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Research Article

The Investigation Effects of Different Luteal Support Protocols on the Patients who Applied Ovulation Induction with Gonadotropines and Intrauterin Insemination

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Abstract

To evaluate the effect of different luteal phase protocols on the success of pregnancy in patients undergoing Intrauterine Insemination (IUI), 80 cycles which assigned into 4 groups (20 cycles each) were included in the study. Luteal phase support was provided by vaginal progesterone gel, vaginal micronized progesterone, intramuscular progesterone and oral progesterone in the respective groups. Groups were randomized according to the luteal support pattern. Luteal phase support was commenced on the day of IUI. Beta Human Chorionic Gonadotropine (ßhCG) was measured on the day 14 after IUI. In patients with positive test result, luteal phase support was maintained until gestational week 8. Pregnancy including 16 clinical pregnancies and one biochemical pregnancy were achieved in 17 in patients in whom Ovulation Induction (OI) and IUI were performed. In patients with clinical pregnancies, pregnancy resulted in miscarriage in 2 patients and live birth in 3 patients (twin in one patient) while there was ongoing pregnancy in 11 patients including 10 single and one triplet pregnancies. There was no significant difference in pregnancy rate (p=0.373) and ongoing pregnancy rate (p=0.18) among groups. In patients underwent OI by gonadotropins and IUI, luteal phase support with oral dydrogesterone, vaginal micronized progesterone, vaginal progesterone gel and intramuscular hydroxyprogesterone have similar effects on clinical pregnancy and live birth. If the absence of difference was confirmed, dydrogesterone should be preferred due to lower cost and better patient compliance. However, the limitation of this study is that only 16 clinical pregnancies are obtained when 4 groups are compared. In addition, luteal support therapy should be initiated after ovulation.

Keywords: Intrauterine insemination; Luteal support; Progesterone

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Introduction

Luteal Phase Deficiency (LPD) is defined as insufficient progesterone stimulation. This causes deterioration in endometrial receptivity leading to reduced implantation and pregnancy rates. The development of LPD causes reduced expression of progesterone and prevents secretions preparing the endometrium for implantation. During the luteal phase, progesterone triggers protein synthesis and a series of morphological changes that prepare the endometrium for implantation. Progesterone is effective through receptors that are regulated by oestrogens. Proliferative endometrium exposed to oestrogen is transformed to secretory endometrium and progesterone prepares it for implantation. It has been suggested that the expression of Luteinising Hormone (LH), which is necessary for the Corpus Luteum (CL) function, is inhibited by estradiol expressed at the supraphysiological level forming negative feedback on the hypothalamo-pituitary axis as a result of multifollicular development in stimulated cycles [1]. The hormonal environment, which changes with high oestrogen levels created in Ovulation Induction (OI) protocols or abnormal oestrogen/progesterone ratios, can affect endometrial receptivity and consequently, embryo implantation.

In contrast, when the luteal phase is supported with progesterone or Human Chorionic Gonadotropin (hCG), electron scanning microscopy and immunohistochemical examinations have shown the endometrial histology of the mid and late luteal phase to have improved [2]. This demonstrates the need for luteal phase support to increase the pregnancy success rates in stimulated cycles [2].

The aim of this study was to compare luteal phase protocols in patients underwent ovulation induction by gonadotropins.

Material and Method

Patient selection

The study included a total of 65 patients who presented at the Infertility Polyclinic of the Obstetrics and Gynaecology Department of Erciyes University Medical Faculty Hospital between February 2015 and November 2015. Following examinations and tests, OI+IUI with gonadotropin was planned for these patients. A total of 80 cycles were evaluated in the study. As the luteal support protocol in Intaruterin Insemination (IUI) cycles is used routinely, Ethics Committee approval for the study was not required in Turkey. Cases of both primary and secondary infertility were included in the study. Informed consent was provided by all the participants.

Inclusion criterias in the study were mild oligoasthenospermia, unexplained infertility, mild endometriosis, Total Motile Sperm Count (TMSC) >5x10^6, at least unilateral tubal passage observed laparoscopically or on Hysterosalpingo Radiograph (HSG) and a normal ovarian reserve (FSH <10 IU/ml, Antral Follicule Count [AFC] >4). Exclusion criterias were untreated hyper or hypothyroidism, hyperprolactinemia, bilateral tube obstruction or hydrops tube, TMSC <5x10^6 (these patients were referred for IVF), or ovulation induction with clomiphene.

Procedure

Follitropin α (Gonal F, rec-FSH, Serono, Turkey) and follitropin β (Puregon, rec-FSH, Organon) were used for ovarian stimulation and urinary Human Menopausal Gonadotropin (hMG) (Menogon) was used in only 1 patient because of hypogonadotropic hypogonadism. The patients included were evaluated for AFC, the presence of ovarian cyst and endometrium thickness on the 2nd day of the menstrual cycle with Transvaginal Ultrasonography (TV-USG). The type and initial dose of Gonadotropin (Gn) were determined according to the age, AFC and Body Mass Index (BMI) of the patient. The patients were called for follow-up examination 7 days after starting the treatment. A chronic low-dose, step-up protocol was applied. To be able to monitor follicle development, the patients were called for regular follow-up examinations, at which follicle development and endometrium thickness were evaluated with TV-USG. If there were no follicles ≥10mm on the 14th day of the cycle, the Gn dose was increased to 37.5 units. When follicle diameter reached 18mm, 250 µcg recombinant hCG was applied Subcutaneously (SC). If there were >3 dominant follicle, the cycle was cancelled. The IUI procedure was applied 36 hours after the administration of hCG.

For the IUI procedure, a speculum was placed in the vagina with the patient in the lithotomy position with a full bladder. After irrigation with saline, the endometrial cavity was entered transcervically with an insemination catheter and sperm were introduced into the cavity for 30 sec without the catheter making contact with the uterine fundus. The patient was kept in the lithotomy position for 15 mins on the table and the IUI procedure was completed. Using the closed envelope method, the patients were randomly separated into 4 groups. Group 1 patients were administered 2x200 mg/day vaginal micronized progesterone (Progestan), Group 2 patients were administered 1x250 mg/day hydroxyprogesterone (Proluton Depot Ampoule) intramuscularly for 5 days, Group 3 were administered 2x10 mg oral dydrogesterone (Duphaston) and Group 4 were administered 1x90 mg/day 8% progesterone vaginal gel (Crinone 8%). Luteal support was started on the day of IUI. On the 14th day after IUI, the patients were evaluated for serum quantitative hCG values. For patients with a positive test result, the luteal support was continued until the 8th week of pregnancy.

Patients with a positive pregnancy test were evaluated after 2 days in respect of an increase in the β-hCG value. Those with a decrease in β-hCG or where the sac could not be observed on USG in follow-up were evaluated as biochemically pregnant. Patients with increased serum quantitative hCG measurements were evaluated approximately 2 weeks later with TV-USG and if the pregnancy sac was observed, they were accepted as clinically pregnant. In the follow-up of the patients, termination of the pregnancy before 20 weeks following observation of the pregnancy sac and/or fetal heartbeat was accepted as spontaneous abortion. At the end of the study, patients with pregnancy that was not spontaneously terminated were defined as continuing pregnancy.

Results

According to the history of infertility, the 65 patients in the study were defined as primary infertility in 42 cases and secondary infertility in 23 cases. Polycystic ovary syndrome was determined in 20/65 patients, mild oligoasthenospermia in 1 and unexplained infertility in 44 (Table 1). When evaluation was made on a cycle basis, IUI was applied because of unexplained infertility in 52 cycles, PCOS in 27 cycles and male factor in 1 cycle. The demographic data of the patients are presented in table 2. No statistically significant difference was determined between the 4 groups in respect of age, BMI, basal hormonal values and AFC (p>0.05).

A statistically significant difference was determined in respect of the total dose between Group 1 (micronised progesterone) and Group 4 (progesterone gel) (p=0.019) and between Group 1 and Group 3 (dydrogesterone) (p=0.027). No statistically significant difference was determined in respect of total dose between Group 3 and Group 4 (p=1.00), between Group 2 (hydroxyprogesterone) and Group 4 (p=0.412), between Group 2 and Group 3 (p=0.092) and between Group 1 and Group 2 (p=0.092). Sperm parameters were examined of rapidly progressive motility, slow non-linear motility, concentration, Total Progressive Motility Sperm Count (TPMSC) and normal morphology (Table 3). No statistically significant difference was determined between the groups in respect of the sperm parameters.

Pregnancy was obtained in 17 patients (21.25%), of which 1 was biochemical pregnancy and 16 were clinical pregnancies. Of the clinical pregnancies, 2 resulted in spontaneous abortion, 10 continued as singleton pregnancies and 1 as triplet pregnancy. Live birth was achieved in 3 patients. No statistically significant difference was determined between the 4 groups in respect of pregnancy rates (p=0.373) and continuing pregnancy rates (p=0.18). At the time of the statistical evaluation, there were still patients with ongoing pregnancy and these were evaluated as clinical pregnancies.

	Groups				
	Hydroxyprogesterone n (%)	Dydrogesterone n (%)	Micronise Progesterone n (%)	Progesterone Gel %8 n (%)	Total%
Unexplained infertility	14 (70)	16 (80)	7 (35)	15 (75)	52 (65)
PCOS	6 (30)	4 (20)	13 (65)	4 (15)	27 (33,8)
Male factor	0 (0)	0 (0)	0 (0)	1(5)	1 (1,3)

Table 1: Number of patients according to causes of infertility.

	Groups				
	Hydroxyprogesterone n (%)	**Dydrogesterone n (%)**	**Micronise Progesterone n (%)**	**Progesterone Gel %8 n (%)**	**Total%**
Age (year)	26.7±3.94	25.9±4.53	26.3±3.11	27.3±4.52	0.719
BMI (kg/m2)	24.7±3.64	27.7±6.47	27.8±4.73	24.6±4.76	0.063
Infertility time	3.7±2.02	4.05±2.66	4.9±3.14	4.5±3.12	0.791
Basal FSH	5.8±1.86	5.6±1.05	6.7±2.16	6.7±2.37	0.231
Basal LH	6.6±7.92	5.7±2.55	6.2±5.75	8.4±9.43	0.769
E2	48.4±37.49	35.1±16.43	43.9±30.17	50.1±40.62	0.409
TSH	1.9±1.15	1.9±0.90	1.8±0.926	1.9±0.779	0.938
Prl	13.3±4.79	14±4.87	17.8±8.30	16.2±7.89	0.196
AFC	8.7±4.53	10.9±4.88	10.4±6.11	11.4±4.18	0.146

Table 2: Demographic characteristics of patients.

FSH: Follicule Stimulation Hormone, E2:Estradiol, TSH: Thyroid Stimulating Hormone, Prl: Prolactine, AFC: Antral Follicule Count, BMI: Body Mass Index

	Groups				
	Hydroxyprogesterone n (%)	**Dydrogesterone n (%)**	**Micronise Progesterone n (%)**	**Progesterone Gel %8 n (%)**	**Total%**
a	9.5 (4-17)	8 (4-12)	8.5 (0-19)	8.5 (4-31)	0.278
b	20 (13-27)	18 (11-25)	22 (11-49.5)	21 (12-29)	0.407
Concentration (million/ml)	34 (16-55)	40 (16-108)	31 (3.7-90)	34.5 (6.7-140)	0.159
TFMSC (million/ml)	18.5 (4.9-75.5)	26.8 (4.3-44.2)	20.9 (3.7-64.9)	32 (0-84.8)	0.227
Normal morphology (%)	6 (2-8)	4 (1-8)	6 (2-7)	6 (1-8)	0.126

Table 3: Examination of sperm parameters according to groups.

a: rapid forward progressive movement, b: Slow non linear motion, TFMSC: Total Forward Motile Sperm Account

When patients were questioned about complaints related to the administration route of progesterone, 2 of the 16 patients in the dydrogesterone group complained of general sleepiness. In the progesterone vaginal gel group, 8 of the 20 patients complained of discharge, vaginal irritation and difficulties in coitus and 3 patients had complaints of difficulties and discomfort during coitus. In the progesterone vaginal tablet group, 5 of the 19 patients complained of discharge, vaginal irritation and difficulties in coitus, and 6 patients had complaints of difficulties and discomfort during coitus. In the hydroxyprogesterone group, 12 of the 19 patients had complaints of long-term pain in the injection site. A clinically significant difference was determined between all the groups in respect of side-effects ($p<0.005$). There weren't any statistically significantly difference determined in respect of the costs of treatment between Group 2 and Group 3 ($p=0.56$), between Group 1 and Group 3 ($p=0.10$) and between Group 1 and Group 4 ($p=0.19$).

Discussion

A successful pregnancy requires both a high-quality embryo and endometrium prepared for implantation. Higher serum estradiol concentrations are found in cycles made with Gn compared to natural cycles and this high estradiol level reduces LH concentrations. By causing a deviation in oestrogen-progesterone ratios, this impairs endometrial receptivity leading to an associated reduction in implantation and pregnancy rates [3]. Therefore, a luteal support protocol is necessary in IUI cycles. In a study by Erdem et al., of 214 patients applied with OI+IUI with Gn, luteal support was provided for 109 patients with vaginal progesterone gel and compared to the control group, the clinical pregnancy rates were found to be significantly high (39.4% vs. 21.1%). Similarly, the rate of live births was higher in the study group than in the control group (35.8% vs. 17.4%) [2]. In a meta-analysis by Miralpeix et al., which included 1271 IUI patients, higher rates of clinical pregnancy and live births were reported in the study group of 951 patients treated with vaginal progesterone, compared to the rates of the control group [1].

Another meta-analysis showed similar effects on clinical pregnancy and the outcomes of continuing pregnancy of the application of vaginal progesterone (3x200 mg tablet and 1x90 mg gel) and intramuscular progesterone (1x50 mg) in IVF cycles. It was also shown that vaginal progesterone had a significantly lower nominal spontaneous abortion rate than intramuscular progesterone [4]. In another multi-centre review, Alan S. Penzias reported that vaginal progesterone and intramuscular progesterone had the same effects in IVF cycles, but oral progesterone was more successful with lower spontaneous abortion rates [5].

In the results of the current study, no significant difference was determined between oral progesterone and the other routes of progesterone administration. Moreover, as oral use was easy, the patients showed better compliance with the treatment. In the current study, vaginal progesterone gel and oral dydrogesterone tablets were determined to have the same success rates and dydrogesterone was found to be more tolerable in terms of patient satisfaction. Of the total 30 patients in the 2 groups taking vaginal progesterone, 15 reported that

usage was easy but they were disturbed by irritation and intermittent itching. Of the 16 patients in the dydrogesterone group, only 2 patients had complaints of sleepiness.

In current practice of induced IUI cycles, micronised progesterone vaginal tablets are administered as 300-600 mg/day divided into 2 or 3 doses. However, to date, no consensus has been reached on the dose of vaginal progesterone used in IUI cycles. In a study of 200 patients by Biberoğlu et al., luteal support was started as 300 mg/day vaginal progesterone tablet in 100 patients and 600 mg/day vaginal progesterone tablet in 100 patients [6]. No statistically significant difference was determined between the groups in respect of pregnancy rates and continuing pregnancies. Therefore, it was recommended that 300 mg vaginal progesterone tablet should be the maximum dose of luteal support in IUI cycles [6].

Although there have been many studies of IVF and IUI proving the need for luteal support, while studies including IVF cycles have been conducted on the subject of which route of application is more effective, there are insufficient studies related to IUI cycles. The only study in literature related to IUI cycles was conducted [7]. A total of 180 patients were separated into 2 groups of 90 administered with dydrogesterone of 2x100 mg/day and vaginal progesterone of 400 mg/day. No statistically significant difference was determined between the groups in respect of pregnancy rates (p=0.582) but patient satisfaction was higher in the dydrogesterone group (85%, p=0.001). In that study, 8 patients in the dydrogesterone group and 7 patients in the vaginal progesterone group withdrew from the study because of OHSS [7].

The fact that there is no difference between the groups is due to the fact that the study is performed with a limited number of patients. As patient satisfaction was higher in the dydrogesterone group and this group had the second lowest costs, it can be considered that dydrogesterone is most suitable as luteal support. A limitation of the current study could be said to be that the number of cycles were not sufficient to be able to definitively determine the efficacy of the protocols used in luteal support. Therefore, there is a need for further, prospective, randomized studies of more extensive patient series.

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