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Do Women Undergoing Intrauterine Insemination Procedures Critically Require Luteal Phase Support? : A Retrospective Case-Control Study

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ABSTRACT

Background: To evaluate the progesterone for luteal phase support in improving clinical pregnancy rates (PRs) in intrauterine insemination (IUI) with ovarian stimulation (OS) and to investigate other factors that may affect PRs. Methods: A total of 579 women underwent OS with gonadotropins. Of 579 patients, 284 cycles received luteal phase support in the form of vaginal micronized progesterone capsules, while 295 cycles did not receive luteal support. Analyses were performed using the statistical package for the Social Sciences, version 21 (SPSS, Chicago, IL). Results: Of IUI cycles, 132 (22.7%) resulted in a clinical pregnancy. In women who conceived, there was no significant difference between any progesterone group (n=59) (%20) and progesterone group (n=73) (%25) in terms of clinical PRs (p=0.055). Clinical PRs were similar to in women underwent OS with rFSH (p=0.41) or hMG (p=0.06) in progesterone group and no progesterone group. However, the pregnancy rates were influenced by age (p=0.03), FSH levels on cycle day 3 (p=0.02) and a number of dominant follicles (p=0.01). Conclusions: Our results did not support the efficacy of routine supplementation of the luteal phase with progesterone in IUI cycles, likely because the endocrine mechanisms normally regulating the luteal phase are not disturbed during IUI cycles with mild OS. On the other hand, there may be more important factors such as age, number of dominant follicles affecting to pregnancy rates.

Keywords: Pregnancy rates, Intrauterine insemination, Ovarian stimulation, Luteal support, Progesterone

INTRODUCTION

Intrauterine insemination (IUI) is a widely used treatment modality for assisted reproductive technology in the management of infertile couples. The success rate of IUI treatment depends on numerous factors such as the woman's age, infertility duration, the cause of infertility, ovarian stimulation (OS) and luteal support[1,2,3]. Compared with only IUI, IUI with OS and gonadotropin is moderately better at improving pregnancy rate (PR)[4,1,2]. In contrast, OS may result in a negative effect on luteal phase quality resulting from inhibition of luteal progesterone production due to supraphysiological concentrations of progesterone and estrogen[5,6].

Progesterone requires a secretory transformation of the endometrium and improvement of endometrial receptivity[7]. Sufficient production of progesterone by the corpus luteum is essential for the establishment of implantation, maintenance of an early pregnancy[8]. The European Society of Human Reproduction and Embryology (ESHRE) Capri Workshop Group, there is no evidence to emphasize that progesterone treatment for luteal phase support (4) another strongly studies prefer to progesterone treatment[9,10].

The purpose of the present study was to evaluate the effectiveness of progesterone treatment for luteal phase support in improving clinical PRs in IUI cycles with OS using gonadotropin and to investigate other factors that may affect PRs.

METHODS

This retrospective case-control study was based on the analysis of the medical records of all patients who underwent OS with gonadotropins, either with rFSH or hMG for IUI cycles, due to a history of anovulation, minimal endometriosis, and mild male factor or unexplained infertility. The study was conducted at 29 May Hospital IVF Center and Bagcilar Training and Research Hospital, Istanbul, Turkey between January 2011 and December 2014. A total of 579 women was included in the present study. Of 579 patients, 284 cycles received luteal phase support in the form of vaginal micronized progesterone capsules (progesterone group) while 295 cycles did not receive luteal phase support (no progesterone group).

The inclusion criteria were as follows: age between 18 to 35 years old with BMI ≤ 25 kg/m^2, patency of both fallopian tubes confirmed by hysterosalpingography, and male subfertility. Total progressive motile sperm count: 5-15 million). Exclusion criteria were as follows: BMI ≥ 25 for patients who have anovulation, basal serum FSH levels >10 mIU/mL, estradiol (E2) >75 pg/mL and progesterone ≥1.4 ng/ml at the initiation of stimulation, in patients who developed more than 3 follicles ≥ 17 mm during ovarian stimulation. The following data were collected: age, the cause of infertility, FSH and E2 levels on cycle day 3, stimulation type, the number of dominant follicles and endometrial thickness (mm) on the hCG day, duration of stimulations and clinical PRs.

OS was started on day 3 of the menstrual cycle after transvaginal ultrasonograghy (TVUSG). A single dose of recombinant hCG (Ovitrelle, 250 µg; Serono, Istanbul, Turkey) was administered when at least one dominant follicle ≥ 18 mm was seen. IUI was performed 36 h after hCG administration. In the progesterone group, luteal phase support was started one day after IUI using vaginal micronized progesterone capsules 200 mg once daily (Progestan, Kocak Farma, Istanbul, Turkey) until pregnancy testing. Serum quantitative beta-hCG levels were obtained at 14 days after IUI. A clinical pregnancy was defined as the presence of a fetal heartbeat visualized by TVUSG examination after 6–8 weeks of amenorrhea. Luteal phase support was continued until the 8th week of pregnancy if the pregnancy test was positive.

STATISTICAL ANALYSIS

Analyses were performed using the statistical package for the Social Sciences, version 21 (SPSS, Chicago, IL). Data were reported as the mean ± SD, number, and percentage. The Chi-square test was used to compare categorical variables. The Kolmogorov–Smirnov test was used to determine whether the variables were normally distributed. Normal distributions of continuous variables were assessed using the t-test. Non-normally distributed metric variables were analyzed using the Mann–Whitney U-test. P values of <0.05 were considered statistically significant. In the multivariate analysis, the possible factors identified with univariate analyses were further entered into a logistic regression analysis to determine independent predictors of pregnancy. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. A sample size and power calculation determined that 139 women in each group were sufficient power (power of 0.80, alpha of 0.03 and a beta of 0.80).

RESULTS

The demographic characteristics, including age (p=0.31), the cause of infertility, FSH and E2 levels on cycle day 3 (p=0.056 and p=0.08, respectively), number of dominant follicles (p=0.18) and endometrial thickness (mm) on hCG day (p=0.07), duration of stimulations (p=0.08) for each group are shown in Table 1. There were no significant differences with regard to the distributions of these characteristics between groups. The groups were similar to each other with regard to the distributions of the cause of infertility.

Of IUI cycles, 132 (22.7%) resulted in a clinical pregnancy. There were no significant differences between the no progesterone (n=59 (20%)) and progesterone group (n=73 (25.7%)) in terms of clinical PRs (p=0.055). Although this result was not statistically significant, there was a trend toward increasing clinical PRs in progesterone group.

The comparison of PRs in women who underwent OS with rFSH or hMG is presented in Table 2. PRs were similar in both groups. The comparison of variables affecting the success rate of IUI treatment for pregnant and nonpregnant groups is shown in Table 3. Pregnant and nonpregnant groups were significantly different from each other with regard to patient ages, FSH levels on cycle day 3 and number of dominant follicles. In women who did not conceive, age and FSH levels on cycle day 3 were significantly higher compared with women who conceived (p=0.03 and p=0.02, respectively). In addition, the number of dominant follicles was significantly lower in women who did not conceive (p=0.01). Multivariable logistic regression analysis revealed that the pregnancy rates were influenced by age, FSH levels on cycle day 3 and number of dominant follicles (Table 4).

DISCUSSION

In the present study, luteal phase support was not increased clinical PRs in IUI cycles with OS using gonadotropin. As we know, progesterone secretion is crucial for preparing the endometrium for implantation; its functions include the secretory transformation of the endometrium, improvement of blood flow to the endometrium, improvement of endometrial receptivity and reducing the contractility of the myometrium (11). Therefore, progesterone secretion during the luteal phase influences PRs in a normal cycle.

Currently, there is no generally accepted consensus for luteal phase support in IUI cycles because the results of studies investigating the effect of luteal phase support during IUI cycles is controversial. Opposite to our study, Erdem et al. investigated the effect of luteal phase support with daily vaginal progesterone gel on 427 IUI cycles with recombinant FSH. This prospective randomized controlled trial showed that clinical PRs were significantly higher in the study group receiving luteal phase support. In another prospective randomized controlled study including 258 IUI cycles with recombinant FSH, daily vaginal progesterone gel for luteal

phase support positively affected the success of IUI cycles (10). However, like to our study, a prospective randomized controlled trial including 893 IUI cycles combined with mild OS using recombinant gonadotropins found that micronized intravaginal progesterone 200 mg once daily for luteal phase support did not seem to improve PRs (12).

It is clearly demonstrated that luteal phase support during IVF cycles improves PRs (13) because luteal phase during IVF cycles is deficient due to various mechanisms, such as the prolonged pituitary recovery by gonadotropin-releasing hormone (GnRH) agonism, luteolysis by GnRH antagonism, the removal of a large amount of granulosa cells during oocyte retrieval, inhibiting LH release by the high number of corpora lutea and LH production suppression by the administration of hCG. In contrast, there is no agreement in the literature for luteal phase support during IUI cycles (13). Luteal phase support may be particularly required in IUI cycles with OS because the supraphysiological levels of steroids resulting from multiple corpora lutea negatively interfere with the regulation of the luteal phase. Unlike our study, the retrospective analysis of 579 IUI cycles combined with gonadotropins (rFSH or hMG) indicated an improvement in clinical PRs and live birth rates in IUI cycles by luteal phase support. In addition, live birth rates were significantly higher in the vaginal progesterone gel group when compared with an unsupported group (14). The desired endpoint of IUI cycles with OS is to produce one to three follicles and thus fewer corpora lutea during IUI cycles with OS. Therefore, the luteal phase support during IUI cycles with OS is still debated.

Although the ESHRE Capri Workshop Group does not recommend luteal phase support to improve PRs in spontaneous or in mildly stimulated (one to two follicles) cycles, a recent review including five randomized controlled trials that evaluated the effect of luteal phase support with vaginal progesterone on IUI cycles indicated that luteal phase support with vaginal progesterone significantly enhanced live birth rates in IUI cycles with OS using gonadotropin (15). Our findings are not concordant with this research finding that asserted the necessity of luteal phase support for IUI cycles. According to the results of our present study, luteal phase supplementation with progesterone does not improve PRs during IUI cycles with OS using gonadotropin, with either rFSH or hMG, and support does not seem to be necessary. However, we also analyzed some factors identified as prognostic factors for the probability of pregnancy between pregnant and nonpregnant groups. We noted that women who conceived were younger had lower FSH levels on cycle day 3 and had more dominant follicles. In the light of our results, the present study indicates that patient age, FSH levels on cycle day 3 and the number of dominant follicles influence PRs for IUI cycles.

Our study's limitation is based on a retrospective analysis and is the small sample size. In addition, our study sample occurred with patients having a different diagnosis such as unexplained infertility, anovulation, and male subfertility. Therefore, luteal phase support may improve PRs in a patient with specific subgroups in IUI cycles like as some studies (9,14).

CONCLUSION

Our results did not support the efficacy of routine supplementation of the luteal phase with vaginal progesterone in IUI cycles with OS to improve PRs, likely because the endocrine mechanisms normally regulating the luteal phase are not disturbed during IUI cycles with mild OS. There may be some other factors, such as age, FSH levels on cycle day 3 and number of dominant follicles, that are more important for PRs. For now, the necessity of luteal phase support for IUI cycles with mild OS is still controversial due to the absence of robust evidence. Further randomized trials are needed to evaluate if luteal support is necessary for selected patients.

CONFLICT OF INTEREST

The authors report no conflicts of interest.

Table 1: Demographic characteristics of groups.

Variables	Progesterone group (n=284)	No progesterone group (n=295)	P value
Age (years)	25.42±4.14	26.00±17.57	0.31
Cause of infertility			
Anovulation	126 (44.3%)	150 (50.8%)	
Mild endometriosis	38(13.3%)	33 (11.1%)	
Mild male factor	68 (23.9%)	60 (20.3%)	
Unexplained infertility	52 ((18.3%)	52 (17.6%)	
FSH levels on cycle day 3	6.28± 1.92	6.69± 1.48	0.056
E2 levels on cycle day 3	36.21± 13.66	42.6884± 14.31	0.08
No of dominant follicles	1.44±0.51	1.43±0.49	0.18
Endometrial thickness (mm) on hCG day	9.31±1.43	9.44±1.64	0.07
Duration of stimulations	9.54± 2.22	10.01± 1.92	0.08
Clinical PRs	73 (25.7%)	59 (20%)	0.055

All values are expressed as mean ±SD, number or percentage. [a] $p < 0.05$, significant difference.

Table 2: The comparision of PRs in women underwent ovarian stimulation with rFSH or hMG.

Groups	Progesterone group (n=284)	No progesterone group (n=295)	P value
rFSH	45/172 (26.2%)	45/200 (22.5%)	0.41
hMG	28/112 (25%)	14/95 (14.7%)	0.06

All values are expressed as number and percentage. [a] $p < 0.05$, significant difference.

Table 3: The comparisions of variables affecting the success rate of IUI treatment for pregnant and nonpregnant groups.

Variable	Pregnant group (n=132)	Nonpregnant group (n=447)	p
Age (years)	28.34±4,367	29.27±4.12	0.03[a]
FSH levels on cycle day 3	6.20±1.60	6.57±1.75	0.02[a]
No of dominant follicles			0.01[a]
1	63	266	
2	67	180	
3	2	1	
Endometrial thickness (mm) on hCG day	9.55±1.53	9.33±1.54	0.14

All values are expressed as mean ±SD or number. [a] $p < 0.05$, significant difference.

Table 4: Multivariable analysis for likelihood of clinical pregnancy.

Variables	OR	P value	95% CI
Age (years)	1,057	0,02	1,007- 1,108
FSH levels on cycle day 3	0,854	0,01	,755- ,967
No of dominant follicles			
1	0,64	0,02	,430- 953
2	4,60	0,21	,403- 52,605

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