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ORIGINAL ARTICLE

Vaginal progesterone versus oral dydrogesterone for luteal phase support in intrauterine insemination cycles: A prospective cohort study

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ABSTRACT

Objective: To compare vaginal progesterone and oral dydrogesterone for luteal phase support in intrauterine insemination (IUI) cycles.

Material and Methods: This study was conducted with patients who applied to the Infertility Clinic of the Department of Obstetrics and Gynecology at İstanbul Medeniyet University Prof. Dr. Süleyman Yalçın City Hospital between June 2021 and December 2021. In this prospective cohort study, 109 IUI cycles of 49 patients were examined. Vaginal progesterone (Progestan® 200 mg Soft Capsule, Koçak Farma) 1×200 mg was given to 54 cycles in the control group, and oral dydrogesterone (Duphaston® 10 mg Film Tablet, Abbott) 2×10 mg was given to 55 cycles in the study group.

Results: Eleven (20.4%) pregnancy test results in the vaginal progesterone group and six (11.1%) pregnancy test results in the dydrogesterone group were found to be positive. There was no significant difference between vaginal progesterone and dydrogesterone groups in terms of end-of-cycle pregnancy positivity, including the subgroup analyses for treatment type and infertility etiology (p>0.05). As a result of univariate analyses, it was determined that follicle-stimulating hormone (FSH) was negatively correlated with end-of-cycle pregnancy positivity (OR: 0.547; 95%CI: 0.328–0.913; p=0.021). One unit increase in FSH level reduces pregnancy positivity by 54%. According to the results of multivariate analysis, one unit increase in FSH level reduces pregnancy positivity by 56%, but it is not statistically significant (OR: 0.565; 95%CI: 0.315–1.012; p=0.055).

Conclusion: Although there were higher pregnancy rates in patients who used vaginal micronized progesterone for luteal phase support in IUI cycles, compared to patients who used oral dydrogesterone, no statistically significant difference was found between the two groups.

Keywords: Intrauterine insemination, luteal phase support, oral dydrogesterone, vaginal progesterone.

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INTRODUCTION

Infertility is defined as the inability to get pregnant despite unprotected intercourse for one year and affects 10–15% of couples in the reproductive period.[1] Intrauterine insemination (IUI) is the process of releasing semen into the endometrial cavity with the help of a special catheter. IUI is performed with indications such as unexplained infertility, cervical factor-related infertility, ovulatory dysfunction, ejaculatory dysfunction, mild male factor, stage 1–2 endometriosis, donor sperm use, and vaginismus. There are many factors affecting the success of IUI, and one of these factors is the quality of the luteal phase. The presence of luteal function and continuous production of progesterone from the corpus luteum are important for implantation and pregnancy.[2–5]

Several theories have been proposed as the cause of luteal phase failure in *in vitro* fertilization (IVF) cycles. One of them is that steroid hormones secreted in supraphysiological doses in the early luteal phase by the multiple corpora lutea developing in stimulated cycles inhibit LH release from the hypothalamo-hypophyseal axis and thus shorten the luteal phase.[6,7] It is thought that this theory is also valid in IUI cycles with ovarian induction (OI-IUI). The study by Erdem et al.[8] showed that pregnancy rates of patients given progesterone for luteal phase support after gonadotropin-stimulated IUI were higher. However, the effectiveness of luteal phase support in OI-IUI is still controversial. Although progesterone support throughout the luteal phase in these cycles is a common approach, the optimal route, dose, duration, and type of administration are unknown.[9]

Available progesterone formulations vary as oral, vaginal, rectal, intramuscular (IM), subcutaneous. There are applications such as oral micronized capsule, vaginal micronized capsule, vaginal cream, IM injections, and dydrogesterone, which is an oral synthetic progesterone. Vaginal micronized progesterone is a natural form of progesterone ve has been used for luteal phase support orally or vaginally for many years. It is more preferred than oral progesterone in luteal phase support because of its higher bioavailability, not undergoing liver first-pass metabolism, rapid absorption ve a less side-effect profile. However, micronized capsule progesterone may have side effects such as discharge, temperature increase, ve irritation secondary to vaginal administration. Dydrogesterone is a selective synthetic progesterone with high oral bioavailability. Side effects of dydrogesterone are migraine, headache, nausea, breast tenderness, ve pain. Dydrogesterone is used in many indications such as dysmenorrhea, menometrorrhagia, menstrual irregularities, endometriosis, recurrent miscarriage treatment, premenstrual syndrome, luteal phase support, ve hormone replacement therapy.[10]

There are limited studies in the literature comparing vaginal progesterone with oral dydrogesterone for luteal phase support after IUI. For this reason, we aimed to compare the effects of vaginal natural progesterone ve oral dydrogesterone for luteal phase support after IUI on pregnancy outcomes.

MATERIAL AND METHODS

Our prospective cohort study was conducted with 49 patients in 109 IUI cycles who applied to the Infertility Clinic of the Department of Obstetrics and Gynecology at İstanbul Medeniyet University Prof. Dr. Süleyman Yalçın City Hospital between June 2021 and December 2021.

Patients who were older than 18 years old and younger than 40 years old, had at least 1 year of infertility, anti-Müllerian hormone (AMH) value >1 ng/ml, basal follicle-stimulating hormone (FSH) level <14 mIU/ml, normal cervical cytology result, and appropriate indications for IUI such as unexplained infertility, ovulatory dysfunction, mild male factor, and mild endometriosis were included in our study. Patients with an indication for IVF, bilateral tubal obstruction on hysterosalpingography (HSG), severe male factor, contraindications for progesterone therapy, and clinically significant systemic, endocrine, or metabolic diseases were excluded from the study. All patients were informed about the study and consent was obtained. This study was approved by the hospital ethics committee (2021/0317) and was conducted in accordance with the principles of the Declaration of Helsinki 2013.

Semen analysis was requested and taken from all male partners under appropriate conditions. The results were evaluated according to World Health Organization (WHO) standards. Those with normal or mildly impaired semen analyses were included in the study. Sperm samples prepared by removing the supernatants were prepared using soft catheters or using a cannula with a guided wire for cases where cervical passage could not be achieved. In all female partners, basal transvaginal ultrasonography was performed by a single physician in the first week of their cycle after a bimanual examination. After evaluating all the results, basal transvaginal ultrasonography was performed on the 2nd day of the patients' cycle, and IUI preparations were started. Patients who were started on clomiphene citrate (Klomen® 50 mg, oral, Koçak Farma) or r-FSH, Follitropin alfa (Gonal-f® 75 IU, 5.5 microgram, subcutaneous, Merck) were called for the follow-up of follicle development by transvaginal ultrasonography at regular intervals from the 6th day of their cycles. The antral follicle number and development were followed, and dose adjustments were made when necessary. The initial and total doses of clomiphene citrate and gonadotropin administered to all patients, the number of days of treatment, the days of human chorionic gonadotropin (hCG) administration, and the endometrial thickness on the days of hCG administration were recorded. In our patients for whom we planned monofollicular development, the cycles of those with 2 or more dominant follicles were canceled and excluded from the study. Subcutaneous administration of 250 mg/0.5 mL choriogonadotropin alfa-recombinant hCG (Ovitrelle®, Merck) was applied to all our patients with preovulatory follicles of approximately 18–20 mm.

IUI was performed 36 hours after hCG. IUI procedures were started with the preparation of the samples by a single embryologist in our andrology laboratory within 1 hour. Then, the cervix of the female partners who were placed in the lithotomy position was visualized with a speculum and washed with saline solution. After the uterocervical angle was optimized, sperm samples were slowly given to the uterine cavity within about 10–30 seconds. The procedures were completed after the patients were placed in the supine position for 10–15 minutes after the procedure.

Table 1: Demographic data of the patients

	Vaginal progesterone (n=54)	Oral dydrogesterone (n=55)	p
Age (years)[a]	30.5 (21–43)	28 (22–40)	0.254
BMI (kg/m2)[a]	24 (16.5–42)	25.90 (18.30–42.00)	**0.035**
Duration of infertility (months)[a]	30 (8–84)	24 (8–87)	0.409
Number of ovulation induction[a]	1 (1–3)	2 (1–5)	**0.020**
Etiology[b]			
Unexplained	18 (33.3%)	20 (36.4%)	0.896
Male factor	6 (11.1%)	11(20.0%)	0.310
Anovulation (PCOS)	34 (63.0%)	32 (58.2%)	0.610
Endometriosis	3 (5.6%)	2 (3.6%)	0.679
Type of infertility[b]			
Primary	50 (92.6%)	41 (74.5%)	**0.023**
Secondary	4 (7.4%)	14 (25.5%)	
Treatment[b]			
Clomiphene citrate	27 (50.0%)	29 (52.7%)	0.776
Gonadotropin	27 (50.0%)	26 (47.3%)	

a: Mann Whitney U test was performed and results were shown as median (minimum-maximum); b: Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); BMI: Body mass index; PCOS: Polycystic ovary syndrome.

As luteal phase support, on the day of intrauterine insemination, vaginal natural micronized progesterone (Progestan® 200 mg Soft Capsule, Koçak Farma) 1×200 mg was given to the control group patients, and oral dydrogesterone (Duphaston® 10 mg Film Tablet, Abbott) 2×10 mg was given to the study group patients and continued until the 10th week in those with a positive pregnancy test result. In the 4th–5th week after intrauterine insemination, the patients who had positive pregnancy results in blood tests were re-examined with transvaginal ultrasonography to define fetal cardiac activity. All the patients who had positive β-hCG results were found to be clinically pregnant. Therefore, all of them were included in the study.

Statistical analysis

Data were analyzed using SPSS Statistics 18 (IBM Corp., Armonk, NY, USA) software. Conformity of continuous variables to normal distribution was examined by Kolmogorov-Smirnov and Shapiro-Wilk tests. Categorical variables in the study were presented with frequency (n) and percentage (%), and continuous variables with mean±standard deviation (SD), median (minimum and maximum) values. Pearson Chi-square and Fisher Exact were used in the analysis of categorical variables. Student t-test was used when parametric test assumptions were met, and Mann-Whitney U test was used when parametric assumptions were not met in the comparison of two groups' mean. Univariate and multivariate logistic regression analysis was performed to determine the independent risk factors associated with dependent variables, and variables with p<0.02 in univariate analyzes were included in the multivariate model. Obtained results are presented with odds ratio (OR) and 95% confidence intervals (CI). The statistical significance level was accepted as 0.05 in the study.

RESULTS

In this study, 109 cycles of 49 patients were evaluated because some patients had more than one IUI cycle. Two groups were formed as the control group and the study group. Vaginal progesterone was given to 54 cycles in the control group, and oral dydrogesterone was given to 55 cycles in the study group.

Pregnancy was achieved in 17 (15.6%) of 109 cycles. Demographic data of the patients are summarized in Table 1. The BMIs of the patients given dydrogesterone were found to be statistically significantly higher than those given vaginal progesterone (25.90 [18.30–42.00] and 24 [16.5–42], respectively, p=0.035). The total number of ovulation induction cycles in the dydrogesterone group was higher than those in the vaginal progesterone group, and this difference was statistically significant (2 [1–5] and 1 [1–3], respectively, p=0.020). While primary infertility was detected in 92.6% and secondary infertility in 7.4% of the group given vaginal progesterone, primary infertility was detected in 74.5% and secondary infertility in 25.5% of the dydrogesterone group. The rate of secondary infertility was found to be significantly higher in the dydrogesterone group (p=0.023).

Patient and cycle characteristics are shown in Table 2. The median TSH value of the female partner was 1.68 (0.40–4.69) mIU/ml in the vaginal progesterone group and 1.99 (0.73–4.14) mIU/ml in the dydrogesterone group. This difference was statistically significant (p=0.049). The median prolactin value of the female partner was 14.20 (2.24–64.03) ng/ml in the vaginal progesterone group and 17.90 (4.70–64.03) ng/ml in the dydrogesterone group. This difference was statistically significant (p=0.015). There was no significant

Table 2: Characteristics of partners and cycles

	Vaginal progesterone (n=54)	Oral dydrogesterone (n=55)	p
Hormone profile of female partner[a]			
FSH (mIU/ml)	6.00 (2.80–12.30)	6.00 (2.80–8.70)	0.667
LH (mIU/ml)	5.00 (1.70–52.00)	4.80 (0.00–17.00)	0.308
TSH (mIU/ml)	1.68 (0.40–4.69)	1.99 (0.73–4.14)	**0.049**
Prolactin (ng/ml)	14.20 (2.24–64.03)	17.90 (4.70–64.03)	**0.015**
AMH (ng/ml)	3.10 (1.04–16.00)	2.86 (1.21–16.30)	0.868
Estradiol (pg/ml)	35.00 (5.00–63.00)	35.00 (4.99–58.70)	0.484
Sperm parameters of male partner[a]			
Sperm count (10 million/ml)	44.00 (8.70–263.00)	49.00 (11.50–590.00)	0.316
Normal morphology (%)	7.00 (2.00–70.00)	7.00 (4.00–85.00)	0.768
Total sperm motility (%)	49.00 (34–88)	57.00 (25–94)	0.361
Progressive motility (%)	35.00 (0–77)	44.00 (0–77)	0.243
Cycle characteristics[a]			
Gonadotropin dose (IU) (n=27/26)	600 (150–1650)	562.5 (225–1350)	0.695
Clomiphene citrate dose (mg) (n=27/29)	250 (12.5–1250)	250 (30–750)	0.846
***hCG-Ovitrelle (days) (n=52/54)	10 (6–23)	10 (5–24)	>0.99
Endometrial thickness (mm) (n=54/55)	9 (5.10–16.00)	9.20 (4.00–14.70)	0.587
Patient satisfaction[b]			
Easy to use	14 (25.9%)	55 (100%)	**<0.001**
Difficult to use	40 (74.1%)	0 (0%)	

a: Mann Whitney U test was performed and results were shown as median (minimum–maximum); b: Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; AMH: Anti Mullerian hormone; hCG: Human chorionic gonadotropin.

Table 3: Pregnancy outcomes

	Vaginal progesterone	Oral dydrogesterone	p
Positive pregnancy test	11/54 (20.4%)	6/55 (10.9%)	0.273
Treatment type			
Clomiphene citrate	6/27 (22.2%)	3/29 (10.3%)	0.288
Gonadotropin	5/27 (18.5%)	3/26 (11.5%)	0.704
Etiology			
PCOS	8/34 (23.5%)	3/32 (9.4%)	0.226
Unexplained	3/18 (16.7%)	3/20 (15.0%)	0.999

Pearson Chi-square and Fisher Exact tests were performed, and the results were shown as number (n) and percentage (%); PCOS: Polycystic ovary syndrome.

difference in sperm parameters and cycle characteristics (p>0.05). When patient satisfaction was evaluated, it was observed that all patients in the dydrogesterone group expressed easy use, while the majority (74.1%) of the patients in the vaginal progesterone group expressed difficult use, and this difference was found to be statistically significant (p<0.001).

In terms of end-of-cycle pregnancy test results, 11 (20.4%) results in the vaginal progesterone group and 6 (10.9%) results in the dydrogesterone group were found to be positive (Table 3). There was no significant difference between vaginal progesterone and dydrogesterone groups in terms of end-of-cycle pregnancy test positivity, including the subgroup analyzes for treatment type and infertility etiology (p>0.05).

Table 4: Results of univariate and multivariate logistic regression analysis of factors affecting end-of-cycle pregnancy test positivity

Variables	Univariate		Multivariate	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.019 (0.918–1.131)	0.727		
BMI (kg/m^2)	1.100 (0.998–1.211)	0.054	1.115 (0.994–1.251)	0.064
Infertility duration (months)	0.996 (0.965–1.027)	0.785		
Number of ovulation induction	0.585 (0.304–1.123)	0.107	0.764 (0.369–1.582)	0.468
Unexplained infertility	1.023 (0.346–3.022)	0.968		
Secondary infertility	1.100 (0.281–4.304)	0.891		
Anovulatory infertility (PCOS)	1.233 (0.419–3.626)	0.703		
Gonadotropin dose (IU)	1.002 (0.999–1.004)	0.160		
Clomiphene citrate dose (mg)	1.001 (0.999–1.004)	0.410		
hCG-Ovitrelle (days)	1.100 (0.987–1.225)	0.085	1.058 (0.930–1.203)	0.393
Endometrial thickness (mm)	0.881 (0.712–1.090)	0.244		
FSH (mIU/ml)	0.547 (0.328–0.913)	0.021	0.565 (0.315–1.012)	0.055
LH (mIU/ml)	1.044 (0.974–1.120)	0.223		
TSH (mIU/ml)	0.848 (0.450–1.598)	0.610		
Prolactin (ng/ml)	0.986 (0.945–1.030)	0.525		
AMH (ng/ml)	1.058 (0.910–1,229)	0.464		
Estradiol (pg/ml)	0.979 (0.942–1.018)	0.285		
Sperm concentration (10 million/ml)	1.003 (0.997–1.008)	0.400		
Normal morphology (%)	1.017 (0.986–1.048)	0.285		
Total sperm motility (%)	1.012 (0.981–1.044)	0.449		
Progressive motility (%)	1.022 (0.994–1.051)	0.121	1.029 (0.995–1.064)	0.097
Difficult to use	2.214 (0.778–6.300)	0.136	1.725 (0.226–13.149)	0.599
Vaginal progesterone	2.089 (0.712–6.126)	0.179	1.668 (0.221–12.596)	0.620

Variables with p<0.02 in univariate analysis were included in multivariate analysis (Nagelkerke R Square: 0.234). BMI: Body mass index; PCOS: Polycystic ovary syndrome; FSH: Follicle stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; AMH: Anti-Mullerian hormone; hCG: Human chorionic gonadotropin; OR: Odd ratios; CI: Confidence interval.

In Table 4, univariate and multivariate logistic regression analysis results of factors affecting end-of-cycle pregnancy test positivity are presented. As a result of univariate analyzes, it was determined that FSH was negatively correlated with end-of-cycle pregnancy test positivity (OR: 0.547; 95% CI: 0.328–0.913; p=0.021). One unit increase in FSH value reduces pregnancy positivity by 54%. According to the results of multivariate analysis, one unit increase in FSH value reduces pregnancy positivity by 56%, but it is not statistically significant (OR: 0.565; 95% CI: 0.315–1.012; p=0.055).

DISCUSSION

Our study shows that the clinical pregnancy rate was 20.4% with the use of vaginal micronized progesterone for luteal phase support in IUI cycles, while this rate was found to be 10.9% with oral dydrogesterone. However, no statistically significant difference was found between the two groups (p=0.273). In our demographic data, the BMI of the group using oral dydrogesterone was found to be significantly higher than the BMI of the vaginal progesterone group (p=0.035). This may have caused a difference between the pregnancy rates of the two groups. In the regression analysis, in which we examined the factors affecting end-of-cycle pregnancy test positivity, it was seen that FSH was negatively correlated with end-of-cycle pregnancy test positivity, and a one-unit increase in FSH level decreased pregnancy positivity by 54%. Again, in the regression analysis, the rate of pregnancy test positivity was 2.08 times higher in patients in the group given vaginal progesterone than in patients given dydrogesterone; however, both regression analyses results were not statistically significant (p>0.05).

Although the role of luteal phase support in IUI cycles is still debated, the general opinion is in favor of applying luteal phase support in IUI cycles. In a meta-analysis published by Green et al.,[11] which included 11 randomized controlled studies, 2,842 patients, and 4,065 cycles, it was observed that luteal phase support with progesterone

increased clinical pregnancy and live birth rates in the group that underwent ovulation induction with gonadotropins and IUI. For this reason, it seems reasonable to give luteal phase support in OI-IUI cycles.

Many different forms of progesterone can be used for luteal phase support, such as oral/vaginal micronized capsules, vaginal cream, IM injections, vaginal gel, tablet, pessary, and oral dydrogesterone. There are studies in the literature comparing vaginal micronized progesterone and oral dydrogesterone in IVF cycles. In the multicenter randomized controlled Lotus 1 study published in 2017, 30 mg dydrogesterone and 600 mg vaginal micronized progesterone were compared for luteal phase support in IVF cycles.[12] As a result of the study, it was reported that pregnancy and live birth rates were similar and oral dydrogesterone was as effective as vaginal progesterone. It was also reported that patients tolerated dydrogesterone better and that the side-effect profiles of the two drugs were similar. In a meta-analysis that investigated the use of oral dydrogesterone and vaginal progesterone for luteal phase support in IVF cycles, oral dydrogesterone was reported to be at least as effective as vaginal progesterone.[13] In this study, clinical pregnancy rates and live birth rates were similar in both treatment regimens.

Although there are many studies in the literature reporting that oral dydrogesterone is at least as effective as vaginal micronized progesterone for luteal phase support in IVF cycles, there are limited studies that make this comparison in IUI cycles. In a randomized controlled trial published by Khosravi et al.,[14] vaginal progesterone and oral dydrogesterone were compared for luteal phase support after IUI. A total of 180 people were included in this study, and the groups were divided into 90 people using vaginal progesterone and 90 using dydrogesterone. As a result of this study, the clinical pregnancy rates of both groups were similar (vaginal progesterone 25.7% vs. oral dydrogesterone 29.7%, p=0.582).

The strengths of this study are that it is prospective, the distribution of study groups is similar, and patient satisfaction is measured. If we compare this study with our study, both studies were prospective, but our study was a cohort study, while the study by Khosravi et al.[14] is a randomized controlled study. Since our study could be conducted for 6 months, only 109 cycles were evaluated. However, Khosravi et al.'s[14] study was conducted with a larger sample. In our study, the clinical pregnancy results of the use of dydrogesterone and vaginal progesterone were statistically similar, but the total number of pregnancies in the vaginal progesterone group was approximately two times higher than in the dydrogesterone group, despite the low-dose vaginal progesterone application.

In our study, luteal phase support was also applied to patients diagnosed with PCOS, and although the number of patients treated with vaginal progesterone and dydrogesterone was almost equal, it was observed that pregnancy rates were much higher in the vaginal progesterone group than in the dydrogesterone group. However, there was no statistically significant difference (p>0.05). An important difference of our study from this study is that while we aimed to develop a monofollicle in our ovulation inductions, multifollicular development was aimed for, and at least 2–3 dominant follicles were formed in each cycle in Khosravi et al.'s[14] study because all of the patients were in an unexplained infertile group. The multifollicular dominant follicles they obtained may be the reason for the higher pregnancy rate. However, it is not clear whether the reason for this pregnancy rate in this study is the high number of developing follicles or the form, dose, and duration of the luteal phase support.

In a retrospective single-center study published by Taş et al.,[15] oral dydrogesterone and vaginal micronized progesterone were compared for luteal phase support in IUI cycles. A total of 620 cycles of 432 patients with unexplained infertility were included in the study. Dydrogesterone was administered to 233 patients (337 cycles), while vaginal progesterone was administered to 199 patients (233 cycles). Dydrogesterone was administered at a dose of 3×10 mg/day, and vaginal micronized progesterone was administered at a dose of 3×200 mg/day. As a result of that study, a total of 58 pregnancies were obtained in 620 cycles, 41 of which resulted in live births. Although clinical pregnancy and live birth rates were higher in the vaginal progesterone group, no statistically significant difference was found between the groups in terms of total, chemical and clinical pregnancy, abortion, and live birth rates (p>0.05). However, both the dydrogesterone and progesterone doses used in this study were higher than in our study, and there were patients with multifollicular development. While the pregnancy rate was 15.6% in our study, it was 9% in this study. The advantage of this study is that the sample size is large and live birth and miscarriage analyzes are performed, while the advantage of our study is that it is prospective and has patient satisfaction analysis.

There are strengths and limitations to our study. The strengths are the prospective design, similar demographic characteristics between the groups, homogeneous distribution of treatment regimens, luteal phase support applied to patients diagnosed with PCOS, and similar pregnancy rates despite monofollicular development with a lower progesterone dose compared to other studies in the literature. However, the small sample size and the inability to report the live birth, miscarriage, and multiple pregnancy rates are important limitations.

CONCLUSION

Although there were higher pregnancy rates in patients who used vaginal micronized progesterone for luteal phase support in IUI cycles, compared to patients who used oral dydrogesterone, no statistically significant difference was found between the two groups. With further studies, the role of dydrogesterone in luteal phase support in IUI will become clearer.

Statement

Ethics Committee Approval: The İstanbul Medeniyet University Clinical Research Ethics Committee granted approval for this study (date: 16.06.2021, number: 2021/0317).

Author Contributions: Concept – NHD, ED; Design – NHD, AT; Supervision – ED, AT; Resource – NHD; Materials – ED; Data Collection and/or Processing – NHD, ED; Analysis and/or Interpretation – AT, ED; Literature Search – NHD; Writing – NHD; Critical Reviews – ED.

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