Journal of Gynecology Obstetrics and Human Reproduction 48 (2019) 329–333

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Original article

Double mild stimulation and egg collection in the same cycle for management of poor ovarian responders

T Madani[a], M Hemat[a,*], A Arabipoor[a,*], SH Khodabakhshi[a], Z Zolfaghari[b]

[a] Department of Endocrinology and Female Infertility, Reproductive Biomedicine Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran
[b] Department of Epidemiology and Reproductive Health, Reproductive Epidemiology Research Center, Royan Institute for Reproductive Biomedicine, ACECR, Tehran, Iran

ARTICLE INFO

Article history:
Received 11 September 2018
Received in revised form 8 December 2018
Accepted 12 December 2018
Available online 12 December 2018

Keywords:
Poor ovarian response
Double stimulation
Luteal-phase ovarian stimulation
Mild stimulation

ABSTRACT

Purpose: To evaluate the effect of double stimulations during the follicular and luteal phases in women with poor ovarian response (POR) in *in-vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) cycles.
Basic procedures: This prospective clinical study was performed in Royan Institute from October 2014 to January 2016. 121 patients were diagnosed as POR on the basis of Bologna criteria were included. Double stimulations were performed during the follicular and luteal phases by Letrozole, Clomid, hMG and GnRH-agonist. The patients' present cycle outcomes were compared with those of the previous cycle results using appropriate statistical tests.
Main finding: The total of 104 (85.9%) patients completed the stimulation stages. The analysis revealed the number of retrieved oocytes after the first and second stimulations did not differ ($P = 0.2$); however, the fertilization rate and the number of frozen embryos after the first stimulation were significantly higher than those of in the second stimulation ($P < 0.001$ and $P = 0.03$), indicating the better quality of retrieved oocytes after the first stimulation. The mean number of MII oocytes and the fertilization rate after Shanghai protocol were higher than those of the previous antagonist protocol with a substantial trend toward significance ($P = 0.06$), which can be clinically important. The cancellation rate (33%) due to no ovarian response and no embryo formation was still high in these patients.
Principal conclusion: Since the intensity of stimulation in both stages was mild, this protocol can be considered a time-efficient and patient friendly regime; however, more studies are required with emphasis on its cost-effectiveness.

Introduction

The birth of a healthy baby is the ideal goal of assisted reproductive technology (ART) cycles, relying on numerous factors. It is argued that ovarian stimulation (OS) is the cornerstone of this procedure. [1] Ovarian stimulation for poor responders is still a challenging and frustrating issue for both patients and clinicians. [2] Although various intervention protocols have been applied to improve the outcomes in poor responders, there is no adequate evidence to determine the best protocol [1,3], and optimal treatment options remain subjective and not evidence-based. [4] Currently, the Bologna criteria have been considered to uniform a standard definition for universal use in the research to detect the most effective protocol in patients with poor ovarian response (POR) [5].

Recently, mild stimulation using low dose of gonadotropins during OS protocol by gonadotropin-releasing hormone (GnRH) antagonist [6] or oral compounds (e.g. anti-estrogenic or aromatase inhibitors) [7,8], or both during short or long GnRH agonist protocol has been proposed as a cost-effective and patients-friendly strategy to optimize the balance between outcomes and risks of treatment. [9,10] The mild stimulation in POR patients had similar outcomes in comparison to the conventional OS, even though this protocol is associated with slightly better pregnancy rate in patients over 37 years old. [7]

Kuang et al. presented a novel protocol in the management of POR hypothesizing that more oocytes and embryos could be

* Corresponding authors at: Number 12, East Hafez Avenue, BaniHashem Street, Resalat Highway, P.O. Box: (16656-59911), Tehran, Iran.
E-mail addresses: tmadani@royaninstitute.org (T. Madani), m.hemat@royaninstitute.org (M. Hemat), arezoo.arabipoor@gmail.com (A. Arabipoor), shabnamkhodabakhshi@gmail.com (S. Khodabakhshi), za_zolfaghary@yahoo.com (Z. Zolfaghari).

http://dx.doi.org/10.1016/j.jogoh.2018.12.004
2468-7847/

obtained by continuing OS in luteal phase after the first oocyte retrieval from mild stimulation in the early follicular phase. [2] However, to the best of our knowledge, few studies have been conducted on this topic. [11,2,12] The present study was designed to evaluate the efficacy of double stimulation and egg collection (Shanghai protocol) in POR patients undergoing IVF /intracytoplasmic sperm injection (ICSI) cycles.

Materials and methods

This prospective clinical trial was performed in the Female Infertility and Reproductive Endocrinology Department of Royan Institute, Tehran, Iran. Eligible women undergoing IVF-ICSI cycles were recruited from October 2014 to January 2016. The trial protocol was approved by the Review Board and Ethics Committee of Royan Institute. The present study was launched by the virtue of Helsinki Declaration for Medical Research. The study goals were explained to all the participants and the informed consent was signed by them prior to starting the treatment cycle. Poor ovarian response (POR) was defined according to the Bologna criteria. All participants had a previous history of POR (retrieved oocytes ≤ 3) treatment cycle by the conventional stimulation protocol. Moreover, the patients had to meet at least one of the following two criteria: 1) advanced maternal age ($\geq$40 years) or any other risk factors for POR (e.g. a history of ovarian surgery) and 2) abnormal ovarian reserve test (i.e. antral follicle count (AFC) <5–7 follicles or anti-Műllerian hormone (AMH) <0.5–1.1 ng/ml). Patients with premature ovarian failure diagnosis (basal FSH above 20 IU/l or no antral follicle in ultrasound examination), unilateral oophorectomy, and endometriosis grade 3 or higher were excluded from the study.

A venous blood sample was collected for measurement of the basal AMH, follicular stimulating hormone (FSH), luteinizing hormone (LH), Prolactin (PRL) and Thyroid-stimulating hormone (TSH) levels on the day 2 or 3 of menstrual cycle in all women. The OS namely Shanghai protocol, consisting of two stimulation phases was carried out according to Kaung et al.'s study [2] (Fig. 1).

In the first stage, OS was performed by clomiphene citrate (Ovumid, Iran Hormones Company) 25 mg per day with co-treatment of letrozole (LZ) (Letrofem, Iran Hormones Company) 2.5 mg per day started from day 3 of menstrual cycle. LZ was prescribed for 4 days and clomiphene citrate was continuously administered until the day before the final ovarian triggering. Human menopausal gonadotrophin (HMG) (Menopur, Ferring, Switzerland) (150 IU) was injected every other day starting on the day 6 of stimulation. Cycle monitoring was conducted every 1–2 days, starting from the cycle day 6 using a transvaginal ultrasound (TVS) assessment to record the number of growing follicles. The final oocyte maturation triggering was performed with 0.5 mg of Buserelin acetate (Suprefact, Avensis) when one or two dominant follicles (18 mm in diameter) were observed. Ibuprofen (600 mg) (Ibuprofen coated tablets, Iran Najo Company, Iran) was prescribed on the triggering day and the day after for prevention of possible follicle rupture before ovum pick-up (OPU). TVS-guided oocyte retrieval was performed 34–36 h after oocyte triggering. All follicles of less than 12 mm were put aside for the second stimulation in the luteal phase. Standard IVF and/or ICSI procedures were conducted in all the MII oocytes. Embryo quality was determined according to the number and regularity of blastomeres and the degree of embryonic fragmentation that has been explained previously[13]. All good quality embryos were cryopreserved by vitrification method on the second or third day after ovum pick up as described more in *detail* elsewhere[14].

The day after the first OPU, a TVS was done to examine the criterion for continuation of the second OS. 225 IU HMG and 2.5 mg LZ were prescribed daily for stimulation of follicle development provided that at least two antral follicles (2-8 mm in diameter) were observed. The first monitoring was performed 4 days later. TVS monitoring was done every 1–2 days and also the hormonal measurements were carried out as needed. LZ consumption stopped when the dominant follicles reached 14 mm in diameter. When the diameter of a dominant follicle reached 18 mm, the final stage of oocyte maturation was induced again with 0.5 mg of Buserelin acetate (Suprefact, Avensis) subcutaneously. Again, ibuprofen (0.6 g) was prescribed on the day of oocyte triggering and the following day. All of the oocyte retrieval, fertilization, embryo evaluation, and cryopreservation procedures were similar to the first stimulation stage.

A programmed frozen embryo transfer *(FET)* protocol was applied for all patients as previously were described in detail. [14] When the endometrial thickness was appropriate ($\geq$7 mm), the GnRH agonist administration stopped, and estradiol valerate continued with the same dose, and 50 mg progesterone (Progestin®, Aburaihan Pharmaceutical. Co., Tehran, Iran) was intramuscularly administered for 2 or 3 days. Then the embryos were transferred. The intramuscular (IM) progesterone (50 mg/day) and oral estradiol valerate Estraval®, Aburaihan CO, Tehran, Ira (4 mg/day) continued until the first obstetrics ultrasound at 6–7 weeks gestation. After the observation of the fetal heartbeat, the IM progesterone changed to vaginal progesterone (400 mg/ day). Estradiol valerate (4 mg/ day) and vaginal progesterone (400 mg/ day) continued until 10 weeks of pregnancy, respectively.

Statistical analysis

The statistical analysis was made by using the Statistical Package for the Social Sciences Software (SPSS, Version 20.0, SPSS Inc. Chicago, IL, USA). The number of oocytes retrieved was the primary outcome, and the number of MII oocytes, fertilization rate, the number of good quality embryos and the pregnancy outcomes after FET were secondary endpoints. The implantation rate was considered as the total number of gestational sacs divided by the total number of transferred embryos. Clinical pregnancy was defined as the detection of the gestational sac with yolk sac and

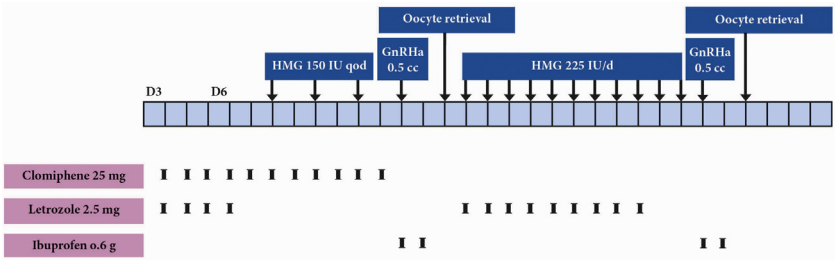

Fig. 1. The protocol of double stimulation during the same menstrual cycle (Shanghai protocol) in the patients with poor ovarian response.
GnRHa, gonadotropin-releasing hormone agonist; HMG, human menopausal gonadotropin; acetate; qod, every other day; IU, international unit.

heartbeat on ultrasound 4-6 weeks after ET. Miscarriage was defined as the spontaneous loss of a clinical pregnancy before 20 complete weeks of gestational age. The cycles were canceled when no follicle ≥11 mm in size on ultrasound evaluation on the day 8 of stimulation. The OS outcomes after first oocyte retrieval were compared with those of the second oocyte retrieval by Student's *t*-test, Mann Whitney U and Chi-squared tests where they were appropriate. Accordingly, the outcomes of the present protocol were compared with those of the previous OS protocol in each patient by using Paired samples *t*-test, Wilcoxon test and Chi-squared test as appropriate. The significance level was considered as $P < 0.05$.

Results

In total, 121 eligible patients were enrolled in the present study. Fig. 2 shows the patients' recruitment and follow-up process after applying Shanghai protocol. The second stimulation was canceled due to the low AFC (<2) in 17 patients (14%). Consequently, 104 (85.9%) patients completed the two stages of stimulation protocol, and totally, 164 viable embryos were obtained from double stimulations in 81 patients (67%). The cancellation rate in the second stimulation was 19% (23/121) due to no oocyte retrieval (n = 17) and no embryo formation (n = 9). Finally, as shown in Fig. 2, the clinical pregnancy and live birth rates after frozen embryo transfers were19.7% and 16%, respectively.

The mean ± standard deviations of age, body mass index and serum AMH level of the target patients were 37.46 ± 4.84, 26.40 ± 3.61 and 0.52 ± 0.51 respectively. 17.2% of the patients had male factor along with ovulatory factor diagnosis as infertility causes (Table 1).

Table 2 shows the cycle characteristics and outcomes of double stimulation in Shanghai protocol after the first and second oocyte retrievals in the target patients. The analysis revealed that the number of retrieved oocytes after the first and second stimulations did not make difference (P = 0.2), but the fertilization rate and the number of frozen embryo were significantly higher after the first stimulation (P < 0.001 and P = 0.03), indicating the better quality of retrieved oocytes after the first stimulation (Table 2).

Of the 81 patients who had completed double stimulation regimes, 66 patients had data of the previous OS protocol. Table 2 indicates the cycle characteristics and outcomes of Shanghai protocol in the studied patients compared with their previous OS protocol. The results revealed that the fertilization rate after Shanghai protocol was higher than those of previous cycles with long agonist and antagonist protocols (P = 0.001 and P = 0.004, respectively).

Table 1
Baseline characteristics of the study population (n = 121).

Age (Year)	37.46 ± 4.84
BMI (kg/m^2)	26.40 ± 3.61
Duration of infertility (Year)	7.41 ± 5.39
Serum level of FSH (mIU/l)	10.11 ± 5.21
Serum level of LH (mIu/l)	5.11 ± 3.25
Serum level of PRL (ng/ml)	11.20 ± 14.57
Serum level of TSH mIU/L	1.73 ± 0.85
Serum level of AMH (ng/ml)	0.52 ± 0.51

BMI; body mass index, FSH; follicle-stimulating hormone, LH; luteinizing hormone, PRL; prolactin, TSH; thyroid-stimulating hormone, AMH; anti-müllerian hormone.

The outcomes of Shanghai protocol made no difference between the patients who underwent miniflare protocol in their previous IVF/ICSI cycle. The number of MII oocytes after Shanghai protocol was higher than those of other protocols (agonist, antagonist and mini-flare); however, the difference did not reach a significant level (P = 0.6, P = 0.06 and P = 0.4, respectively) (Table 3).

Discussion

The results of present study indicated that the mean number of MII oocytes and fertilization rate after Shanghai protocol were higher than those of the previous antagonist protocol with a substantial trend toward significance; in addition clinical pregnancy and live birth rates were 19.7% and 16% which can be clinically important. In spite of the satisfactory results, the cancellation rate (33%) due to no ovarian response and no embryo formation was still high in this group of patients.

At First, Kuang and colleagues invented Shanghai protocol, and reported this protocol in 68.4% of POR patients, resulting at least 1–6 embryos after double OS in the same cycle. Moreover, the obtained embryos have similar development potential. [11] Likewise, in the present study, 67% of the patients had at least 1–7 embryos after double OS in the same cycle. Recent evidence shows that folliculogenesis occurs in a wave-like model during the

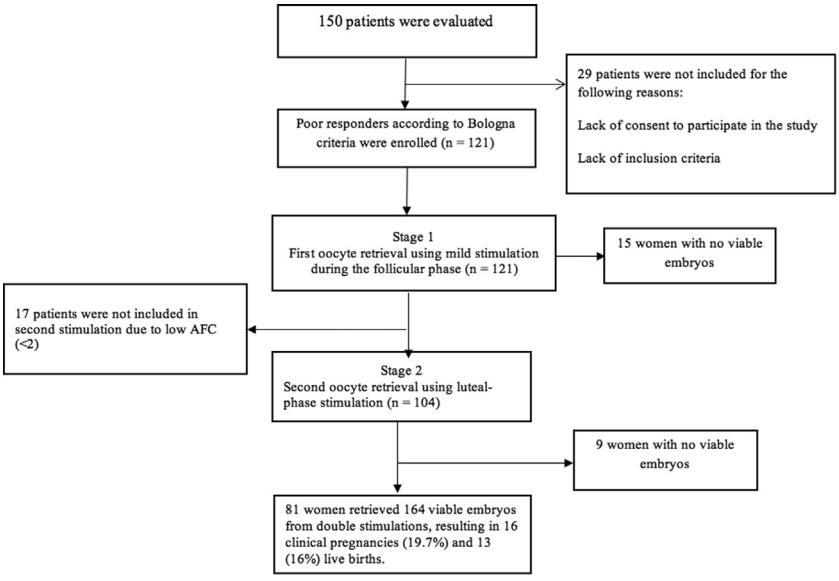

Fig. 2. The study flowchart.

Table 2
Comparison of the cycle characteristics between the first and second stimulations in patients with poor ovarian response (n = 81).

Variables	First stimulation	Second stimulation	P-value
Duration of stimulation day (mean ± SD)	8.0 ± 2.6	7.8 ± 2.8	0.6
Used HMG dose (IU)(mean ± SD)	343.5 ± 196.2	1726.8 ± 682.3	<0.001
No. of follicles < 14 mm on trigger day(mean ± SD)	0.50 ± 0.79	0.64 ± 1.06	0.2
No. of follicles 14-17 mm on trigger day(mean ± SD)	0.60 ± 0.91	0.82 ± 1.06	0.07
No. of follicles >17 mm on trigger day (mean ± SD)	1.23 ± 0.89	1.25 ± 0.83	0.8
Total number of retrieved oocytes (mean ± SD)	1.52 ± 1.16	1.50 ± 1.98	0.9
No. of MII oocytes (mean ± SD)	1.44 ± 1.04	1.20 ± 1.59	0.2
No. of MI oocytes (mean ± SD)	0. 02 ± 0.15	0.02 ± 0.15	0.9
Fertilization rate (mean ± SD)	0.69 ± 0.41	0.35 ± 0.45	<0.001
No. of frozen embryos (mean ± SD)	1.75 ± 0.99	0.85 ± 1.22	0.03
Cancelation rate n (%)	12 (9.9)	23(22.1)	0.1
No oocyte rate n (%)	13 (10.7)	17 (16.3)	0.05
No embryo rate n (%)	15 (12.4)	9 (8.6)	0.1

HMG, human menopausal gonadotropin, IU; international unit, MII; Metaphase II, MI; Metaphase I, No.; number, SD; standard deviation.

Table 3
Comparison of the outcomes of the previous and present cycles (Shanghai protocol) in the studied patients (n = 66).

Variables	Previous cycle Long agonist (n = 24)	Shanghai protocol (n = 24)	P-value	Previous cycle Antagonist (n = 22)	Shanghai protocol (n = 22)	P-value	Previous cycle Mini-flare (n = 20)	Shanghai protocol (n = 20)	P-value
Total No. of retrieved oocytes	2.9 ± 2.5	3.1 ± 2.7	0.7	2.1 ± 1.5	3.1 ± 2.4	0.1	2.5 ± 1.7	3.1 ± 3.1	0.6
No. of MII oocytes	2.6 ± 2.3	3.0 ± 2.0	0.6	1.7 ± 1.3	3.0 ± 2.3	0.06	2.0 ± 1.7	3.0 ± 3.3	0.4
No. of MI oocytes	0.5 ± 0.9	0.0 ± 0.0	0.02	0.3 ± 0.6	0.06 ± 0.2	0.1	0.2 ± 0.4	0.0 ± 0.0	0.1
Fertilization rate	0.4 ± 0.35	0.7 ± 0.3	0.001	0.4 ± 0.2	0.8 ± 0.3	0.004*	0.5 ± 0.4	0.62 ± 0.3	0.6
No. of cancelation	8(27.6%)	7 (24.1%)	0.36	5(27.8%)	3(16.7%)	0.3	1(8.3%)	0	0.9

* Significant difference, No.; number.

menstrual cycle; therefore, multiple follicular recruitment waves could occur in the same cycle. [15] By virtue of this fact, Shanghai protocol with two stimulation stages in the same cycle provides new opportunity for clinicians to manage women with diminished ovarian reserve (DOR). [2,15]

In the current protocol, both clomiphene citrate and LZ are used in the early follicular phase to increase ovarian response. Kaung et al. presumed that these drugs may have co-ordinated actions in concomitant use. [2] Clomiphene citrate acts to increase pituitary FSH secretion by reducing the negative oestrogen feedback; on the other hand, LZ blocks aromatization of androgens into oestrogens and releases the hypothalamic–pituitary axis from negative oestrogen feedback; consequently, the increase of intraovarian androgens could strengthen the primary follicle growth and improve IVF outcomes. [16] Recently, LZ has been suggested as a novel and effective adjuvant agent with GnRH antagonist for patients with POR. [16–19] Bastu et al. [19] in a randomized clinical trial evaluated the IVF outcomes after OS with different gonadotropins doses with or without LZ, and concluded that using a mild stimulation along with LZ was as effective as stimulation with higher doses of gonadotropins alone.

In the present study, the number of retrieved oocytes after the first stimulation (combination of clomiphene and LZ) and the second stimulation (LZ alone) did not have significant difference; however, higher fertilization rate was observed probably due to better quality of oocytes after the first stimulation. The cancelation rate (no response and no oocyte) in the present study was 28.5%, which is almost the same rate as reported by Kuang and colleagues (31.6%). However, in the present study, 14.9% of the patients were not undergone FET cycle due to lack of embryo formation.

In a recent study, Ubaldi et al. [20] evaluated forty-three DOR patients with an AMH level of <1.5 ng/mL, AFC < 6 follicles, and/or <5 oocytes retrieved in a previous cycle were evaluated. They found that double stimulation is successful for this cohort of patients, resulting in a similar number of MII phase oocytes after both follicular and luteal phase stimulations. It was concluded that this novel stimulation strategy provided opportunities to retrieve more oocytes and obtain more euploid blastocysts within a single menstrual cycle to be applied in the urgent situations. [20]

The limitation of the present study was that it was not designed as a randomized clinical trial with control group; therefore, we compared the outcomes of Shanghai protocol with the results of the previous OS cycle in each patient. The power of the study was not high in relation to the comparison between Shanghai protocol and the previous stimulation protocol due to the low sample size in the subgroups; however, to the best of authors' knowledge, it was the first study to make a comparison between new protocol and other standard OS protocols. It is argued that further studies with larger sample size are essential to confirm or disprove these findings. This prospective before-and- after trial is one of the limited studies for evaluation of new OS in POR patients who were diagnosed on the basis of Bologna criteria, so it can be the strength of the present study.

It is assumed that the collection of oocytes from several consecutive OS cycles and the consideration of FET programs in POR patients may be associated with better outcomes [21]. However, these procedures are exhausting, and highly dependent on the individual clinics' success rates for FET program. Shanghai protocol would provide the acceptable option with a more time-efficient and less expensive treatment regime for POR patients. Since the type of stimulation in both stages was mild, it seems that this new therapeutic strategy is appropriate and patient-friendly for the target groups. However, some data have shown that the cumulative pregnancy rates for milder protocols are equivalent over time as compared to conventional pregnancy rates; on the other hand, since the mild approach require more IVF cycles, it is not clear if mild stimulation IVF is cost-effective or not. [22] Therefore, our results are in preliminary phase and further studies

are required with emphasis upon the comparison of its cost-effectiveness with that of other standard OS protocols in POR patients.

Disclosure

The authors have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgments

We extend thanks to our colleagues in Royan Institute and all the women participated in this survey.

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