Impact of the Duration of Controlled Ovarian Stimulation on Assisted Reproduction Cycle Outcomes

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ABSTRACT

OBJECTIVE: To investigate the impact of duration of controlled ovarian stimulation in vitro fertilization outcomes.

STUDY DESIGN: Medical records of 3194 in vitro fertilization and intra cytoplasmic sperm injection cycles from the assisted reproduction unit of a tertiary hospital were retrospectively analyzed using a computer-based database. Characteristics of cycles with duration of stimulation ≤8 days (group I), 9 to 12 days (group II) or ≥13 days (group III) were studied retrospectively. Subgroup analysis was also done for poor responders, patients with polycystic ovary syndrome and normoresponders.

RESULTS: Estradiol on trigger day, the number of retrieved oocytes, mature oocytes and fertilized oocytes were significantly higher in group II compared to the other two groups when all cycles were analyzed (p<0.001). No significant difference was observed regarding clinical and ongoing pregnancy rates between groups. Regarding poor responders, the number of mature oocytes and the number of fertilized oocytes were higher in group II compared to the other groups (p=0.028, p=0.038, respectively). Ongoing pregnancy rates were significantly lower in group III compared to other groups (p=0.041). In patients with polycystic ovary syndrome, number of retrieved oocytes was significantly lower in group III compared to group II (p=0.047) and number of mature oocytes was significantly lower in group III compared to the other groups (p=0.005). No significant difference was found in the clinical and ongoing pregnancy rates. The number of retrieved oocytes, clinical and ongoing pregnancy rates were comparable between three groups for normoresponders.

CONCLUSION: Prolonged cycles have a detrimental effect only on ongoing pregnancy rates in poor responders.

Keywords: Controlled ovarian stimulation, Normoresponder, Poor responder, Polycystic ovary syndrome

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Introduction

Assisted reproductive technologies (ART) have been widely used worldwide. However, since their first successful use in 1978, many efforts have been made to identify the factors that affect ART success (1,2). Female age and ovarian reserve are the strongest determinants, which cannot be modified (2,3). Other factors are the duration of infertility and previous successful pregnancies (2). On the other hand, modifiable factors such as controlled ovarian stimulation (COS) are also an important part of ART treatment that affects outcome. The outcome is influenced by many factors and difficult to predict accurately. Ovarian response to stimulation mainly determines the COS parameters and length of stimulation. It is generally accepted by many clinicians that there is an ideal stimulation length and that a longer or shorter duration is a cause of concern. However, the literature regarding this subject is sparse and there is no clarity regarding the optimal duration required to achieve oocyte maturity. Although the prolonged duration of stimulation was reported to decrease ART success by some authors (1,4-6), others demonstrated no association between the length of stimulation and treatment outcome (2,3,7-9).

The aim of this study was to investigate whether the duration of controlled ovarian stimulation affects the in vitro fertilization (IVF)/intra cytoplasmic sperm injection (ICSI) outcome in the general ART population, and in the subgroups of poor responders, patients with polycystic ovary syndrome (PCOS) and normoresponders.

Material and Method

Medical records of all fresh IVF and ICSI cycles from the assisted reproduction unit of a tertiary hospital for the period between May 2007 and October 2016 were retrospectively analyzed using a computer-based database. The study was approved by the local ethics committee of the institute (21/12/2016-Number: 219). Frozen embryo transfer cycles were excluded. Age, body mass index (BMI), basal serum follicle stimulating hormone (FSH), duration of infertility, and characteristics of COS were recorded.

Controlled ovarian stimulation was performed using long GnRH agonist, microdose flare-up or antagonist protocols. The type of gonadotropin used was either pure recombinant follicle-stimulating hormone (FSH) or human menopausal gonadotropin (hMG). Gonadotropin doses were individualized for each patient. Ovarian response was monitored by serial follicular ultrasound and serum estradiol assessments, and gonadotropin dose was adjusted according to the response. Recombinant human chorionic gonadotropin (hCG) (Ovitrelle, Serono, Istanbul, Turkey) was administered when at least three follicles showed a mean diameter of 17 mm. Oocyte pick up (OPU) procedures were performed by transvaginal ultrasound-guided aspiration 35.5-36 h after the hCG injection. As a policy of the clinic, ICSI is the procedure done routinely for all our patients, whereas classic IVF is reserved only for cases when the number of retrieved oocytes exceeds 20. IVF and ICSI are both performed in these cases. Evidence for fertilization was assessed approximately 16-18 h after insemination. Embryo transfer (ET) was performed on day 2,3 or 5 under ultrasound guidance. Luteal phase support was provided by vaginal progesterone (Crinone 8% gel, Serono, UK) twice daily or a combination of intramuscular (Progestan amp, Koçak Farma, Turkey) and vaginal progesterone. Pregnancy was determined by the β-hCG level in blood tests performed 12 days after embryo transfer and clinical pregnancy was defined as the presence of a gestational sac with accompanying fetal heartbeat by ultrasound 4 weeks following the ET procedure.

Cycles were categorized into three groups according to the length of ovarian stimulation: less than or equal to 8 days (group I), 9 to 12 days (group II) and greater than or equal to 13 days (group III). After the evaluation of all cycles, subgroup analysis was done for poor responders, which was determined by the Bologna criteria (10), and in PCOS patients as defined by the Rotterdam criteria (11). After the exclusion of PCOS patients and poor responders, the normoresponder group was analyzed separately.

Statistical analysis was performed using IBM SPSS Statistics Software (20.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to test the distribution of variables. Analysis of variance (ANOVA) test was used for multiple comparisons. Post-hoc analysis was done using Tukey's HSD test. Data are presented as mean± standard error (SE). Statistical significance was assumed with a probability error of $p<0.05$.

Results

A total of 3194 cycles were analyzed. Indications of the patients were classified as follows: 1349 (42.2%) male factor, 193 (6%) tubal factor, 516 (16.2%) diminished ovarian reserve and 1136 (35.6%) unexplained infertility. The long protocol was used in 42.5% of the cycles, and the antagonist and microdose flare protocols were used in 42.3% and 15.2% of cycles, respectively.

Regarding all cycles, a statistically significant difference was determined between basal FSH values on day 3 and BMI between group III and group I and II ($p<0.001$ and $p=0.002$, respectively). Total gonadotropin dose used in group III was significantly higher compared to the other two groups ($p<0.001$). Estradiol (E2) on hCG day, number of retrieved oocytes, mature oocytes and fertilized oocytes were significantly higher in group II compared to the other groups ($p<0.001$). No significant difference was observed in clinical and ongoing pregnancy rates between groups ($p>0.05$). In regression analysis, the duration of stimulation was found to have no effect on clinical and ongoing pregnancy rates ($p=0.89$ and $p=0.620$, respectively) (Table 1).

When poor responders were analyzed separately, total gonadotropin dose and E2 on hCG day was significantly higher in group III compared to the other groups ($p<0.001$). The number of mature oocytes and fertilized oocytes was higher in group II compared to the other two groups ($p=0.028$ and $p=0.038$, respectively). Although there was no significant difference regarding clinical pregnancy rates between groups, ongoing pregnancy rates were significantly lower in group III ($p=0.041$) (Table 2).

When patients with PCOS were evaluated, BMI and total gonadotropin dose were significantly higher in group III compared to the other two groups ($p=0.003$ and $p=0.033$, respectively). The number of retrieved oocytes was significantly lower in group III compared to group II ($p=0.047$) and the number of mature oocytes was significantly lower in group III compared to the other two groups ($p=0.005$). No significant difference was found in the clinical and ongoing pregnancy rates between the groups ($p>0.05$) (Table 3).

Regarding normoresponders, BMI, total gonadotropin dose and E2 on hCG day was significantly higher in group III compared to group I and group II ($p=0.003$, $p<0.001$ and $p<0.001$, respectively). No difference was found in other de-

Table 1: *Demographic characteristics and controlled ovarian stimulation parameters of all cycles*

	Group I (n=806)	Group II (n=2165)	Group III (n=223)	*p* value
Age (years)	30.96±5.67	31.07±5.43	31.58±5.52	0.334
BMI (kg/m^2)	26.04± 4.83	25.99±4.7	27.47±5.26	0.001
Basal FSH (mIU/mL)	7.86±4.66	7.75±3.93	8.84±5.83	0.002
Total gonadotropin dose (IU)	1854.66±722.62	2729.42±1055.88	4018.93±1696.51	0.001
E_2 on hCG day (pg/mL)	2089.51±1570.85	2467.36±1598.93	2113.16±1594.78	0.001
Number of ≥17 mm follicles on hCG day	2.97±2.28	3.01±2.32	2.71±2.69	0.225
Endometrial thickness on hCG day (mm)	9.57±2.03	9.99±2.14	10.11±2.14	0.001
Number of oocytes retrieved	10.74±7.59	11.58±7.49	9.62±7.03	0.001
Number of mature oocytes	7.45±5.75	8.51±5.87	6.54±5.86	0.001
Number of fertilized oocytes	3.84±3.68	4.3±3.73	3.27±3.13	0.001
Clinical pregnancy rate (%)	30. 55	30.52	26.72	0.643
Ongoing pregnancy rate (%)	26.75	25.17	22.53	0.587

BMI: Body mass index, FSH: Follicle stimulating hormone, E_2: Estradiol, hCG: Human chorionic gonadotropin

Table 2: *Demographic characteristics and controlled ovarian stimulation parameters of cycles of poor responders*

	Group I (n=80)	Group II (n=238)	Group III (n=40)	*p* values
Female age (years)	35.54 ±5.79	34.74±5.63	35.03±6.03	0.561
BMI (kg/m^2)	25.99±4.92	27.01±5.01	26.1±4.94	0.231
Basal D_3 FSH (mIU/mL)	10.71±7.86	9.23±5.05	11.48±7.82	0.058
Total gonadotropin dose (IU)	3176.67±1171.58	3246.88±693.67	3930.03±1350.24	0.001
E_2 on hCG day (pg/mL)	1234.38±855.34	1923.35±1171.57	2073.05±1510.47	0.001
Number of follicles ≥17 mm on hCG day	2.06±1.55	2.33±1.65	1.95±1.79	0.245
Endometrial thickness on hCG day hCG (mm)	9.25±2.37	9.63±2.05	10.31±2.76	0.076
Number of retrieved oocytes	6.16±5.72	7.26±4.52	5.93±4.44	0.092
Number of mature oocytes	4.41±4.38	5.59±3.81	4.35±4.25	0.028
Number of fertilized oocytes	2.42±2.07	3.09±2.25	2.51±2.76	0.038
Clinical pregnancy rate (%)	22.5	21.0	10.0	0.642
Ongoing pregnancy rate (%)	22.5	15.9	7.5	0.041

FSH: Follicle stimulating hormone, E_2: Estradiol, hCG: Human chorionic gonadotropin

Table 3: *Demographic characteristics and controlled ovarian stimulation parameters of cycles of polycystic ovary syndrome*

	Group I (n=46)	Group II (n=120)	Group III (n=27)
Age (years)	28.21±4.32	27.98±4.55	28.89±3.78
BMI (kg/m^2)	26.65±4.96	26.34±4.94	30.17±6.26
Basal D_3 FSH (IU/L)	5.73±1.47	6.22±1.49	5.75±1.42
Total gonadotropin dose (IU)	1584.45±704.66	1752.61±798.81	2205±1101.1
E_2 on hCG day (pg/mL)	3041.49±1608.17	2932.33±1599.3	3407.14±1655.41
Number of follicles ≥17 mm on hCG day	4.67±3.93	4.25±2.85	3.56±3
Endometrial thickness on hCG day (mm)	9.71±2.06	10.14±1.88	9.76±1.49
Number of retrieved oocytes	17.02±6.95	17.35±9	13.04±5.85
Number of mature oocytes	12.26±5.33	13.04±6.92	8.48±5.72
Number of fertilized oocytes	6.76±4.05	6.63±4.64	4.63±2.96
Clinical pregnancy rate (%)	39.1	35.8	40.7
Ongoing pregnancy rate (%)	32.6	27.5	37.03

BMI: Body mass index, FSH: Follicle stimulating hormone, E_2: Estradiol, hCG: Human chorionic gonadotropin

mographic factors and controlled ovarian stimulation parameters (p>0.05). Clinical and ongoing pregnancy rates were comparable between the three groups (Table 4).

Discussion

The results of this study demonstrated that the highest number of oocytes and mature oocytes were retrieved when stimulation was between 9-12 days in all fresh cycles, although clinical pregnancy rates and ongoing pregnancy rates were not affected by the length of stimulation. In poor responders, the number of mature oocytes and fertilized oocytes was higher when the duration of stimulation was between 9-12 days. With prolonged duration of stimulation, the ongoing pregnancy rate was decreased, but not the clinical pregnancy rate. In patients with PCOS, although the number of retrieved and mature oocytes was decreased in prolonged stimulations, clinical and ongoing pregnancy rates were not affected.

The duration of stimulation is determined by the response of the ovaries to gonadotropins, which is the time for two or three follicles to become 17-18 mm in diameter (2). Although the optimal length is yet to be determined, it is thought that a shorter duration may lead to insufficient time for oocyte maturation and endometrial development. Limited literature exists addressing the impact of duration of stimulation on the number of retrieved oocytes (2,7,9,12). Mardesic et al. reported that the number of follicles on hCG day and the number of retrieved oocytes are not different in cycles with 8 days or shorter stimulation compared to longer stimulations (>8 days) in patients with antral follicle count <20 (12). In another retrospective analysis of 555 IVF cycles, it was reported that there was a higher number of oocytes retrieved in cycles with shorter stimulation phase length (11.2±6, 10.3±1.2 and 9.2±5 for stimulation duration 6-9 days, 10-11 days and ≥12 days, respectively) (2). On the other hand, others reported no influence of stimulation length on the number of oocytes retrieved (4). In line with previous studies, our results revealed that short and also prolonged stimulation resulted in a decreased number of retrieved and mature oocytes in all fresh cycles and in cycles with poor ovarian response. But in the PCOS group, only prolonged cycles (>13 days) resulted in a decreased number of retrieved and mature oocytes without an effect on pregnancy rates. Our results from the PCOS group support the study of Ryan et al., documenting stimulation longer than 13 days were not associated with decreased ART success for women with PCOS (5). In a meta-analysis of 793 cycles with PCOS and 1116 matched controls, it was demonstrated that the duration of stimulation was 1.2 days longer in the PCOS group than in controls (13). It was also demonstrated that high E2 levels in PCOS patients might be detrimental to oocyte maturation and embryonic development (14). The highest E2 level of all groups in our study was the group with stimulation longer than 13 days. So it could be hypothesized that the longer stimulation with high E2 levels may be detrimental to oocytes in the PCOS group, which leads to a decrease in the number of retrieved oocytes.

The impact of duration of stimulation on pregnancy rates is also controversial. A few studies report a negative association between stimulation length and clinical pregnancy rates (5,6) and live birth rates (1), whereas others demonstrated no association (2,7-9). In their retrospective analysis of 699 cycles, Chuang et al. reported that stimulation longer than 13 days was associated with significantly lower clinical pregnancy rates and live birth rates (1). Ryan et al. also demonstrated a 34% lower chance of clinical pregnancy in women with 13 days or longer of stimulation compared to those with shorter cycles (5). In contrast, analysis of 555 cycles revealed that clinical and ongoing pregnancy rates were not affected by the duration of stimulation, suggesting that the success of ART treatment depends on the ability of oocytes to develop follicles

Table 4: *Demographic features and controlled ovarian stimulation parameters of the cycles of normoresponders*

	Group I (n=401)	Group II (n=1175)	Group III (n=75)	*p* value
Age (years)	30.02±5.01	30.34±4.9	30.52±4.85	0.474
BMI (kg/m^2)	25.92±4.68	25.81±4.62	27.73±5.14	0.003
Basal D_3 FSH (mIU/mL)	6.84±2.31	7.23±2.82	7.35±4.16	0.068
Total gonadotropin dose (IU)	2348.22±980.68	2361.70±985.06	3164.33±881.46	0.001
E_2 on hCG day (pg/mL)	2153.02±1326.37	2695.51±2297.96	2928.47±1525.12	0.001
Number of follicles ≥17 mm on hCG day	3.41±2.26	3.23±2.38	3.2±2.83	0.408
Endometrial thickness on hCG day (mm)	9.78±1.98	10.06±2.05	9.93±1.72	0.073
Number of retrieved oocytes	12.34±7.16	12.98±6.89	12.13±7.67	0.213
Number of mature oocytes	9.08±5.28	9.68±5.54	9.05±6.16	0.135
Number of fertilized oocytes	4.87±3.47	5.05±3.49	4.41±2.89	0.242
Clinical pregnancy rate (%)	31.1	31.9	30.7	0.261
Ongoing pregnancy rate (%)	29.6	26.8	25.3	0.681

BMI: Body mass index, FSH: Follicle stimulating hormone, E_2: Estradiol, hCG: Human chorionic gonadotropin

to appropriate size, but not the speed of the ovaries to perform this action (2). Our results are in accordance with Martin, except for the poor responders, demonstrating that the duration of stimulation has no impact on ongoing and clinical pregnancy rates.

The main limitation of this study was its retrospective nature. However, to the best of our knowledge, this is the first study reporting a large number of cycles with subgroup analysis of poor responders, normal responders and patients with PCOS.

In conclusion, an appropriate starting dose of gonadotropins should be selected for ART treatment cycles to achieve oocyte maturation with optimal duration of stimulation. Special attention should be paid to poor responders, since prolonged stimulation could be detrimental to pregnancy rates in this subgroup of patients.

:Conflict of Interest: The authors report no conflict of interest.

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