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Progesterone vaginal capsule versus vaginal gel for luteal support in normoresponder women undergoing long agonist IVF/ICSI cycles

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ABSTRACT

Objectives: The aim of the study was to investigate the effects of two different vaginal progesterone forms, administered for luteal phase support, on pregnancy outcomes in normoresponder women aged < 35, who underwent long agonist IVF/ICSI-ET cycles.

Material and methods: A retrospective cohort analysis was designed. Normoresponders with primary infertility, who underwent IVF/ICSI-ET cycles employing GnRH analogue and who received progesterone as either capsule or gel form for LPS following a single embryo transfer, were analyzed. The cycles were categorized into two groups: micronized progesterone vaginal capsule 600 mg/day (Group 1, n = 78) and progesterone vaginal gel 180 mg/day (Group 2, n = 99). Positive β-hCG, clinical pregnancy and ongoing pregnancy rates were analyzed.

Results: Both, demographic and stimulation characteristics were comparable between the groups. No difference was observed between the capsule and the gel groups regarding positive β-hCG (33.3% and 28.3%, respectively; p = 0.580), clinical pregnancy (26.9% and 22.2%, respectively; p = 0.584), and ongoing pregnancy rates (21.8% and 20.2%, respectively; p = 0.942) after treatment completion.

Conclusions: In long agonist IVF/ICSI-ET cycles, positive β-hCG, clinical pregnancy and ongoing pregnancy rates do not significantly differ between normoresponder patients receiving micronized progesterone vaginal capsule and those receiving progesterone vaginal gel for LPS.

Key words: progesterone, vaginal gel, vaginal capsule, long agonist protocol, in vitro fertilization

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INTRODUCTION

Despite significant advances in contemporary reproductive medicine, the clinical pregnancy rate per embryo transferred cannot exceed a certain level. Since the early days of *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI), implantation failure has constituted a significant proportion of treatment failures and remains the cause of considerable psychological and physical burden for the patients. Luteal-phase deficiency (LPD) is a common problem in current assisted reproductive technologies (ARTs) and has been described in cycles using pituitary down-regulation with gonadotropin releasing hormone agonists (GnRHa), as well as in those using GnRH antagonists [1]. Normal luteal function is considered to be essential for maintaining pregnancy, as indicated in one study where removal of the corpus luteum during early pregnancy resulted in complete abortion [2]. Over the years, these results have been supported by placebo-controlled trials [1, 3], and it became clear that luteal phase support (LPS) had a positive effect on the outcome of IVF cycles using GnRHa protocols, as well as GnRH antagonist [1, 3]. To date, progesterone remains to be the treatment of choice although many agents, including hCG, progesterone, estradiol and GnRHa, or their combinations, have been proposed for luteal support [1, 3–6].

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Progesterone, as a complementary part of different IVF regimens, is administered for LPS through different routes, most commonly by intramuscular injection and vaginal insertion. However, due to some major side-effects of intramuscular progesterone injection, including pain, skin inflammation and rarely infection, vaginal preparations, which are generally well tolerated, have become increasingly popular over time. Additionally, considerable differences in the efficacy of diverse forms of vaginal progesterone are the cause for concern. Hence, numerous LPS-related issues, including the most proper agent, timing, duration and route of administration, remain unresolved [7–10].

OBJECTIVES

The aim of the study was to compare pregnancy outcomes of patients with normal ovarian reserve who received either micronized progesterone vaginal capsule (600 mg/day) or progesterone vaginal gel (180 mg/day) for LPS following IVF/ICSI-ET cycles using long GnRH agonist protocol.

MATERIAL AND METHODS

The Institutional Review Board waived the requirements for approval of the study and patient consent since it is a retrospective assessment of conventionally treated patients. No intervention was involved beyond routine and standard arrangement and treatment, and no patient-identifying information was included. This is a retrospective study conducted using the files of patients who were admitted to the Assisted Reproduction Department of Zeynep Kamil Training and Educational Hospital due to the desire to have children, between January 2013 and December 2013.

The analysis was limited to either the first or the second IVF/ICSI cycles using long agonist protocol. Normoresponders, aged 23–35 years, with primary infertility and a body mass index (BMI) of 18–28 kg/m^2, were included into the study. We defined normoresponders as having E2 on the day of hCG between 800 and 4000 pg/mL and the number of the retrieved oocytes between 4 and 18. Figure 1 demonstrates the inclusion and exclusion criteria. After the exclusion of the patients described in Figure 1, the final number of 177 cycles

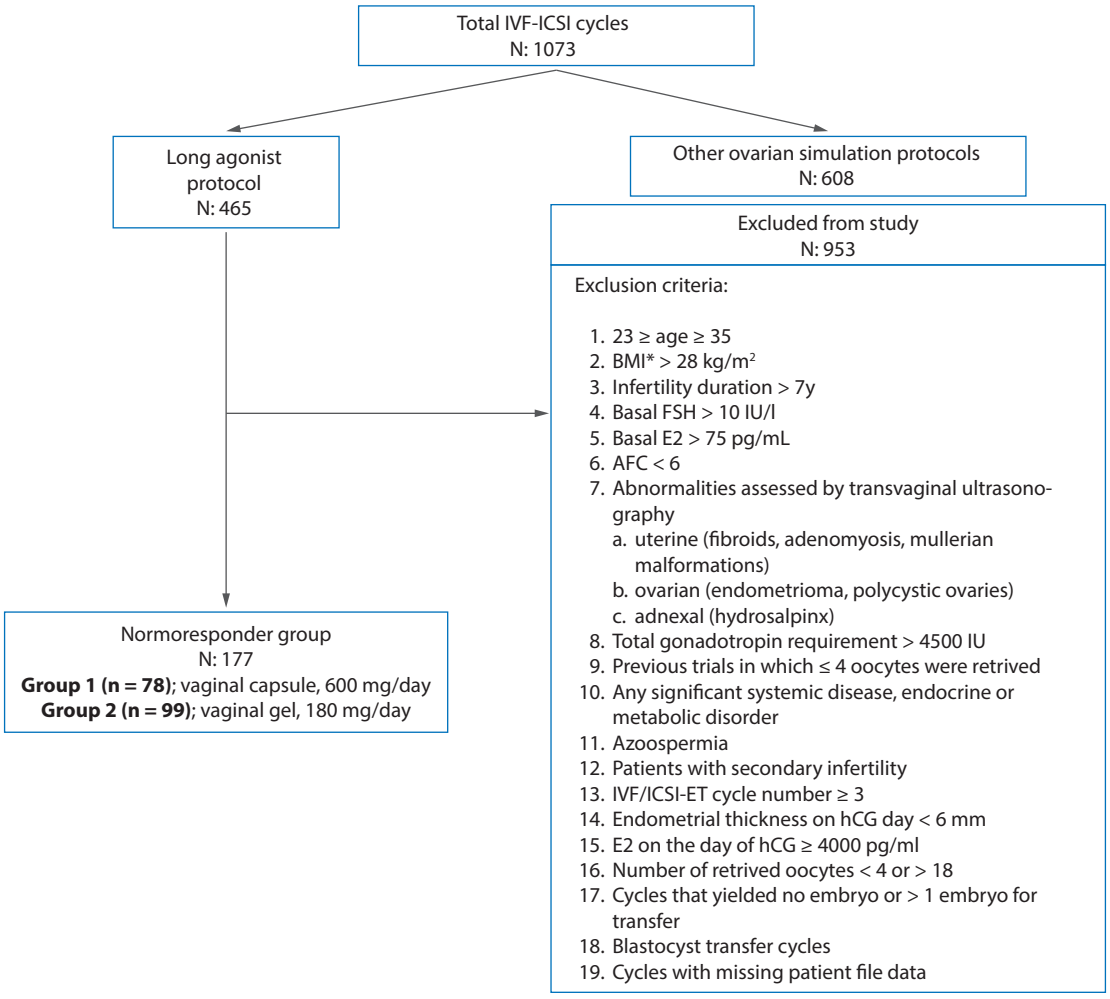

Figure 1. Flow chart of the study: included and excluded cycles. BMI — body mass index, E2 — estradiol, AFC — antral follicle count

was enrolled into the study. Demographic characteristics, basal hormone profile values, basal transvaginal ultrasonography findings, stimulation characteristics, and treatment outcomes were obtained from patient files.

In the classical agonist long protocol, pituitary down-regulation was performed by triptorelin acetate (Decapeptyl®; Ferring Pharmaceuticals A.S.), 0.1 mg/day by the subcutaneous route, on day 21 of the previous cycle. GnRHa continued until the day of hCG administration to induce ovulation. On day 2 of the cycle, transvaginal ultrasonography was performed and serum estradiol (E2) concentration was measured. Gonadotropin treatment was initiated if no follicles > 10 mm in diameter were observed and the E2 level was below 50 pg/mL. The initial gonadotropin dose was individualized according to patient age, BMI, ovarian reserve determined by antral follicle count and basal follicle stimulating hormone (FSH), and experience from previous cycles. Serial ultrasonographic control examinations and E2 level measurements were done until 3 follicles ≥ 17 mm and serum E2 level of > 500 pg/mL were detected. Choriogonadotropin alpha 250 µg s.c. (Ovitrelle®; Merck Serono, Turkey) was administered to induce final follicular maturation. Transvaginal ultrasound-guided oocyte retrieval was performed 35.5 h after hCG administration. Fertilization was assessed at 16–18 h after ICSI and one embryo with the best morphological grade was transferred into the uterine cavity under ultrasound guidance (GE Logiq Alpha 200). National health policy of Turkey allows the transfer of two embryos in women over the age of 35 and in those with previous recurrent implantation failures. In the absence of the two of the above mentioned conditions, the transfer is limited to only 1 embryo. Hence, we included only single embryo transfer cycles in our study since more than 1 embryo transfers belonged to either women over the age of 35 or those with recurrent implantation failures. Biochemical pregnancy was defined as a positive pregnancy test result (β-hCG levels > 20 mIU/ml) 12 days after embryo transfer. Clinical pregnancy was defined as fetal cardiac activity observed by vaginal ultrasonography 4 or 5 weeks after oocyte retrieval and ongoing pregnancy was defined as ultrasound check of the embryo after 9 weeks of gestation.

Luteal support commenced on the night of oocyte retrieval and continued until the day of pregnancy testing. Methylprednisolone (Prednol 16 mg tablet®, Mustafa Nevzat, Turkey) 16 mg/day, also was given orally to all patients for 4 days to minimize the potential immune reaction for the transferred embryos. If the test was positive, progesterone treatment was continued for up 9 weeks of gestation. The patients were categorized into two groups according to the luteal support treatment: group 1 received 600 mg/day micronized progesterone capsule (Progestan® 200 mg, soft capsule, Koçak, Tekirdag, Turkey) by the vaginal route in three equal doses (Capsule Group), whereas group 2 received 90 mg progesterone gel (Crinone 8% gel®, Merck Serono, Turkey) by the vaginal route twice daily (Gel Group). The groups were compared with regard to their demographic and stimulation characteristics, as well as treatment outcomes.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences for Windows 15.0 software (SPSS, Chicago, IL., USA). Descriptive statistics were given as mean, standard deviation, frequency, and percentage. Parametric comparison was done using Student's t test, whereas non-parametric comparison was done with the Mann-Whitney U test. Categorical data were evaluated using the χ^2 test. Statistical significance was defined as $p < 0.05$.

RESULTS

From January 2013 until December 2013, a total of 1073 cycles (of 987 patient files) were analyzed. Among those, 465 cycles employed GnRH agonist long protocol. A total of 177 women who met the inclusion criteria were included in the study (Figure 1). Overall, mean age ± standard deviation (SD) was 30.66 ± 3.12 years (from 24 to 35) and 59.9% of the indications for IVF were unexplained infertility. The study population was divided into two groups: 78 cycles received micronized progesterone vaginal capsule 600 mg/day (Group 1), and 99 cycles received progesterone vaginal gel 180 mg/day (Group 2) for luteal support.

Patient and treatment characteristics such as patient age, duration and cause of infertility, antral follicle count (AFC) on day 1 (D1), D3 FSH, D3 estradiol, average dose of gonadotropin, endometrial thickness on the day of hCG, serum E2 level on the day of hCG, total number of oocytes retrieved, and the number of fertilized oocytes were similar in both groups, regardless of the type of progesterone supplementation used for luteal support (Tables 1 and 2). Demographic characteristics of the groups are presented in Table 1. Accordingly, no significant differences were found regarding the duration and causes of infertility, basal antral follicle count and basal hormone levels between the two groups. Stimulation characteristics and treatment outcomes of the cycles are shown in Table 2. There were no significant differences in stimulation characteristics such as mean total gonadotropin doses, E2 levels on hCG day, total number of oocytes, number of fertilized oocyte between the groups. Treatment outcomes did not show statistically significant differences between the two groups regarding the positivity of β-hCG per cycle (33.3% and 28.3%; p = 0.580, respectively), the clinical pregnancy rate (26.9% and 22.2%; p = 0.584, respectively), and the ongoing pregnancy rate (21.8% and 20.2%; p = 0.942, respectively) (Table 2).

Table 1. Demographic characteristics of the patients in the groups

	Capsule Group (n = 78)	Gel Group (n = 99)	P
Age (years)	30.64 ± 3.15	30.67 ± 3.11	0.957[a]
Duration of infertility (years)	4.47 ± 1.64	4.46 ± 1.78	0.971[a]
Number of antral follicles on day 1	12.42 ± 3.50	12.88 ± 3.52	0.397[a]
D3 FSH [IU/L]	7.44 ± 1.60	7.22 ± 1.70	0.375[a]
D3 estradiol [pg/mL]	46.76 ± 13.93	45.32 ± 16.03	0.531[a]
Infertility diagnosis, n (%)			
Unexplained	47 (60.26%)	59 (59.6%)	0.929[b]
Male factor	11 (14.1%)	8 (8.1%)	0.298[b]
Mixed	20 (25.64%)	32 (32.3%)	0.422[b]

Data are presented as mean ± SD and number (percent). [a]Student t test, [b]χ^2 test. FSH — follicle stimulating hormone, LH — luteinizing hormone

Table 2. Stimulation characteristics and treatment outcomes of 177 cycles

	Capsule Group (n = 78)	Gel Group (n = 99)	P
Average gonadotropin dose [IU]	2834.04 ± 967.90	2696.59 ± 1024.8	0.365[a]
Endometrial thickness on the day of hCG [mm]	9.74 ± 1.79	9.75 ± 1.87	0.989[a]
E2 on the day of hCG [pg/mL]	1967.72 ± 756.54	2071.62 ± 830.63	0.392[a]
Number of total oocytes retrieved	8.46 ± 3.78	8.15 ± 3.56	0.591[a]
Number of MII oocytes	6.46 ± 3.28	6.08 ± 2.97	0.445[a]
MII oocytes/total oocytes retrieved (%)	76.4%	73.8%	0.311[b]
Number of the fertilized oocytes	3.90 ± 2.35	3.81 ± 2.08	0.785[a]
ET day	2.56 ± 0.50	2.57 ± 0.52	0.814[a]
Positivity rate of β-hCG/cycle (%)	33.3%	28.3%	0.580[b]
Clinical pregnancy rate/cycle (%)	26.9%	22.2%	0.584[b]
Ongoing pregnancy rate/cycle (%)	21.8%	20.2%	0.942[b]

Data are presented as mean ± SD and number (percent). [a]Student t test, [b]χ^2 test. FSH — follicle stimulating hormone, hCG — human chorionic gonadotropin, E2 — estradiol, ET — embryo transfer

DISCUSSION

Despite considerable advances in the field of assisted reproduction technologies, the mechanisms involved in the implantation process remain to be fully elucidated. Implantation is the outcome of a synchronized communication of a hormonally prepared functional uterus and the blastocyst complex [10]. It has long been known that this communication is impaired in the IVF cycles using down-regulated controlled ovarian hyperstimulation (COH), and that it must definitely be replaced via the LPS treatment [1, 3, 11–14]. Numerous mechanisms may have their roles in the deterioration of the luteal phase physiology in IVF treatment cycles, e.g. the blockage of LH release with the negative feedback effect of the steroids synthesized secondary to the corpora lutea which are numerous, LH suppressive effect of GnRHs, possible early developmental effect of short-term supranormal estrogen and progesterone levels on the endometrium during the luteal phase in the induced cycles, and aspiration of the granulosa cells during the oocyte pick-up (OPU) procedure [4, 15–17].

To date, various agents including progesterone, hCG, estradiol and GnRHa, or their combinations, have been proposed to support the luteal phase [1, 3–5]. Despite the fact that hCG alone has been reported to be superior to progesterone in a limited number of studies [1, 3], it has never been popular due to the potential risk of ovarian hyperstimulation syndrome (OHSS) [3]. However, the need for additional estrogen treatment remained debatable [3, 5, 18]. Recently, additional GnRHa treatments administered along with progesterone have been reported to generate better result than progesterone treatment alone [4]. While the scientific debate continues, progesterone has become the treatment of choice, regardless of the fact that the literature offers conflicting data on the optimal route of progesterone administration during IVF [1, 3, 6]. Previous studies claimed that due to the first passing effect through the liver, oral progesterones were the least effective forms, contrary to the intramuscular forms, which were reported to be the most efficient [19]. Nevertheless, later studies and meta-analyses

suggested that there were no differences between the two [3, 20, 21]. A recent randomized controlled trial comparing the efficacy of subcutaneous and vaginal progesterone forms reported that positive β-hCG, clinical pregnancy and take-home baby rates were comparable between the groups [22]. In a prospective study by Silverberg et al. [23], live birth rates were reported to be higher in the vaginal progesterone group than in intramuscular progesterone arm. Dose-related studies on progesterone have remained limited in number and the question whether utilization of different doses of progesterone fosters a significant effect on clinical pregnancy rates has not yet been fully clarified [3]. Besides, the timing of initiation and discontinuation of LPS treatment has also not been thoroughly researched yet. To the best of our knowledge, there is only one study dealing with the initiation time of the treatment. It suggested that initiating LPS treatment on either hCG day, oocyte retrieval day or embryo transfer day makes no difference as far as the ongoing pregnancy rates are concerned (respectively 20.8%, 22.7% and 23.6%) [7].

The general global approach to LPS in IVF treatments has been to use vaginal progesterone, particularly vaginal gel, due to its minimal side-effect spectrum and ease of application [24–28]. However, studies comparing different vaginal progesterone formulations with regard to IVF success did not go beyond a limited number [24–30]. Detailed analysis of the available literature revealed a very limited number of studies investigating the differences of the vaginal forms, except for two recent large randomized trials [28, 30]. Furthermore, except for the work of Stadtmauer et al. [30], no study provided live birth rates and none had sufficient power to distinguish whether any difference between the varying doses and formulations existed. Two recent comprehensive studies provided solid evidence that there were no differences between the vaginal gel and vaginal ring or tablet groups regarding the clinical pregnancy rates, ongoing pregnancy rates, or live birth rates [28, 30].

In the present study, we investigated whether pregnancy outcomes differ between two different vaginal progesterone formulations which were started on the night of oocyte retrieval for LPS, in normoresponders aged ≤ 35 years, undergoing a fresh, single embryo transfer using GnRH agonist for ovarian stimulation. Our study results revealed no differences between the groups receiving micronized vaginal progesterone capsule 600 mg/day and vaginal progesterone gel 180 mg/day with regard to biochemical pregnancy (33.3 and 28.3, p = 0.580, respectively), clinical pregnancy (26.9 and 22.2, p = 0.584, respectively) and ongoing pregnancy (21.8 and 20.2, p = 0.942, respectively) rates. These results are consistent with the previously published reports comparing vaginal capsules and gel.

The comparison of two populations similar to each other in terms of basic patient characteristics is one of the strengths of our study. The exclusion and inclusion criteria were defined so strictly that the patients included were limited to a rather narrow spectrum. Our study is subject to several limitations, e.g. its retrospective design, small sample size, and lack of data on live birth rates.

CONCLUSIONS

Based on our findings, we conclude that there were no statistically significant differences between the use of micronized vaginal progesterone 600 mg/day and vaginal gel 180 mg/day for LPS treatment, in terms of positivity of β-hCG per cycles, the clinical pregnancy rate, and the ongoing pregnancy rate, in normoresponder women undergoing long agonist IVF/ICSI cycles. More comprehensive, prospective, multi-arm, randomized studies are required in order to better define the optimum daily drug doses, administration route, as well as the initiation and cessation time of the drug.

Conflict of interests

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors. The authors state that there are no conflicts of interest regarding the publication of this article.

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