactive voice response system, which ensured an equal number of patients per treatment group across the study centers and stratification factors.

Randomization occurred the day of or day after oocyte retrieval, with study drug (Endometrin twice daily, Endometrin three times daily, or gel) initiated on the day after oocyte retrieval. Embryo transfer (ET) generally occurred on day 3 or day 5, according to the site's IVF guidelines. The only restriction on ET was that no more than three cleaving embryos (day 3 after retrieval) or no more than two blastocysts (day 5 after retrieval) could be transferred per patient, and only fresh embryos from the study cycle could be used.

Approximately 14 days after ET, a serum pregnancy test was performed to document biochemical pregnancy. Because of the variability in timing of the ET, and to allow more flexibility for scheduling, the initial pregnancy test was obtained at 14 ± 5 days after ET. If positive, a repeat serum pregnancy test was performed 2 days later. If the first test was negative, the physician had the option of doing a second, confirmatory test. If the patient did not have a confirmed biochemical pregnancy, she underwent follow-up procedures and was discontinued from the study. At 14 ± 5 days after the second positive serum pregnancy test, transvaginal ultrasound was performed to confirm clinical pregnancy, defined as the presence of an intrauterine gestational sac. Ongoing pregnancy, defined as the presence of detectable fetal heart motion, was either confirmed on that ultrasound or the patient continued taking the study drug and a second transvaginal

ultrasound was performed at approximately 6 weeks' gestation to identify fetal heart motion. Although study drug was administered on an open-label basis, the study was assessor-blinded; the person who performed the transvaginal ultrasound examinations to confirm clinical and ongoing pregnancy was blinded to the patient's treatment group assignment. The patients who were pregnant continued taking the study medication for 10 weeks total, until 12 weeks' gestational age. A final visit was scheduled upon completion of the tenth week of study drug (on the day of the last dose or within 3 days from the last dose). In addition, the study center contacted each patient by telephone or mail at the expected time of delivery to obtain birth data.

Outcome Measures

The primary efficacy variable was ongoing pregnancy. Biochemical pregnancy (defined as positive β-hCG pregnancy test results 12–14 days after ET), clinical pregnancy (defined as presence of a gestational sac on ultrasound examination approximately 4 weeks after ET), ongoing pregnancy (defined as identification of fetal heart movement at approximately 6 weeks after ET), and live birth rates were determined.

Statistical Analysis

The primary analysis was performed to determine whether the ongoing pregnancy rate for each Endometrin regimen was non-inferior to the comparator, using a two-sided 95% confidence interval for the difference in pregnancy rates and a prespecified non-inferiority lower bound of 10%. A step-down procedure was used. First, ongoing pregnancy rates were compared between Endometrin three times daily and the comparator. If non-inferiority was substantiated from this comparison, the pregnancy rate ascribed to Endometrin twice daily was compared with that of the comparator. Similar step-down procedures were performed for biochemical and clinical pregnancy rates and live birth rates. Efficacy analyses were performed among all randomized patients (intent-to-treat [ITT] population) and among randomized patients who underwent ET (efficacy population).

To have at least 80% power to demonstrate the non-inferiority of Endometrin vs. comparator in ongoing pregnancy rates, a sample size of no less than 330 evaluable patients per treatment group was estimated to be required. This sample size, using a non-inferiority margin of 10%, was based on an estimated pregnancy rate of 30%. The necessary sample size would increase as the pregnancy rate improves.

Statistical software (SAS 8.2 or higher; SAS Institute, Cary, NC) was used for all data analysis.

RESULTS

A total of 1,211 patients underwent oocyte retrieval and were randomized to treatment; 404 patients each were randomized to Endometrin twice daily and Endometrin three times daily, and 403 patients were randomized to the comparator. Patients ranged in age from 19 to 42 years. As expected in a large IVF population, the majority of patients were <35 years of age and had adequate ovarian reserve as reflected by baseline FSH levels <10 IU/L. The etiology of infertility was "male factor" in approximately one third of the patients and "tubal factor" in approximately one third. Patients could have more than one infertility diagnosis.

Table 1 presents the patient characteristics and infertility diagnoses of each treatment group. Demographic and infertility diagnoses were similar across the three treatment groups, with no statistically significant differences.

All patients were treated with a combination of Bravelle and Menopur from the first day of the stimulation phase. Overall the patients responded well to this gonadotropin combination. Patients were stimulated for an average of 10.2 days, with a mean of 13.8 oocytes retrieved. Embryo transfer occurred for 97% of the patients, with a mean of 2.4 embryos transferred overall, a mean of 2.6 on day 3 and 2.0 on day 5.

Of the 1,211 randomized patients, 36 (3%) did not undergo ET. For the 1,175 patients who had an ET (efficacy population), 54% had positive β-hCG pregnancy test results.

The biochemical pregnancy rate for all randomized patients (ITT population) was 52%. Clinical pregnancy rates were similar and high in all three groups, exceeding 40%. Ongoing pregnancy rates were approximately 40% in each of the treatment groups, with live birth rates of 37% overall. Among the patients who had a documented ongoing pregnancy, 90% in each treatment group had a live birth. No clinically meaningful differences were observed across the groups in biochemical, clinical, or ongoing pregnancy or live birth rates (Table 2). Despite restricting the total number of embryos allowed to be transferred per patient (no more than three cleaving embryos or two blastocysts per patient), the pregnancy and delivery rates were high.

On the basis of the lower bound of the 95% confidence interval, Endometrin twice daily and three times daily were non-inferior to the comparator in ongoing pregnancy and live birth rates and yielded comparable results.

At the time of randomization, patients were stratified by the specific criteria of age (by SART categories) and baseline FSH, because these factors are known to have an impact on pregnancy rates. However, the study was not powered for analyses of these subpopulations. The data for the subgroups of these two categories are presented in Table 3.

Multiple pregnancy rates were similar in the three treatment groups. The majority of patients who became pregnant had single gestational sacs; 14%–17% of patients conceived twins, and 1%–2% conceived triplets. No multiple pregnancies were observed with more than triplets.

Adverse events were reported by 53% of the Endometrin twice daily group, 54% of the Endometrin three times daily group, and 52% of the comparator group. Adverse event

TABLE 1

Demographic and infertility characteristics.

Characteristic	Endometrin 100 mg twice daily (n = 404)	Endometrin 100 mg three times daily (n = 404)	P_4 8% gel (n = 403)	*P*
Race[a]				.786
Caucasian	304 (75)	299 (74)	306 (76)	
African American	20 (5)	24 (6)	30 (7)	
Asian	20 (5)	21 (5)	20 (5)	
Hispanic	40 (10)	43 (11)	34 (8)	
Other	20 (5)	17 (4)	13 (3)	
Age (y), mean (SD)[b]	33.1 (4.30)	33.0 (4.40)	33.1 (4.34)	.987
Infertility diagnosis[c]				
Male factor	139 (34)	147 (36)	144 (36)	.836
Tubal factor	117 (29)	138 (34)	132 (33)	.260
Endometriosis	94 (23)	76 (19)	100 (25)	.100
Ovulatory dysfunction	81 (20)	85 (21)	80 (20)	.915
Uterine factor	10 (2)	13 (3)	16 (4)	.467
Unexplained infertility	83 (21)	91 (23)	90 (22)	.765

Note: Values are number (percentage) unless otherwise noted.
[a] *P* value from χ^2 test.
[b] *P* value from one-way analysis of variance.
[c] *P* value from Fisher's exact test.

Doody. Endometrin for luteal phase support. Fertil Steril 2009.

profiles were generally similar across the three treatment groups. All adverse events reported to the investigators were collected and reported, including those that might be related to the use of vaginal P_4 products (e.g., vaginal irritation, discharge, bleeding, difficulty with insertion); these were not among the more common events. The most common adverse events in the study overall were pain after oocyte retrieval (26%), abdominal pain (12%), nausea (8%), and ovarian hyperstimulation syndrome (7%), all known to be associated with IVF stimulation and oocyte retrieval (Table 4). No serious adverse events occurred that were related to the study medication (Table 4).

DISCUSSION

Patients undergoing IVF typically receive P_4 supplementation during the luteal phase to maintain pregnancy after controlled ovarian hyperstimulation protocols; P_4 supplementation has been shown to improve pregnancy rates (1–3). In the present study, patients responded well to ovarian stimulation with a combination of Bravelle and Menopur,

TABLE 2

Pregnancy rates and live birth rates by treatment.

Variable	Endometrin 100 mg twice daily (n = 404)	Endometrin 100 mg three times daily (n = 404)	P_4 8% gel (n = 403)
Biochemical pregnancy rate	198 (49)	225 (56)	212 (53)
Difference between Endometrin and gel	[−10.5]	[−3.8]	
Clinical pregnancy rate	163 (40)	183 (45)	174 (43)
Difference between Endometrin and gel	[−9.6]	[−4.7]	
Ongoing pregnancy rate	156 (39)	171 (42)	170 (42)
Difference between Endometrin and gel	[−10.3]	[−6.7]	
Live birth rate	141 (35)	154 (38)	153 (38)
Difference between Endometrin and gel	[−9.7]	[−6.5]	

Note: Values are number (percentage) and [95% confidence interval lower bound for difference].

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TABLE 3

Pregnancy outcomes by age and by ovarian reserve.

Variable	Endometrin 100 mg twice daily (n = 404)	Endometrin 100 mg three times daily (n = 404)	P_4 8% gel (n = 403)
Age <35 y	(n = 247)	(n = 247)	(n = 243)
Ongoing pregnancy rate	111 (45)	117 (47)	108 (44)
Live birth rate	102 (41)	109 (44)	98 (40)
Age 35–37 y	(n = 89)	(n = 93)	(n = 98)
Ongoing pregnancy rate	27 (30)	37 (40)	41 (42)
Live birth rate	23 (26)	31 (33)	37 (38)
Age 38–40 y	(n = 55)	(n = 46)	(n = 53)
Ongoing pregnancy rate	16 (29)	12 (26)	16 (30)
Live birth rate	14 (26)	9 (20)	14 (26)
Age 41–42 y	(n = 13)	(n = 18)	(n = 9)
Ongoing pregnancy rate	2 (15)	5 (28)	5 (56)
Live birth rate	2 (15)	5 (28)	4 (44)
FSH <10 IU/L	(n = 350)	(n = 347)	(n = 350)
Ongoing pregnancy rate	140 (40)	150 (43)	147 (42)
Live birth rate	127 (36)	136 (39)	133 (38)
FSH 10–15 IU/L	(n = 46)	(n = 51)	(n = 49)
Ongoing pregnancy rate	16 (35)	20 (39)	23 (47)
Live birth rate	14 (30)	17 (33)	20 (41)

Note: Values are number (percentage).

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yielding high overall ongoing pregnancy and live birth rates, 41% and 37%, respectively. These rates are especially good, considering the liberal inclusion criteria for this study: age up to 42 years, body mass index up to 34 kg/m^2, baseline FSH up to 15 IU/L, and smokers. No clinically meaningful differences were observed across the three treatment groups in pregnancy rates or live birth rates. In all treatment groups, biochemical pregnancy rates were greater than 49%; clinical pregnancy rates were at least 40%, ongoing pregnancy rates were at least 39%, and the live birth rates were at least 35% (Table 2).

Live birth rates were high and similar in all three treatment groups in the ITT population: 35% of the Endometrin twice daily group and 38% of the Endometrin three times daily and comparator groups had live births.

Many factors affect fertility and impact the success rates of infertility treatments. Notably, age and ovarian reserve (as reflected by serum FSH level) have strong correlations with pregnancy success rates and are primary clinical factors in determining treatment regimens that are tailored for each patient. It is acknowledged that higher gonadotropin doses are generally required for older women and for women with diminished ovarian reserve (FSH $\geq$10 IU/L). Similarly, the dose of P_4 supplementation is often increased in these women (8).

Given the impact of age and ovarian reserve on response to hormonal treatment, the study population was prestratified and randomized according to age and baseline FSH level. As would be expected in a large population undergoing IVF, the majority of patients in this study were <35 years of age (61%) and had FSH <10 IU/L (88%). These two subgroups had sufficient numbers of patients to make meaningful comparisons between Endometrin and the comparator, whereas the other subgroups did not. In the subgroup of women aged <35 years, the biochemical pregnancy rates for Endometrin and the comparator were at least 56%, and the live birth rates were 40% or greater (Table 3).

These data demonstrate that the use of Endometrin for luteal support in ART patients results in excellent single-cycle pregnancy rates, compared with data from the Centers for Disease Control and Prevention (9), even though there were limitations on the number of embryos transferred and extremely liberal inclusion criteria for this study. The relatively high success rates in this Endometrin study are the result of many factors, including successful ovarian stimulation using a combination of Bravelle with Menopur from day 1 of the stimulation phase. Endometrin clearly provides more than adequate luteal support, on the basis of the live birth rates compared with clinical pregnancy rates. In conclusion, Endometrin provides a safe, well-tolerated, and effective method for providing luteal phase support in women undergoing IVF.

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TABLE 4

Tolerability: adverse events and serious adverse events.

Adverse events	Endometrin 100 mg twice daily (n = 404)	Endometrin 100 mg three times daily (n = 404)	P_4 8% gel (n = 403)
Subjects with ≥1 adverse event	215 (53)	217 (54)	210 (52)
By maximum severity			
Mild	128 (32)	138 (34)	141 (35)
Moderate	71 (18)	72 (18)	62 (15)
Severe	16 (4)	7 (2)	7 (2)
Adverse events by relationship to treatment			
Not related	178 (44)	174 (43)	161 (40)
Uncertain	34 (8)	38 (9)	45 (11)
Probable	3 (1)	5 (1)	4 (1)
Most frequently reported adverse events			
Post-oocyte retrieval pain	115 (28)	102 (25)	102 (25)
Abdominal pain	43 (11)	45 (11)	62 (15)
Nausea	32 (8)	29 (7)	31 (8)
Ovarian hyperstimulation syndrome	30 (7)	27 (7)	26 (6)
Abdominal distension	18 (4)	17 (4)	18 (4)
Headache	15 (4)	13 (3)	18 (4)
Serious adverse events (not related to study medication)	14 (3)	8 (2)	9 (2)

Note: Values are number (percentage).

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