Intracytoplasmic Sperm Injection: Clinical Result Comparison of Oral Dydrogesterone and Micronized Vaginal Progesterone Gel Use for Luteal Phase Support in Embryo Transfer Cycles

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Research Article

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Abstract

Objective: The aim of this study was to prospectively compare the effects of oral dydrogesterone and micronized vaginal progesterone (MVP) gel for luteal phase support on the pregnancy outcomes of intracytoplasmic sperm injection (ICSI) and embryo transfer (ET) cycles with controlled ovarian hyperstimulation using gonadotropin-releasing hormone in antagonists protocol.

Materials and Methods: Women with infertility who attended the gynecology and obstetrics department of Meram Medical Faculty Hospital between January 2017 and January 2021 were evaluated. For the purpose of this research study, 301 patients who underwent ICSI-ET were divided into two groups. Micronized vaginal progesterone (Crinone 8% 90 mg gel with 1 time daily) was administered to 147 patients in the first group; and oral dydrogesterone (Duphaston 10 mg with 3 time daily), to 154 patients in the second group from the day of oocyte pick-up. On the twelfth day post-transfer , the ß-hCG and serum progesterone levels were measured, and the results were evaluated. A β-hCG value of ≥ 20 mIU/mL was considered to be a positive result. The rates of biochemical pregnancy, clinical abortion, clinical pregnancy, and ongoing pregnancy were compared between the two groups.

Results: Among the women who underwent ICSI-ET, those who received vaginal progesterone gel and oral dydrogesterone on the day of oocyte retrieval showed similar serum progesterone levels and β-hCG positivity, biochemical pregnancy, clinical abortion, clinical pregnancy, and ongoing pregnancy rates. In terms of side effect profile, vaginal discharge and irritation complaints were found to be significantly lower in the oral progesterone group.

Conclusion: The clinical results obtained from the patients who were given vaginal progesterone and oral dydrogesterone supplementation were similar. Oral progesterone support is an effective method that is more easily tolerated by patients and can be safely used for luteal phase support.

Introduction

Infertility is the inability to conceive despite having unprotected sexual intercourse two or three times per week on a regular basis for a year. Infertility affects 10%–15% of couples in the reproductive age range (1). Causes can include delayed marital age, obesity, lack of exercise, unhealthy diet, smoking, and exposure to environmental pollutants. 30%–40% are due to male factor. Among all cases of female infertility, approximately 30%–40% are due to ovulatory dysfunction, 30%–40% are due to tubal and pelvic pathologies, and 30% result from other unexplained causes (2). As the cause of unexplained infertility is unknown, treatments are empirical. The recommended treatment modalities are intrauterine insemination, ovulation induction with clomiphene citrate or gonadotropins, in vitro fertilization (IVF) with controlled ovarian hyperstimulation, and assisted reproductive techniques (ART). A functional (receptive) endometrium is needed during the luteal phase in order for implantation. This endometrial preparation begins in the proliferative phase and continues throughout the luteal phase. The luteal phase in a natural post-ovulation cycle results in the formation of the corpus luteum (CL), which secretes estradiol (E2) and

progesterone (P). In the midluteal phase, the CL secretes approximately 40 mg/day of progesterone and plays an essential role in the formation of the secretory transformation required for implantation of a normal endometrium (3). In gonadotropin-induced cycles—as opposed to natural cycles—supraphysiological oestradiol and progesterone levels in the early luteal phase cause an anterior shift in endometrial development. Thus, asynchronization occurs between the embryo and endometrial development during the implantation period. This causes luteal phase defects (LPD), particularly in IVF cycles. Insufficient progesterone stimulation due to a LPD causes impaired endometrial receptivity and, consequently, decreased implantation and pregnancy rates. In this prospective study, we aimed to compare pregnancy outcomes between administration of 30 mg/day of oral dydrogesterone and 90 mg/day of micronized vaginal progesterone gel to provide luteal phase support after ICSI and ET.

Materials And Methods

Our study included 301 patients who attended the Assisted Reproductive Center Unit of the Necmettin Erbakan University Meram Medical Faculty between January 2017 and January 2021 to underwent intracytoplasmic sperm injection and embryo transfer cycle. Our study was conducted prospectively. Each patient was included in the study only once. Patients with ages ranging from 20 to 44 years, with body mass index values between 18 and 32 kg/m^2, whose early follicular phase serum follicle-stimulating hormone (FSH) values were <15 IU/L, whose serum estradiol (E2) values were <80 pg/mL as measured on the second and/or third days of the menstrual cycle, who were not diagnosed with chronic diseases, and whose serum E2 serum values on the day of hCG treatment were <4000 pg/mL were included in the study. Patients with more than three failed IVF attempts and those with recurrent pregnancy losses were excluded due to their low pregnancy rates and the need for further outcome classification. Patients whose medical histories were recorded at the first admission and those who underwent physical and pelvic examinations—as indicated in their medical files—were included in the evaluation. The endometrial cavity, ovaries, and fallopian tube of each patient included in the evaluation were examined using ultrasonography and hysterosalpingography. Sperm motility and the number of sperm were evaluated using a spermiogram in accordance with the criteria of the World Health Organization (4). A diagnosis of low ovarian reserve was made when the anti-Müllerian hormone level was <0.5–1.1 ng/mL or when the total number of antral follicles in both ovaries was <7–10 on transvaginal ultrasonography (TVUSG) on the third day of the menstrual cycle. (5) The diagnosis of maternal coagulation disorder was noted in patients who were diagnosed with thrombophilia based on evidence from laboratory or genetic test results before starting treatment with antagonist protocol (6). Basal serum FSH, luteinizing hormone (LH), E2, prolactin, and thyroid-stimulating hormone (TSH) levels were measured in all the patients on the second or third day of the cycle. These patients were prepared for ICSI-ET for indications due to male factors, insufficient ovarian reserve, endometriosis, polycystic ovary syndrome, tubal factors, uterine factors, and unexplained factors. The fullest extent of our work was carried out with a fresh cycle. In our study, a similar protocol with a GnRH antagonist was applied to all patients. The treatment of the patients was started on the second day of menstruation. Ovulation induction was initiated with recombinant FSH (rFSH) in the patients. FSH (GONAL-f 450 IU/0.75 ml -

follitropin alfa, Merck Serono) was administered subcutaneously. The daily dose of gonadotropin is 150–300 IU, and doses were determined by reviewing the patient's age, body mass index (BMI), basal serum E2 level, basal serum FSH level, number of antral follicles and previous ovulation induction response. Serial TVUSG and serum E2 measurements were performed to monitor the follicular response. In patients who developed at least 2–3 follicles larger than 18 mm and E2 level larger than 500 pg/mL human chorionic gonadotropin (hCG) (Ovitrelle® 250 µg/0.5 ml, Merck Serono) was administered intramuscularly. Oocyte pick up (OPU) was performed 35-37 hours after the hCG injection. The 6.5 MHz vaginal probe (General Electric Logiq™ α 200) was fixed by attaching a metal guide. The needle (Wallace® Oocyte Recovery Set Single Lumen 17 g x 33 cm echo tip needle fitted with 950 mm aspiration tubing ONS 1733) was connected to the aspirator (Cook Aspiration Unit™ K-MAR S100, William A. Cook Australia PTY-LTD), and the probe was placed in the vagina and localization of the chosen ovary. The follicle chosen for aspiration was aspirated with an average pressure of -150 mmHg. Oocytes were classified as GV, MI, and MII according to their development. The MII (mature oocyte) was prepared for ICSI. Meanwhile, the semen taken from the male partner was processed and floated. The urologist applied the TESE (testicular sperm extraction) procedure with spouses with azoospermia. The ICSI procedure was applied. The second and third day developments of the embryos were evaluated. Embryos were classified as A quality, B quality, and C quality (Table 1, Table 2).Our gradings was done under inverted microscope (Nikon TE 300).

Table 1

For days 2 and 3 transfers our grading parameters (Slightly modifed from Reference:7). If fragmentation percent and cell symmetry was incompatible we marked as the lower grade for the embryo. *Expected blastomer number (N) as; for day 2 is 4 and for day 3 is 8.

Grade	Number of cells*	% Fragmentation	Cell symmetry
A	N	≤10 % fragmentation	Equal blastomeres
B	N-2	≤30 % fragmentation	Almost equal blastomeres
C	N-3	>50 % fragmentation	Unequal blastomeres

Table 2

For day 5 transfers our grading parameters.

Grade	Image	Symmetry	Inner Cell Mass
A	Blastocoel cavity prominent	Equal	Coherent
B	Blastocoel cavity small	Partially	Small
C	Early blastocyte, compact morula	Not case	Not any

Embryo transfer was decided on the 2nd, 3rd, or 5th day, according to the age of the patient, the sperm status of the spouse, the number of embryos, and the morphology and quality of the embryo development. Hormonal measurements—including E2 measurements (catalogue number 10491445), LH measurements (catalogue number 102212941), and β-hCG measurements (catalogue number 0064953)—were studied using the chemiluminescence immunoassay method on the ADVIA Centaur® CP Immunoassay System Siemens device. FSH measurements were studied with the solid phase two-stage chemiluminescence immunometric assay method on the IMMULITE® 2000 Immunoassay System Siemens device using a commercial kit (catalogue number L2KF56). Treatment for luteal phase support was initiated on the day of oocyte retrieval. For embryo transfer, the patients were prepared on the operating table in the dorsal lithotomy position with their bladders full. After the embryos were observed under the microscope, they were taken into the catheter (Wallace® Sure-Pro® Embryo Replacement Catheter with soft obturator, 23 cm) in approximately 20–30 µL of medium, gently passed through the cervix under the guidance of abdominal ultrasonography, and conveyed to the cavity. The number of embryos delivered as well as the quality of each embryo were recorded. The number of embryos transferred ranged between 1–2 embryos for each patient. Serum β-hCG and progesterone levels of all patients were measured 12 days after embryo transfer. β-hCG values of 20 mIU/mL and above were considered positive, and these patients attended a follow-up visit. Patients whose GS and FKA (fetal heart rate) were monitored on USG were included within the 'clinical pregnancy' group. Patients with β-hCG (+) but no gestational sac (GS) on the ultrasound (USG) and a decrease in β-hCG value in serial follow-ups were classified under the 'biochemical pregnancy' group. Patients who aborted before the 23rd gestational week according to the last menstrual period after monitoring the gestational sac (GS) or fetal heart rate (FKA) on USG were included in the 'clinical abortion' group. Pregnant women who reached live birth after the 23rd gestational week according to their last menstrual period were placed in the 'ongoing pregnancy' group.

Statistical method

The data obtained in this study were analyzed with the SPSS 22 package program. As the data were not normally distributed, the Mann-Whitney U test was used for comparisons between groups. The relationship between categorical data was examined with Chi-Square analysis.

The value of 0.05 was used as the significance level. It was stated that there was a significant difference/relation in the case that $p < 0.05$. No significant difference/relation was specified in the case that $p > 0.05$.

Results

Table 3

Comparison of groups according to demographic characteristics, infertility duration, parity and maternal smoking habit

	Oral dydrogesterone (n = 154)	Micronized vaginal progesterone (n = 147)	P-value
BMI	24.8 ± 4.0	24.8 ± 3.7	0.912[b]
Male age	35 ± 6	36 ± 5	0.116 [b]
Female age	31.5 ± 5.5	32.5 ± 5.3	0.116 [b]
Infertility term (month)	71.6 ± 42.7	79.6 ± 41.7	**0.032** [b]
Smoking habit of the mother	11 (7.1)	17 (11.6)	0.262 [a]

Data are presented as n(%)[a] based on mean ± standard deviation[b].
P-value was obtained by Chi-Square test[a] and independent T-test[b].

Table 4

Comparison of the groups according to the causes of infertility

	Oral dydrogesterone (n = 154)	Micronized vaginal progesterone (n = 147)	P-value
Endometriosis	12 (7.8)	17 (11.6)	0.361[a]
Polycystic ovary syndrome	20 (13.0)	23 (15.6)	0.244 [a]
Decreased ovarian reserve	44 (28.6)	34 (23.1)	1.16 [a]
Maternal coagulopathies	4 (2.6)	4 (2.7)	0.999 [a]
Uterine factor	33 (21.4)	24 (16.3)	0.259 [a]
Tubal factor	13 (8.4)	14 (9.5)	0.899 [a]
Unexplained factor	47 (30.5)	34 (23.1)	0.141 [a]
Presence of azoospermia and TESE procedure	12 (7.8)	11 (7.5)	0.999 [a]
Oligosperm	33 (21.4)	41 (27.9)	0.193 [a]
Decreased motility	42 (27.3)	49 (33.3)	0.252 [a]

Data are presented as n(%)[a]. P-value was obtained by Chi-Square test[a].

Table 5

Comparison of the characteristics of the groups

	Oral dydrogesterone (n = 154)	Micronized vaginal progesterone (n = 147)	P-value
Embryo transfer day	2.6 ± 0.8	2.8 ± 0.8	**0.021** [b]
Estradiol (E2) level (pg/mL) (OPU day)	1753.0 ± 1347.2	1968.7 ± 1364.8	**0.093** [b]
Endometrial thickness (mm)	10.5 ± 2.3	10.3 ± 2.5	0.409 [b]
Mean daily dose of gonadotropin used	238.6 ± 53.2	245.4 ± 51.6	0.303 [b]
hCG level (12. day) mIU/mL	37.4 ± 73.2	42.1 ± 77.8	0.61 [b]
Progesterone level ng/mL (12.day)	19.0 ± 21.4	21.9 ± 19.3	**0.038** [b]
FSH level monitored on the 2nd day of the cycle (mIU/mL)	6.6 ± 3.5	6.7 ± 3.2	0.859 [b]
LH level monitored on the 2nd day of the cycle (mIU/mL)	6.72 ± 3.69	6.09 ± 3.24	0.139 [b]
E2 level monitored on the 2nd day of the cycle (pg/mL)	39.3 ± 22.0	45.1 ± 22.1	**0.008** [b]
Number of oocytes retrieved	9 ± 5	10 ± 6	0.273 [b]
Number of embryos developted	2.5 ± 1.6	2.6 ± 1.6	0.319 [b]
A quality embryo	184 (70.7)	198 (77)	0.267 [a]
B quality embryo	42 (16.7)	33 (12.8)	0.267 [a]
C quality embryo	34 (13.1)	26 (10.2)	0.267 [a]
2 Embryos	109 (70.7)	96 (68.1)	0.240 [a]
1 Embryo	45 (29.3)	47 (31.9)	0.240 [a]

Data are presented as n(%)[a] based on mean ± standard deviation[b].
P-value was obtained by Chi-Square test[a] and independent T-test[b].

Table 6

Comparison of pregnancies in each group according to clinical features and side effects

	Oral dydrogesterone (n = 154)	Micronized vaginal progesterone (n = 147)	P-value
β-hCG Positive	50 (32.5)	52 (35.4)	0.594 [a]
Clinical Pregnancy	43 (27.9)	43 (29.2)	0.699 [a]
Biochemical pregnancy	7 (14.0)	9 (17.3)	0.684 [a]
Clinical Abortion	15 (30)	18 (34.6)	0.684 [a]
Ongoing Pregnancy	28 (56.0)	25 (47.9)	0.684 [a]
Vaginal discharge or irritation	3 (1.9)	20 (13.6)	**0.0001[a]**
Vaginal bleeding	17 (11.0)	20 (13.6)	0.615 [a]
Abdominal pain	7 (4.5)	6 (4.0)	0.518 [a]

Data are presented as n(%)[a] based on mean ± standard deviation[b].
P-value was obtained by Chi-Square test[a] and independent T-test[b].

No significant difference was found between the progesterone groups in terms of BMI, male age, and female age (all p-values >0.05). However, there is a significant difference between the progesterone groups in terms of the 'infertility duration (months)' variable (p = 0.032). The values of 'infertility duration (months)' were higher in the micronized vaginal progesterone group compared to the oral dydrogesterone group (Table 3). No significant dependency was found between oral dydrogesterone and micronized vaginal progesterone groups and causes of infertility (all p-values >0.05) (Table 4). There is a significant difference between the progesterone groups in terms of the embryo transfer day (p = 0.021). Additionally, values are higher in the micronized vaginal progesterone group. No significant difference was found between the progesterone groups in terms of estradiol (E2) level on OPU day, endometrial thickness on the embryo transfer day, the daily gonadotropin dose, and the hCG level on the 12th day after embryo transfer (p = 0.61). There is a significant difference between the progesterone groups in terms of the progesterone level measured on the 12th day after embryo transfer (p = 0.038). Values are higher in the micronized vaginal progesterone group. There is also a significant difference between the progesterone groups in terms of the E2 level (pg/mL) variable measured on the 2nd day of the cycle (p = 0.008). E2 basal values were higher in the micronized vaginal progesterone group than in the oral dydrogesterone group. No significant difference was found between the progesterone groups in terms of FSH and LH levels (mIU/mL) measured on the 2nd day of the cycle (all p-values >0.05). No significant difference was found between the progesterone groups in terms of the number of oocytes collected and the number of embryos formed, the number of embryos transferred, and embryo quality (all p-values >0.05) (Table 5). No significant dependency was found between the progesterone groups and the rates of 'clinical

pregnancy presence', 'biochemical pregnancy', 'clinical abortion', and 'ongoing pregnancy' (all p-values >0.05). In this study, patients included in two different progesterone groups were asked whether they experienced the any of side effects of abdominal pain, vaginal discharge or irritation, and/or vaginal bleeding. Both groups were compared in terms of these three side effects. There is a significant dependence between the progesterone groups and the 'vaginal

discharge or irritation' variable (p = 0.0001). The rate of those without vaginal discharge or irritation in the oral dydrogesterone group (98.1%) is higher than in the micronized vaginal progesterone group (86.4%) (Tablo 6). Ectopic pregnancy, blighted ovum, and intrauterine fetal death were not observed among any of the 301 patients included in the study. Of the 301 patients included in both groups participating in the study, babies born to the patients who had a live birth at the 24th week and after were examined in terms of major congenital malformations.

Discussion

A convenient endometrium is required for the implantation of the blastocyst and the maintenance of the pregnancy. Proper preparation of the endometrium occurs with the effect of estrogen in the follicular phase and progesterone in the luteal phase (8). In stimulated cycles in which GnRH antagonists are used, it has been shown that progesterone production is impaired and LH pulsatility is suppressed with the loss of corpus luteum support (9,10). Low sex steroids in the luteal phase have been associated with inadequate implantation and pregnancy rates (11). With these data, luteal phase support has become a routine practice associated with IVF cycles. When using progesterone for luteal phase support, the most convenient and tolerable mode of administration for the patient should be used. Our aim should be to provide a high implantation and pregnancy rate. In reviewing the literature, it can be seen that quite a number of studies have mainly compared vaginal progesterone with intramuscular progesterone. In Lotus I and Lotus II studies, vaginal progesterone and oral progesterone were compared. Lotus I is a randomized, multicenter controlled phase III clinical trial that provides evidence that oral dydrogesterone is as effective as current treatments in luteal phase support for women undergoing IVF (12,13). In this study, 1,031 patients undergoing IVF or intracytoplasmic sperm injection with a fresh single or double embryo transfer after controlled ovarian stimulation were randomized to one of the two treatment arms on the day of oocyte retrieval. MVP 200 mg capsules were administered three times a day to the experimental group patients. Oral dydrogesterone was administered to the control group as 10 mg tablets three times a day. The treatment was initiated on the evening of the oocyte retrieval day, and this was continued until the 12th gestational week if pregnancy was observed on the 12th day of β-hCG. Considering the data collected in this study, dydrogesterone showed a positive benefit/risk profile. The mean age of women in the LOTUS I study was 32.5 years. The mean body mass index was 23 kg/m^2, and 43% of the patients had a single embryo transfer. The LOTUS I trial has conclusively proven that oral dydrogesterone is not inferior to micronized vaginal progesterone. In our study, there was no significant difference between the oral dydrogesterone and vaginal progesterone groups in terms of the male age, female age, and BMI variables. The number and quality of embryos transferred are similar. According to

the Lotus I study, the primary purpose of progesterone supplementation given in the luteal phase was to maintain the fetal heartbeat of the 12-week old embryo. The Lotus I study demonstrated that the impact of oral dydrogesterone and micronized vaginal progesterone were similar in terms of fetal heart rate. Continued pregnancy rates were 37.6% and 33.1% (difference is 4.7%; 95% CI: −1.2–10.6%) in the oral and vaginal treatment groups, respectively. Similar results were observed for the live birth rates of 34.6% and 29.9% (difference 4.9%; 95% CI: −0.8–10.7%) for the oral and vaginal treatment groups, respectively (13). Once again, according to this study, data on neonatal safety collected at birth were similar between groups. In other words, in the Lotus I study, the dydrogesterone and micronized vaginal progesterone used to support the luteal phase in IVF for both mother and fetus had similar safety and side-effect profiles (13). Within the scope of our study, oral dydrogesterone and vaginal progesterone groups with β-hCG positive or negative rates on the 12th day after embryo transfer were similar. When the progesterone

groups are compared in terms of the clinical status of their pregnancies, no significant differency is observed in terms of biochemical pregnancy, clinical abortion, and ongoing pregnancy rates ($p > 0.05$).

Lotus II was a randomized, multicenter Phase III study conducted from August 2015 to May 2017 at 37 IVF centers in 10 countries worldwide (14). A total of 1,034 premenopausal women (>18 to <42 years of age) were randomized into two groups to receive 30 mg oral dydrogesterone or 8% MVP gel 90 mg daily. Subjects received oral dydrogesterone (n = 520) or MVP gel (n = 514) on the day of oocyte retrieval. Luteal phase support continued until the 12th gestational week. The primary measure of success was the presence of fetal heartbeats at the 12th week of pregnancy. Pregnancy rates at the 12th gestational week in the oral dydrogesterone and MVP gel groups were 38.7% (191/494) and 35.0% (171/489), respectively (adjusted difference is recorded as 3.7%; 95% CI: −2.3 to 9.7). However, when secondary target analysis was performed for the oral dydrogesterone and MVP gel groups, live birth rates of 34.4% (170/494) and 32.5% (159/489) were obtained, respectively (adjusted difference 1.9%; 95% CI: -4.0 to 7.8). Accordingly, when compared to MVP, the success of oral dydrogesterone was not lower than that of vaginal progesterone. Miscarriage rates were similar in the two treatment groups, although this was not directly and explicitly investigated in the study. Overall, these findings were consistent with the results of the Lotus I study (13). Results from Lotus I and Lotus II, two multicentric studies in IVF, indicate that oral dydrogesterone is a viable alternative to micronized vaginal progesterone gel for luteal phase support. A prospective clinical study conducted by Kahraman S. et al. compared the effectiveness of vaginal progesterone gel versus intramuscular progesterone for luteal phase support, and it was assumed that a relationship existed between endometrial thickness and pregnancy rates (15). In another study investigating the effects of vaginal progesterone on post-transfer hormonal parameters and endometrial thickness , patients were compared (16) and the endometrial thickness was found to be higher in patients receiving vaginal progesterone than in patients who were not receiving ($p < 0.01$). These findings suggest that progesterone supplementation affects pregnancy rates by increasing endometrial thickness, thus increasing endometrial receptivity. In our study, no significant difference was observed between the oral dydrogesterone and vaginal progesterone groups with respect to endometrial thickness on the day of embryo transfer ($p > 0.05$). However, the progesterone level measured on the 12th day after embryo transfer was higher in the vaginal progesterone group ($p < 0.05$). A number of studies in the literature

reveal that female age is one of the most effective predictors of ART success (17). In general, the highest pregnancy rates in these studies were obtained in cases where the female age was below 35 years. The most likely explanation for this is that age is a direct indicator of oocyte quality. With advancing age, the number of follicles, granulosa function, oocyte quality, and endometrial receptivity decrease in women. In our study, IVF was performed on patients between the ages of 18–44. The mean age in the oral dydrogesterone group was 31.5 ± 5.5, and the mean age in the micronized vaginal progesterone group was 32.5 ± 5.3. No statistically significant difference was found between the groups. In another randomized controlled study, the effect on IVF results was compared by examining sperm parameters in patients who underwent ICSI. Consequently, it was observed that sperm parameters did not correlate with ICSI results (18). In our study, spermiogram results were similar between the progesterone groups ($p > 0.05$). The most important advantage of vaginal progesterone is its local endometrial effect, also known as the uterine first pass effect. Due to direct transport from the vagina to the uterus, high endometrial concentrations are achieved despite low circulating progesterone levels. Since vaginal use allows targeted drug delivery to the uterus (19), it is expected to be more effective in supporting the luteal phase with ART. However, the results of the Lotus I study showed that dydrogesterone had similar success with micronized vaginal progesterone gel (13). On the other hand, luteal phase support with the use of progesterone is usually initiated after oocyte pick-up. As such, there is a risk of exposure of progesterone and its excipients into the uterine cavity when the embryo transfer catheter is passed through the cervical canal. Moreover, supraphysiological progesterone concentrations in the vagina can alter the local microbiome, and this has recently become the focus of attention in the IVF context (20). Tomic et al. (21) reported that the instances of perineal irritation, vaginal bleeding, vaginal discharge, and/or interference with sexual activity were significantly higher in patients receiving vaginal progesterone gel compared to those who were receiving oral dydrogesterone. The most important tolerability issue with vaginal progesterone is discharge and irritation. In our study, the rate of vaginal discharge or irritation was higher in the micronized vaginal progesterone group (13.6%) than in the oral dydrogesterone group (1.9%). This finding is statistically significant ($p < 0.05$).

Conclusion

In general, in the Lotus I and Lotus II studies (13,14), it was reported that oral use was as effective as vaginal use in terms of luteal support, and both usage methods retained similar pregnancy results. No safety concerns have been associated with the use of either agent. In our study, similar pregnancy rates and live birth rates were found with the use of oral dydrogesterone and micronized vaginal progesterone gel. However, patients using oral progesterone expressed more satisfaction in that they experienced significantly less vaginal discharge and irritation. In addition to efficacy and safety, women generally tend to prefer oral use, and it can be asserted that oral dydrogesterone should be considered as the ‘gold standard’ treatment for luteal support in assisted reproductive techniques. That said, it must be noted that this our prospective study carries the limitations in the sample size. For a more objective evaluation, the parameters in our study should be further examined in prospective studies, particularly those with larger population patient groups and homogeneous demographic characteristics.

Declarations

Availability of data and material

Not applicable.

Code availability

Not applicable.

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Ethics declarations

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical standards

It was approved by the ethics committee of Necmettin Erbakan University Meram Faculty of Medicine.

Consent to participate

Not applicable.

Consent for publication

Not applicable.

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