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Minimal Stimulation Using Gonadotropin Combined with Clomiphene Citrate or Letrozole for Intrauterine Insemination

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Objective: In this study we aimed to evaluate the administration efficiency of first-line drugs such as clomiphene citrate (CC), letrozole (L), and the gonadotropin follicle stimulating hormone (FSH) to be used in ovulation induction for intra uterine induction (IUI) in Mongolian patients. **Methods:** In this prospective single center study we recruited 158 infertile women with polycystic ovarian syndrome (PCOS). **Results:** In the FSH group, 15 patients (31.2 %) had mycoplasma. On the other hand, the group CC and the L group had a significantly higher number of pregnancies compared than the FSH group. Moreover, there was a trend for an increasing volume of menstruation in the CC group. 38.6 % having a medium volume of menstruation, while 59.6 % had a big volume of menstruation. Stimulation characteristics of patients shows that estradiol on started day (SE2) was significantly higher in the FSH group (768.91 ± 575.64), while it was 523.66 ± 435.84 and 419.36 ± 326.30 in the CC and the L groups, respectively. **Conclusions:** A minimal stimulation protocol using FSH, CC and L separately was done in Mongolian women with polycystic ovarian syndrome (PCOS). Clinical pregnancy rates were 1.46 ± 0.50 in the FSH group, 1.35 ± 0.48 in CC group, and 1.38 ± 0.49 in L group.

Keywords: Intrauterine insemination, minimal stimulation, gonadotropin, letrozole, clomiphene citrate

Introduction

Controlled ovarian stimulation (COS) is an initial essential part of the in vitro fertilization (IVF) process which occurs in order to produce an optimum number of mature oocytes. Moreover, it provides a preferences for the most viable embryos for fertilization [1]. But in spite of some limitation of response to COS, which covers ovarian hyperstimulation syndrome (OHSS) and inadequate response, it causes IVF cycle cancellation. In addition, the response to COS is unsteady and difficult to predict

[2, 3]. In terms of OHSS, it is results in an exaggerated reaction to excess hormone and may advance to possible complications, ascites, hypovolemia and hemoconcentration, because of the extravasation of leaked fluid into the abdominal cavity [4, 5].

The first line treatment option for women with polycystic ovary syndrome is a controlled ovarian stimulation combined with intrauterine insemination [6, 7]. Further, the success of the combined treatment highly depends on growing multiple eggs at once. There are several fertility drugs which have been used to stimulate the growth and maturation of egg follicles to produce more than one egg. One of them is clomiphene citrate (CC), an oral agent that inhibits estrogen action on the hypothalamus which in turn results in increased pituitary gonadotropin release. It has been suggested that CC leads to multiple ovulations and increases the chance of twins [8, 9]. Another one is letrozole, an oral agent used for ovulation induction since 2001. Letrozole is a non-steroidal aromatase inhibitor which reversibly binds to the P450 aromatase enzyme in the estrogen biosynthesis pathway. The down-regulation of the conversion of testosterone to estradiol and androstenedione to estrone increases the secretion of pituitary follicle-stimulating hormone (FSH) as feedback to stimulate ovulation [10, 11].

Despite the acceptance as the first-line drugs in COS as well as the cost-effectiveness of CC and letrozole, several studies demonstrated that follicle-stimulating hormone is still superior to CC [12]. Gregoriou et al revealed that pregnancy rate (PR) per cycle was 8.9 % in the letrozole group as compared with 14 % in the gonadotropin IUI group [13]. Berker et al also showed that the number of preovulatory (≥ 17 mm) follicles on the day of hCG administration was significantly greater in the recombinant FSH group than in the CC group (1.7 vs. 1.4, $p = 0.01$). Multi-follicular growth was observed in 35.1 % in the CC group and 54.8 % in the FSH group ($p = 0.01$). The authors concluded that the recombinant FSH is superior to CC for enabling multi-follicular development in OS/IUI cycles [14]. On the other hand, the meta-analysis by Franik revealed that letrozole appears to improve live birth and pregnancy rates in sub-fertile women with anovulatory polycystic ovary syndrome, compared to CC. There is high-quality evidence that OHSS rates are similar with letrozole or CC [15].

Selecting of most efficient treatment as well as the use of minimal stimulation is the most desirable goal of ovulation induction. Especially, minimal stimulation has been considered to reduce complications while maintaining overall pregnancy rates. Further, the European Society of Human Reproduction and Embryology Capri Workshop Group suggested that, compared to expectant management, IUI with stimulation might lead to improved clinical outcomes. Although, numerous studies including the above mentioned research have proposed models with different treatment regimens and combinations, there is still lack of evidence regarding the regimen to be selected in the clinical field. Therefore, we have aimed in this study to determine the administration efficiency of first-line drugs (CC and letrozole) and gonadotropin (FSH) to be used in ovulation induction for IUI at Mongolian patients.

Materials and Methods

Study design

The study was conducted from May 2021 to April 2022 based on the Infertility and Reproductive Center at the National Center for Maternal and Child Health. We employed a retrospective single center study. The sample size was calculated within the hypothesis of proportion in an infinite population. A total of 158 participants were chosen in the study. The selected participants were divided into three groups: the follicle-stimulating hormone (FSH) group ($n = 48$), the clomiphene citrate (CC) group ($n = 57$), and the letrozole (L) group ($n = 53$). We have chosen a confidence interval of 95, a margin of error 5 %, and a predictive value 0.5 in this calculation.

Data collection method

Antral follicle count (AFC): An experienced sonographer measured the ovaries by using transvaginal ultrasonography, Samsung H60, as in before the COS procedure was done on the second day of the menstrual cycle. The AFC was considered when follicles measured up to 10 mm.

Hormonal measurements: We collected peripheral blood samples through a puncture of the participants' forearm vein on the second or third day of the menstrual cycle prior to the ovarian induction. Using competition immunoassay, we evaluated FSH and Estradiol levels. We used an AMH assay to measure AMH levels.

ORPI: We used the following data to calculate the ORPI index: AMH levels, AFC, and age of the patients. ORPI is calculated by multiplying the AMH serum level (ng/mL) by AFC, and the result

is divided by the age [ORPI =AMH*AFC/women's age].

Procedure: The ovarian simulation procedure begins on the 2nd or 3rd day of the participants' menstrual cycle. 1. Timing intercourse: Simulation procedure begins on the 2nd or 3rd day of the menstrual cycle. b. take clomiphene citrate 50 - 150 mg for 5 days, c. Letrozole 2.5 mg orally intake for 7 days, d. Inject recombinant FSH (GonalF) 3 - 5 days after oral administration of clomiphene citrate 50 - 150 mg for 5 days. 2. IUI: Take clomiphene citrate 50 - 150 mg for 5 days, Letrozole 2.5 mg orally for 7 days, Inject recombinant FSH (GonalF) 3 - 5 days after oral administration of clomiphene citrate 50 - 150 mg for 5 days. 3. IVF: The procedure begins on the 2nd or 3rd day of menstrual cycle. Take clomiphene citrate 50 - 150 mg for 5 days. Letrozole 2.5 mg orally for 7 days. Inject recombinant FSH (GonalF) 3 - 5 days after oral administration of clomiphene citrate 50 - 150 mg for 5 days. 4. ICIS: Simulation procedure begins on the 2nd or 3rd day of the ICU. Take clomiphene citrate 50 - 150 mg for 5 days. Letrozole 2.5 mg orally for 7 days. Inject recombinant FSH (GonalF) 3 - 5 days after oral administration of clomiphene citrate 50 - 150 mg for 5 days.

On the 12th day after using the ovarian simulation procedure, the maternal plasma hCG is measured. A biochemical pregnancy is considered when serum hCG is measured to be more than 5 IU/L.

Ovarian response definition: A normal response was referred to as 3 to 5 follicles measuring greater than 14 mm following 6 days of ovarian induction. When at least 3 follicles measuring up to 14 mm had developed or > 5 follicles had developed, it is considered an adequate response. According to this description, we divided the study participants into 2 groups, hypo-response and hyper-response.

Inclusion criteria: We included women who underwent the first cycle of assisted reproduction treatment, aged younger than 50 and had no evidence of endocrine diseases such as hyperprolactinemia, thyroid dysfunctions, or polycystic ovary syndrome.

Exclusion criteria: Patients with endometriosis or who underwent chemo/radiotherapy were excluded from the current analysis.

Statistical analysis

Continuous variables (age) are presented as the central and variability. Continuous variables included hormonal measurements, and other variables. All continuous variables were normally distributed. The one-way ANOVA was used to determine the (continuous variables) difference between study groups (FSH vs CC vs Lr) followed by the Tukey test as a multiple comparison. Descriptive analysis of category variables was calculated as frequency and percentages. In category variables, association between study 2 groups was found by applying Pearson's chi-square and Fisher exact test. The chi-square test was only used when the number of participants per cell was sufficient. A p value < 0.05 was considered statistically significant. Data were analyzed using the STATA software package, version 14.0.

Ethical statements

The study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Ethical Committee of the Mongolian National University of Medical Sciences (Protocol №2021/3-08).

Results

Clinical characteristics of the participants are shown in Table 1. The present study included 158 women: 48 patients were allocated to the FSH group, 57 to the CC group and 53 to the L group. There were no differences noted between these three groups in age, menstrual cycle length, pregnancy rate, and BMI. However, group FSH had a significant difference in having a first time pregnancy as well as no experience of delivery.

Demographic characteristics are shown in Table 2. In the FSH group, 15 patients (31.2 %) had mycoplasma. On the other hand, group CC and L had a significantly higher number of pregnancies compared to that in the FSH group.

As shown in Table 3, more patients in the FSH group had urea plasma but it was not statistically significant. As expected, there was a trend for an increasing volume of menstruation in the CC group. 38.6 % having a medium volume of menstruation, while 59.6 % had a big volume of menstruation.

Furthermore, follicles and medical histories are given in Table 4. There were no significant differences between the 3 groups in terms of the right and left basal follicles, abortion experience, or usage of medicine. However, there was a significant difference in pre-surgery and cervical PCR among the 3 groups. The infection status was also examined and showed that more participants in CC and L groups did not have any infection, while 66.7 % of the

Table 1. Clinical characteristics of study participants.

Variables	FSH (n = 48)	CC (n = 57)	L (n = 53)	Total (n = 158)	*p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	
Age, years	33.73 ± 4.89	33.87 ± 6.19	33.28 ± 4.76	33.63 ± 5.33	0.836
Age of first period	14.02 ± 1.07	14.39 ± 1.82	13.92 ± 1.40	14.12 ± 1.50	0.837
Menstrual cycle length	29.21 ± 7.04	28.56 ± 2.95	28.91 ± 4.31	28.87 ± 4.9	0.797
BMI	25.15 ± 3.30	25.48 ± 4.27	24.53 ± 3.89	25.06 ± 3.86	0.287
Pregnancy rate	1.46 ± 0.50	1.35 ± 0.48	1.38 ± 0.49	1.39 ± 0.49	0.512
First time pregnancy (yes)[a]	0.77 ± 0.93	1.51 ± 1.49	1.15 ± 1.22	1.16 ± 1.28	0.011
Delivery (no)[b]	0.08 ± 0.35	0.63 ± 0.96	0.32 ± 0.64	0.36 ± 0.74	0.005
Infection duration	52.31 ± 32.41	42.12 ± 28.17	52.76 ± 25.49	48.74 ± 24.94	0.094
Smoking, years	3.3 ± 1.2	6.7 ± 2.58	6.2 ± 2.21	0.55 ± 2.1	0.691

BMI- Body Mass Index; FSH - Follicle stimulation hormone, LH - Luteinizing hormone, E2 - Estradiol, P4- Progesterone, AMH - Anti-muller hormone, ORPI - Ovarian response prediction index, AFC - Antral follicle count, CI - Confidence interval, SE - Sensitive, SP - Specific

*One-way ANOVA; multiple comparisons: [a]FSH vs. L, $p < 0.031$; [b]FSH vs. CC, $p < 0.001$

Table 2. Demographic characteristics of study participants.

Variables	FSH (n = 48)	CC (n = 57)	L (n = 53)	Total (n = 158)	p-value
	N (%)	N (%)	N (%)	N (%)	
Marital status					
Married	42 (87.5)	51 (89.5)	46 (86.8)	139 (88)	0.904
Partner	6 (12.5)	6 (10.5)	7 (13.2)	19 (12)	
Smoke					
Yes	4 (8.3)	6 (10.5)	6 (11.3)	16 (10.1)	0.877
No	44 (91.7)	51 (89.5)	47 (88.7)	142 (89.9)	
Alcohol					
Yes	5 (10.6)	-	9 (16.9)	14 (8.9)	
No	42 (89.4)	57(100.0)	44 (83.1)	143 (91.1)	
Pregnancy number					
None	22 (45.8)	20 (35.1)	20 (37.7)	62 (39.2)	0.011
One	19 (39.6)	11 (19.3)	18 (33.9)	48 (30.4)	
More than one	7 (14.6)	26 (45.6)	15 (28.3)	48 (30.4)	
Contraceptives use					
None	2 (4.2)	-	1 (1.9)	3 (1.9)	
Occasionally	4 (8.3)	17 (29.8)	8 (15.1)	29 (18.4)	
Regularly	42 (87.5)	40 (70.2)	44 (83.0)	126 (79.7)	
Job condition					
Good	44 (91.7)	51 (89.5)	50 (94.3)	145 (91.7)	0.321
Bad	4 (8.3)	6 (10.5)	3 (5.7)	13 (8.3)	
Sex pain					
Yes	2 (4.3)	5 (8.7)	2 (3.8)	9 (5.7)	0.462
No	45 (95.7)	52 (91.3)	51 (96.2)	148 (94.3)	

Continued

Sexual activity					
Good	34 (72.3)	47 (82.5)	44 (83.1)	125 (79.6)	0.333
Bad	13 (27.4)	10 (17.5)	9 (16.9)	32 (20.3)	
Mycoplasma					
No	33 (68.8)	51 (89.5)	45 (84.9)	129 (81.6)	0.018
Yes	15 (31.2)	6 (10.5)	8 (15.1)	29 (18.4)	

Table 3. Menstrual variables.

Variables	FSH (n = 48)	CC (n = 57)	L (n = 53)	Total (n = 158)	p-value
	N (%)	N (%)	N (%)	N (%)	
Urea plasma					
Negative	22 (45.8)	35 (61.4)	35 (66.0)	92 (58.2)	0.100
Positive	26 (54.2)	22 (38.6)	18 (34.0)	66 (41.8)	
Miscarriage					
No	44 (91.7)	52 (91.2)	48 (90.6)	144 (91.1)	0.980
Yes	4 (8.3)	5 (8.8)	5 (9.4)	14 (8.9)	
Mortality in uterus					
No	40 (83.3)	48 (84.2)	45 (84.9)	133 (84.2)	0.980
Yes	8 (16.7)	9 (15.8)	8 (15.1)	25 (15.8)	
Ectopic					
No	43 (89.6)	50 (87.7)	48 (90.6)	141 (89.2)	0.886
Yes	5 (10.4)	7 (12.3)	5 (9.4)	17 (10.8)	
Regular menstruation					
Yes	39 (82.9)	46 (80.7)	41 (77.4)	126 (80.3)	0.775
No	8 (17.1)	11 (19.3)	12 (22.6)	31 (19.7)	
Volumes of menstruation					
Small	7 (14.9)	1 (17.5)	5 (9.4)	13 (8.3)	0.092
Medium	12 (25.5)	22 (38.6)	13 (24.5)	47 (29.9)	
Big	28 (59.6)	34 (59.6)	35 (66.0)	97 (61.8)	

Table 4. Follicles and medical histories.

Variables	FSH (n = 48) Mean ± SD	CC (n = 57) Mean ± SD	L (n = 53) Mean ± SD	Total (n = 158) Mean ± SD	p-value
Right basal follicles	3.26±1.96	3.27±2.08	3.23±2.13	3.25 ± 2.05	0.996
Left basal follicles	3.1±1.95	2.87±1.65	2.81±1.86	2.92 ± 1.81	0.695
Abortion					
No	36 (75)	35 (61.4)	37 (69.8)	108 (68.4)	0.315
Yes	12 (25)	22 (38.6)	16 (30.2)	50 (31.6)	
Medicine					
Yes	5 (10.4)	5 (8.8)	4 (7.5)	14 (8.7)	0.897
No	43 (89.6)	52 (91.2)	49 (92.5)	144 (91.1)	

Continued

Pre-surgery					
Yes	28 (51.3)	33 (57.9)	17 (32.1)	78 (49.4)	0.008
No	20 (41.7)	24 (42.1)	36 (67.9)	80 (50.6)	
Cervical PCR					
Yes	39 (81.3)	34 (59.6)	33 (62.3)	106 (67.1)	0.041
No	9 (18.7)	23 (40.4)	20 (37.7)	52 (32.9)	
Infection					
Yes	32 (66.7)	25 (43.9)	23 (43.4)	80 (50.6)	0.028
No	16 (33.3)	32 (56.1)	30 (56.6)	78 (49.4)	
Normal umbilical hair					
Yes	47 (97.9)	54 (94.7)	51 (96.2)	152 (96.2)	0.697
No	1 (2.1)	3 (5.3)	2 (3.8)	6 (3.8)	

FSH - Follicle stimulation hormone, LH - Luteinizing hormone, E2 - Estradiol, P4- Progesterone, AMH - Anti-muller hormone, ORPI - Ovarian response prediction index, AFC - Antral follicle count, CI - Confidence interval, SE - Sensitive, SP - Specific.

Table 5. Follicles hormones.

Variables	FSH (n = 48) Mean ± SD	CC (n = 57) Mean ± SD	L (n = 53) Mean ± SD	Total (n = 158) N (%)	*p-value
E2	30.25 ± 15.52	29.55 ± 16.01	30.97 ± 15.72	30.24 ± 15.68	0.896
P4	5.7 ± 2.54	5.33 ± 1.94	4.43 ± 1.45	5.1 ± 1.99	0.949
AMH	2.87 ± 4.77	2.71 ± 3.06	3.65 ± 4.83	3.09 ± 4.25	0.477
PRL	23.32 ± 10.56	21.67 ± 8.76	22.53 ± 8.53	22.44 ± 9.21	0.668
TSH	2.06 ± 0.86	2.41 ± 1.91	2.75 ± 2.72	2.41 ± 2.01	0.236
SLH	12.75 ± 12.72	12.81 ± 7.19	11.55 ± 5.89	12.37 ± 8.83	0.715
SE2[a]	768.91 ± 575.64	523.66 ± 435.84	419.36 ± 326.30	561.5 ± 470.5	0.000
SP4	1.07 ± 2.61	0.77 ± 1.93	0.87 ± 2.14	0.89 ± 2.21	0.792
HCG dose injection	6500 ± 0.00	6457.14 ± 253.54	6411.76 ± 358.24	6455.88 ± 254.68	0.369
D	25.52 ± 17.53	27.95 ± 20.44	23.00 ± 15.67	25.61 ± 18.12	0.379
Dom follicles[b]	3.02 ± 1.51	2.16 ± 0.93	1.90 ± 0.72	2.33 ±1.17	0.000
HCG menstruation days	12.6 ± 1.35	12.49 ± 1.13	12.59 ± 0.95	12.56 ±1.14	0.859
NALTH	12.54 ± 16.09	10.47 ± 7.73	15.39 ± 30.20	12.77 ± 20.25	0.449
NATE2	168.17 ± 136.75	197.23 ± 182.78	175.72 ± 102.1	181.34 ± 145.21	0.574
NATP4	0.37 ± 0.45	0.51 ± 1.22	0.68 ± 2.55	0.53 ± 1.68	0.67

FSH - Follicle stimulation hormone, LH - Luteinizing hormone, E2 - Estradiol, P4- Progesterone, AMH - Anti-muller hormone, ORPI - Ovarian response prediction index, AFC - Antral fol. *One-way ANOVA; multiple comparisons: [a]FSH vs. CC, $p < 0.004$; [b]FSH vs. L, $p < 0.009$

FSH group had infections.

Stimulation characteristics of patients undergoing treatments were shown in Table 5. There was no difference in E2, P4, AMH, PRL, TSH, SLH between the 3 groups. However, estradiol on started day (SE2) was significantly higher in the FSH group (768.91 ± 575.64), while it was 523.66 ± 435.84 and 419.36 ± 326.30 in the CC and the L groups, respectively.

Discussion

It has been suggested that 5 % to 10 % of women in reproductive age face polycystic ovary syndrome (PCOS), one of the most

prevalent endocrine disorders in women. Moreover, PCOS causes up to 60 % of ovulation disorders in infertile women [16 - 18]. Therefore, finding and selecting a proper regimen for stimulation of ovulation in women with PCOS is difficult. Nowadays, clomiphene citrate (CC) and letrozole are used as first-line drugs for ovulation induction in infertile women [19 - 20]. Legro et al demonstrated that women who received letrozole had more cumulative live births than those who received clomiphene (103 of 374 [27.5 %] vs. 72 of 376 [19.1 %], $p = 0.007$; rate ratio for live birth, 1.44; 95 % confidence interval, 1.10 to 1.87) without significant differences in overall congenital anomalies, though there were four major congenital anomalies in the letrozole group versus one in the clomiphene group ($p = 0.65$). Moreover, the cumulative ovulation rate was higher with letrozole than with clomiphene (834 of 1352 treatment cycles [61.7 %] vs. 688 of 1425 treatment cycles [48.3 %], $p < 0.001$). Authors also have indicated that clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness [21]. Berker et al also showed that multi-follicular growth was observed in 35.1% in the clomiphene citrate administration group and 54.8 % in the FSH group ($p = 0.01$) [14].

In our study, we have confirmed that there was a trend for an increasing volume of menstruation in the CC group, 38.6 % having a medium volume of menstruation, while 59.6 % had a big volume of menstruation. Moreover, there was a significant difference in pre-surgery and cervical PCR among the 3 groups. The infection status was also examined and showed that less participants in CC and L groups had infections compared to 66.7 % of FSH group who had infections. Stimulation characteristics of patients undergoing treatments (Table 5) showed that there was no difference in E2, P4, AMH, PRL, TSH, SLH between the 3 groups. However, estradiol on started day (SE2) was significantly higher in FSH group (768.91 ± 575.64), while it was 523.66 ± 435.84 and 419.36 ± 326.30 in CC and L groups, respectively. The clinical pregnancy rates in the current study are lower than those reported in previous studies [13, 22 - 24]. It has been demonstrated that, in large population observational studies, the clinical pregnancy rate per cycle was approximately 10 % in IUI with gonadotropin only, however multiple pregnancies represented in 30 % of these cases. In our study, the clinical pregnancy rate was 1.46 ± 0.50 in FSH group, 1.35 ± 0.48 in CC group, and 1.38 ± 0.49 in L group.

Our study has some limitations. The main limitation of this study is related to its low sample size. Also, in the present study, we could not document any physiological symptoms of patients who received hormone treatment. We also have included only participants from rural areas (Ulaanbaatar, mainly). In the future, the study could be strengthened using a larger sample size, and measure more blood parameters related to PCOS such as dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS) as well as fasting insulin.

Conclusion

In conclusion, a minimal stimulation protocol using FSH, CC and L separately was done in Mongolian women with PCOS. Clinical pregnancy rates were 1.46 ± 0.50 in FSH group, 1.35 ± 0.48 in CC group, and 1.38 ± 0.49 in L group. However, the first time pregnancy rate was significantly higher in the CC and L groups, compared to that in the FSH group. As compared with FSH, clomiphene and letrozole was associated with lower mycoplasma and lower SE2 among infertile women with polycystic ovary syndrome.

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