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Research article

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A Randomized Controlled Trial Comparing Medroxyprogesterone Acetate Versus Gnrh Antagonist In Oocyte Donor/Intracytoplasmic Sperm Injection Cycles

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Abstract

Objective: *This study compared the efficacy of medroxyprogesterone acetate (MPA) in the oocyte donation cycles to the GnRH antagonist protocol in the prevention of premature LH surge.*

Methods: *This single-blind randomized controlled trial study was performed on 185 oocyte donors between August 2019 and May 2020. Participants were randomized into two groups 91 patients in GnRH antagonist (group A) and 94 patients in MPA (group B). The LH, estradiol, and progesterone blood levels on the day of triggering, the number of dominant follicles, retrieved oocytes, metaphase II (MII) oocytes, embryos, transferred embryos, and clinical pregnancy and live birth were recorded.*

Results: *This study showed that LH levels on the day of triggering had statistically significant differences [0.7 (0.5, 1.15) and 0.99 (0.2, 1.81)] in groups A and B, respectively, (P=0.004), However, this difference was not clinically significant. There were no significant differences in the number of MII oocytes and embryos, clinical pregnancy, and live birth rates*

(P>0.05) between groups.

Conclusions: *This study showed that to prevent premature LH surge, GnRH antagonist could be replaced by MPA as oral medication which is more cost-effective and feasible for patients with a comparable number of MII oocytes, embryos, clinical pregnancy, and live birth rates.*

Trail registration: *IRCT20081007001306N10*

Keywords: Ivf, Medroxyprogesterone Acetate, GnRH Antagonist, Oocyte Donation, Controlled Ovarian Stimulation

1. Introduction

Controlled ovarian stimulation (COS) involves the administration of exogenous gonadotropins to recruit multiple ovarian follicles for IVF/intracytoplasmic sperm injection (ICSI) cycles [1]. The GnRH agonist and antagonist protocols are well-established methods for COS among patients who undergoing IVF. The best COS protocol for IVF is widely debated in the literature, and the optimal protocol remains controversial [2]. The GnRH antagonist acts with rapid suppression in gonadotropin concentrations and can effectively prevent the surge of LH and premature ovulation [3]. Recently, the use of progestins for pituitary suppression has been promoted because progesterone inhibits the LH surge [4].

In some studies, it has been demonstrated that the use of medroxyprogesterone acetate (MPA) for ovulation suppression results in effective ovulation suppression with similar outcomes such as cycle cancellation rates, oocyte quality and quantity, fertilization rate, cleavage rate, blastocyst quality, and pregnancy rate [5]. However, premature progesterone exposure has adverse effects on the endometrium; so, progestin cycles require freeze-all cycles and a subsequent frozen-thawed embryo transfer (FET). The oral administration of natural micronized progesterone, MPA, or dydrogesterone in the follicular phase, from the beginning of COS, has been used as an effective alternative to conventional protocols for preventing premature LH surge and OHSS, with similar results [5-7].

This new approach which is referred to as progestin-primed ovarian stimulation, has been successfully used in a wide range of patients such as polycystic ovary syndrome (PCOS), endometriosis, and poor responders [5,8-10]. Recent studies showed that MPA enabled successful pituitary suppression in oocyte donors and yielded similar clinical and embryological outcomes compared with the GnRH antagonists. This approach has lower costs [11-13].

On the other hand, in one study reproductive outcomes were lower with MPA than with GnRH antagonists including biochemical, clinical, and ongoing pregnancy rates. Although the live birth rate was not significantly different between groups [11].

The current standard method for ovarian stimulation in ICSI cycles is using GnRH agonist and antagonist. Progestins have an inhibitory effect on LH surge and there are not enough studies in this field to introduce them as a standard method in ART cycles. So, this study was performed to assess the reproductive outcomes of MPA as an oral alternative to GnRH antagonist for COS in oocyte donors.

2. Materials and Methods

2.1 Study Population

This single-blind randomized controlled trial study (IRCT20081007001306N10) was conducted on overall 226 oocyte donors referred to university and private infertility clinics, in Rasht, Iran, between August 2019 and May 2020. This study was evaluated and approved by the ethics committee of Guilan University of Medical Science, Rasht, Iran (approval code: IR.GUMS.REC.1398.148). Before enrollment, all participants were given written informed consent.

The study population consisted of all patients referred to university and private infertility clinics to donate/receive oocytes from day 1 to 3 menstrual cycles. Inclusion criteria for oocyte donors were age 18-35 years old, regular menstrual cycles (intervals 25-35 days), more than 5 and less than 12 antral follicle count (AFC), FSH level below 10 IU/L healthy ovaries without cysts and endometriosis, body mass index (BMI) in the normal range (18-25) and absence of any uncontrolled endocrine diseases. Inclusion criteria for oocyte recipients were age under 50 years old who were candidates for receiving eggs due to lack of suitable eggs, absence of any systemic diseases including hypertension, diabetes, renal and liver dysfunctions, with normal anatomy of the uterus. Oocyte donors with a lack of growth of at least three mature follicles at the time of triggering, and oocyte recipients with improper endometrial growth (≤7 mm thickness, and homogeneous pattern) were excluded from the study.

LH, estradiol, and progesterone levels on the day of triggering, number of dominant follicles, retrieved oocytes, metaphase II (MII) oocytes, total embryos, transferred embryos, and clinical pregnancy, live birth, and OHSS rates were recorded.

2.2 Randomization

Participants were randomized in a 1:1 ratio into two groups: 94 patients in GnRH antagonist (group A) and 94 patients in MPA (group B). Randomization was performed before the start of the study by random allocation software. Each of them was placed in a separate envelope according to the list obtained from the software closed in it and given to the third person. In group A, 3 patients

did not receive the allocated intervention. Also, it should be noted that random allocation was performed in donor but not in recipient groups.

2.3 Drug Regimens

The participant on the day of 1-3 of the menstrual cycle had a transvaginal ultrasound. In the absence of ovarian cysts larger than 12 mm, the COS was started for oocyte donors by daily administration of r-hFSH 225 units (Gonal F, Merck, Germany). Then they underwent serial ultrasound assessment from day 5 of stimulation. In the second half of the stimulation cycle [Follitropin alpha/Nortropin alpha 150/75 IU (Pergoveris Merck, Serono, Germany)] was added and the dose of r-hFSH decreased by 150 IU based on ovarian and hormonal response. When at least three dominant follicles (17-20 mm) were observed, the patient was administrated 0.2 mg triptorelin (Decapeptyl, Merck, Germany) subcutaneously, and 35-38 hours later, the follicles were punctured under ultrasound guidance. We used GnRH agonist for triggering which was safer than HCG for preventing OHSS. LH, E2, and progesterone levels were checked serially if needed and on the day of triggering.

In the GnRH antagonist group, Cetrorelix 0.2 mg (Merck, Germany), started with one subcutaneous injection daily when the diameter of follicles reached to 13 to 14 mm and continued until the day of the triggering. In the MPA group two tablets (5 mg, Aburaihan pharmaceutical company, Iran), were taken daily from the day of gonadotropins injection up to the triggering day.

In oocyte recipients, on the second or third day of a spontaneous or induced menstrual cycle, Estradiol Valerate tablet 2 mg three times daily (Aburaihan Pharmaceutical Company, Iran) started. Ultrasound assessment for endometrial growth monitoring was performed on days 12 to 14 after starting the drug. When the endometrium reached the proper state (≥7 mm thickness, and trilaminar pattern), the suppository progesterone twice daily (Fertigest, 400 mg, Aburaihan pharmaceutical company, Iran) was started for the recipients for luteal phase support. If the endometrial thickness and pattern were not appropriate, the recipient was eliminated from the study.

2.4 Oocyte Injection and Embryo Transfer

After denudation by mechanical pipetting (Kitazato, Japan), the MII oocytes were prepared for insemination by ICSI. Sperm selection was performed by the swim-up method. Injected oocytes were checked for fertilization 18-20 hours post-ICSI. The fertilized oocytes were cultured for 2-3 days (Life Global, USA). Morphological embryo assessment was done on day 2 and day 3 of insemination and a score has been given to them based on the Istanbul consensus workshop on embryo assessment [14]. The embryos (days 2-3) were transferred to recipients. The recipient medications (estradiol and progesterone) were also continued. If the recipient was not ready for embryo transfer for any reason in the same cycle, the embryos were frozen and transferred in a freeze-thawed cycle. If the β-HCG was positive after about two weeks of embryo transfer, an ultrasound was done about 2-3 weeks later to detect viable pregnancy. Reproductive outcomes of the first ET for recipients were recorded.

2.5 Outcomes Definition

The primary outcome was the number of collected MII oocytes. Secondary outcomes were the total gonadotropins dose, number of follicles, total number of embryos, number of transferred embryos, fertilization, clinical pregnancy, and live birth rates as well as the OHSS rate.

2.6 Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences for Windows (SPSS, version 22.0) software. The normal distribution of quantitative variables was investigated using the Kolmogorov-Smirnov test. Median (IQR) was used to describe quantitative variables with abnormal distribution. Qualitative variables were also defined based on numbers and percentages. Then, to compare the two treatment groups (medroxyprogesterone 10 mg recipient and GnRH antagonist), chi-square and the nonparametric Mann-Whitney equivalent were used. The significance level of the tests was considered $p < 0.05$. Also, analysis was performed based on "intention to treat."

3. Results

In this study, 185 eligible oocyte donors/recipients were included. These patients were referred to university and private infertility clinics from day 1 to 3 of the menstrual cycle and were randomized into two groups. The participant's details are presented in Figure 1.

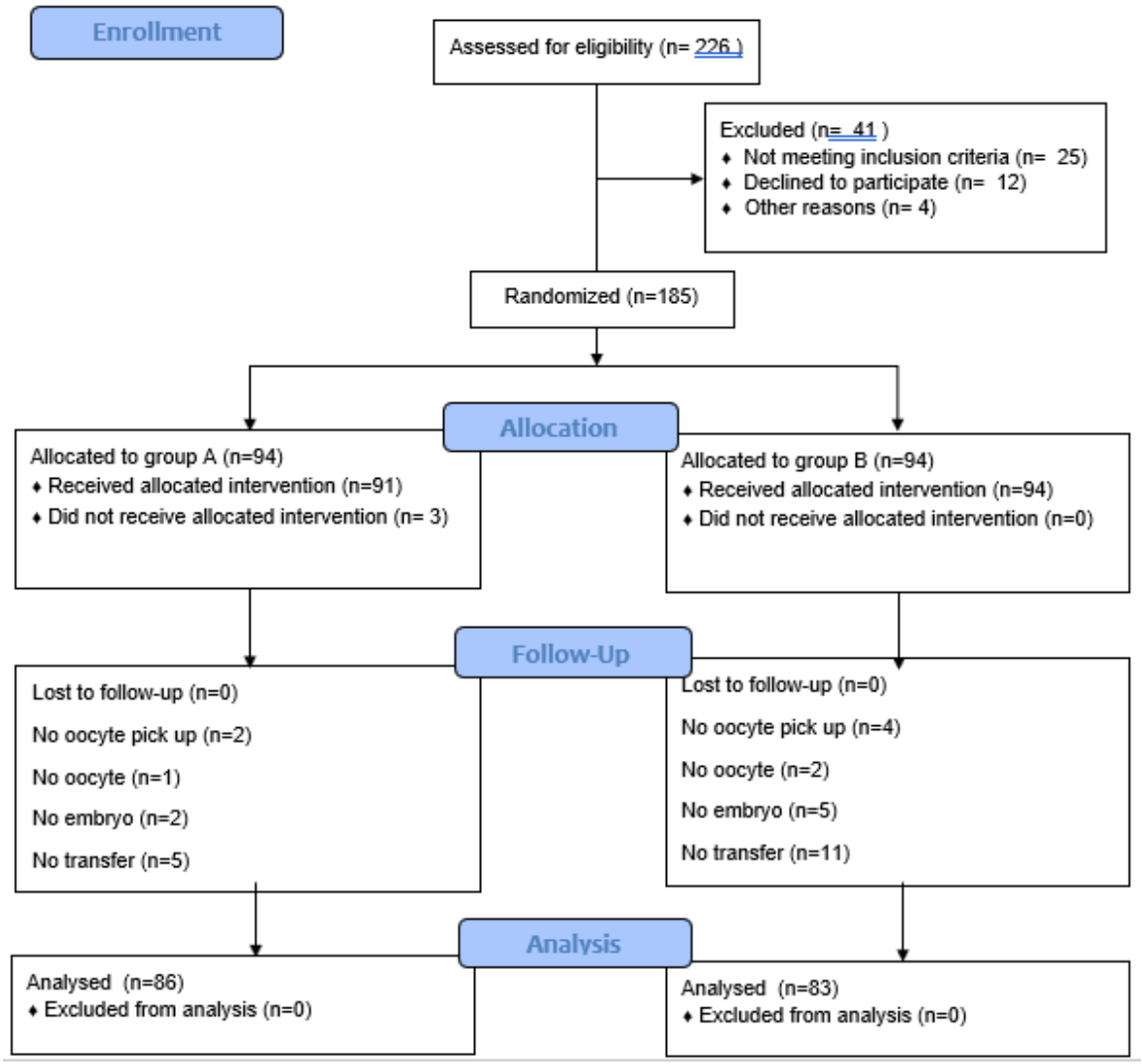

Figure 1: Consort flowchart

Demographic and cycle characteristics of the oocyte donor group based on the two stimulation regimens have been presented in Table 1. There was no significant difference in terms of age (P=0.285) between the groups.

Variables	Group A: Cetrorelix (n=91)	Group B: MPA (n=94)	Statistic	p-value
Age (year) [a]	28 (26, 30)	29 (22, 32)	1.070	0.285
Total gonadotropin dose (IU) [a]	2087.5 (1931.5, 2243.5)	2222.2 (2134.9, 2309.5)	1.891	0.059
Progesterone level on the day of triggering (ng/mg) [a]	1.1 (0.80, 1.57)	1.01 (0.73, 1.30)	0.861	0.389
Estradiol level on the day of triggering (ng/mg) [a]	2500 (1299.0, 3705.0)	2071 (1241.75, 2902.75)	1.555	0.120
LH level on the day of triggering (IU/L) [a]	0.7 (0.5, 1.15)	0.99 (0.2, 1.81)	2.891	0.004
No. of follicles [a]	12.0 (8.25, 20)	12.5 (9.25, 16)	0.052	0.958
No. of oocytes [a]	10.0 (7.0, 16.0)	10.0 (7.0, 14.0)	0.788	0.430
No. of MII oocytes [a]	8.5 (5, 14)	8 (5, 11)	1.135	0.256
No. of the embryos [a]	6 (3, 10)	5 (3, 8)	-1.625	0.104
Fertilization rate [b]	55(53.4)	39(40.6)	3.253	0.071
OHSS rate [b]	0 (0.0)	0(0.0)	-	-

Table 1: Demographic and cycle characteristics of the oocyte donors based on the two stimulation regimens.

According to the Mann-Whitney test results, the median LH level demonstrated a significant difference [0.7 (0.5, 1.15) and 0.99 (0.2, 1.81)], in groups A and B, respectively, (P=0.004). However, there were no significant differences in the median progesterone level, estradiol level, total gonadotropins dose, number of follicles, total number of retrieved oocytes, MII oocytes, number of embryos, and fertilization rate between groups. No OHSS cases have been seen in groups.

Demographic and cycle characteristics of the oocyte recipient's group based on the two stimulation regimens, have been presented in Table 2. There was no significant difference in terms of age (P=0.355) between groups.

Outcome		Group A: Cetrorelix (n=91)	Group B: MPA (n=94)	statistic	p-value
Age (year)[a]		41 (32.0, 45.0)	39.0 (34.25, 44)	-0.925	0.355
No. of transfered embryos [a]		3 (2, 3)	2 (2, 3)	-1.491	0.136
Type of embryo transfer [b]	freeze	35(38.4)	28(29.7)	1.117	0.613
	fresh	51(56.0)	65(69.1)		
	No transfer	5(5.4)	11(11.7)		
Implantation rate [b]		46(44.7)	34(35.4)	1.766	0.184
Clinical pregnancy rate [b]		36 (36.7)	31 (32.0)	0.493	0.483
Live birth rate [b]		31(31.6)	28(28.9)	0.177	0.674
Miscarriage rate [b]		5(13.8)	3(9.67)	0.284	0.716
[a] Median (min, max), [b] number (percentage) of variables have been used.					

Table 2: Demographic and cycle characteristics of the recipient based on the two stimulation regimens.

Due to the abnormal distribution of data, a nonparametric Mann-Whitney test was used to examine the differences between groups A and B. There were no significant differences between groups in implantation, number of transferred embryos, clinical pregnancy, live birth, and miscarriage rates (P>0.05). There was no statistically significant difference in the number of patients who underwent fresh or frozen-thawed embryo transfer between groups (P= 0.613).

4. Discussion

The finding of this study showed that MPA & GnRH antagonists had similar efficacy in oocyte donor/ICSI cycles regarding embryological and clinical outcomes. Serum LH levels on the triggering day were 0.99Iu/L in the MPA group and 0.7IU/L in the cetrorelix group and although a statistically significant difference between the two groups was observed, the difference was not clinically significant, because serum LH levels on the triggering day were lower than basal LH levels in both groups [15].

Animal model studies showed that progestins suppress GnRH surge by progesterone receptors in the hypothalamus, also progestins can block the stimulatory effect of estradiol on GnRH pulse frequency [4,16]. It has been demonstrated that the effect of progesterone is mediated by the progesterone nuclear receptors [17]. Endogenous opioid peptides (EOPs), progesterone receptor membrane component 1 (PgRMC1), and periventricular preoptic area (pePOA) neurons are involved in progesterone negative feedback on pulsatile GnRH secretion certain factors. Although, the exact mechanism remains unexplored [18-20].

Progesterone, as a major inhibitory factor in the luteal phase of the ovarian cycle, inhibits GnRH and LH secretion. This inhibition is critical for the regulation of follicular development in the ovary and maintaining the length of the luteal phase [21].

There are many protocols for COS in ICSI. One of them is luteal phase stimulation in patients who need urgent ovum pick up such as cancer patients. The data of this protocol showed that high progesterone levels in the luteal phase can inhibit LH surge. Compared to conventional COS there was similar oocyte quality and euploidy, and implantation rate [8,22]. So, there was no detrimental effect of progesterone exposure on oocytes. The current standard method for LH suppression in COS is the GnRH analog. Several studies are comparing GnRH analogs with different progestin at varying dosages and protocols in the cycles. Most of them showed no significant difference in outcomes [12,13,23].

In our study in agreement with some previous studies performed on ICSI patients, the number of MII oocytes and embryos, the fertilization, implantation, clinical, and liver birth rates were similar between groups.

Two previous retrospective studies reported no differences between the MPA and antagonist groups in terms of reproductive outcomes [12,23]. In Yildiz et al. study, duration of stimulation, total gonadotropin consumption, and pituitary suppression, were similar in the two groups and there was no premature ovulation in any group. The flexible progestin-primed ovarian stimulation (fPPOS) method yielded a significantly higher number of cumulus-oocyte complexes than GnRH antagonist cycles and fPPOS generated

significantly more metaphase II oocytes than GnRH antagonist cycles. In addition, cleavage, blastulation, implantation, and live birth/ongoing pregnancy rates were similar in both groups MPA enabled successful pituitary suppression in oocyte donors and yielded similar clinical and embryological outcomes compared with the GnRH antagonists. This approach prevents the need for injecting a GnRH antagonist, so, it is a patient-friendly approach and can significantly reduce the economic burden of the patients. They recommended that further studies are needed to confirm these findings, in patients in different populations [12,23].

Martínez et al. demonstrated that on the day of trigger, progesterone was lower in progesterone-primed [PP] compared to GnRH antagonist (antGnRH), whereas no significant differences existed in estradiol or LH. Also, no differences were observed in the number of retrieved oocytes, and clinical pregnancies among recipients [23]. In their study, the total dose of recombinant follicle-stimulating hormone, duration of ovarian stimulation, endocrine profiles of the serum and follicular fluids, and the number of oocytes retrieved were comparable in the MPA and antagonist groups. No statistically significant differences concerning implantation, clinical pregnancy, ongoing pregnancy, live birth, and cumulative live birth rate were observed between the groups. Therefore, they recommended MPA for ovarian stimulation in oocyte donation because it permits a more patient-friendly approach [13].

In our study, also there was no significant difference in terms of total gonadotropin dose (IU) in the two groups of study, and donors were all triggered with GnRH agonist (triptorelin).

There are some reports of the adverse effect of elevated progesterone on oocyte quality, while Lu et al., reported that elevated progesterone levels on triggering day do not hurt outcomes [24-26]. In the study of Martínez et al., on the day after trigger, lower progesterone in desogestrel (DSG) (PP) vs. GnRH antagonist (antGnRH) groups was observed. They hypothesized that the lower serum progesterone observed in the PP group could be related to the prolonged and profound LH suppressive effect of DSG [23]. In our study, serum progesterone levels on the day of triggering were not significantly different between the two groups. Similarly, our finding could be related to the LH suppressive effect of MPA.

Beguería et al (2019) compared MPA and GnRH antagonist protocols. The patients received MPA 10 mg from the first day of stimulation or Ganirelix acetate from the first 7th day of stimulation up to the triggering day with Triptorelin acetate in the doner cycles. Both groups had a similar dosage of gonadotropins and a similar number of MII oocytes, but the clinical pregnancy rate was significantly lower in the MPA group (P=0.006). However, there was no statistically significant difference between the two groups in live birth rate (P=0.10) [11]. In their study, there was no randomization of recipients and there were maybe some differences in prognostic factors for pregnancy between them. These differences can affect the results.

Our study findings did not show a negative effect of MPA on oocyte quality and embryo development. However, the limitation of the present study was that the RCT protocol could not be blinded because of the different administration routes of drugs in the two groups of the study. Another limitation was that we could not randomize recipients. Although there were no significant differences in demographic and cycle characteristics between the two groups. Also, in our study, the donor and recipient were not the same, and due to the possible adverse effects of progesterone on the endometrium, this method could only be used by frozen cycles in patients who want their oocytes.

Conclusions

The findings of this study suggested that GnRH antagonists can be replaced with MPA in COS in ICSI cycles. Similar pregnancy rates showed that the embryos resulting from the two stimulation regimens had the same developmental potential. In addition, the use of MPA is patient-friendly, easier, and more affordable than GnRH antagonists. However, further studies are needed to confirm the results of the present study.

Author Contributions

Ziba Zahiri Sorouri, Roya Kabodmehri was responsible for study design and advice on manuscript structure and content. Zahra Hamidi Madani, Farnoush Farzi, Ahmad Hosseini, Mohammad Hadi Bahadori, and Elham Askari were all closely involved in the data collection. Ziba Zahiri Sorouri, Saeed Alborzi responsible for original manuscript revising. Nasrin Ghanami Gashti is responsible for original manuscript drafting, revising, and final submission. Maryam Ghalandari was responsible for statistical testing and analysis. All authors discussed the results and contributed to the final manuscript.

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