BJFS Bangladesh Journal of Fertility & Sterility

Bangladesh J Fertil Steril, 2021;Vol.1(2):84-87 Original Article

Medroxyprogesterone Acetate Versus GnRH Antagonist for Prevention of Premature Luteinizing Hormone Surge in Primary and Secondary Infertility Patients Undergoing IVF/ICSI Cycles: A Multicentric Study

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Abstract

Background: We conducted a comparative study to evaluate the use of medroxyprogesterone acetate (MPA) and gonadotropin-releasing hormone (GnRH) antagonists in the prevention of prematureluteinizing hormone (LH) surge in patients undergoing *in-vitro* fertilization (IVF).

Materials and Methods: This was a retrospective, multicentric, comparative study where data related to 300 women who underwent GnRH antagonists therapy or MPA therapy as a part of infertility treatment was compared. The primary outcome was a comparison of the incidence of premature LH surge. The secondary outcomes included the number of mature oocytes and viable embryos obtained, and clinical pregnancy from frozen-thawed embryo transfer (FET) cycle. SPSS 16.0 software was used for statistical analysis. A p-value <0.05 was considered statistically significant.

Results: Incidence of premature LH surge was absent, as LH suppression was consistently maintained in both groups. The number of oocytes retrieved was comparable in both groups. The number of mature oocytes was significantly higher in the MPA group. The number and grading of the embryos obtained were statistically insignificant.

Conclusion: Medroxyprogesterone acetate, when used along with a stimulation protocol, seems a better alternative to GnRH antagonists for the prevention of premature LH surge. It yielded a higher number of mature oocytes, thus resulting in good-quality embryos and reduced overall cost. Moreover, MPA has the advantage of oral administration, which is preferred compared to GnRH antagonist injections.

Keywords: Medroxyprogesterone acetate, GnRH antagonist, mature oocytes.

Introduction

The prevalence of infertility is reported to be 10%–15% in couples of reproductive age.[1] One of the common reason for infertility in females is tubal abnormalities, such as congenital or acquired damage to the fallopian tube and infections.[2] On the other hand, polycystic ovarian syndrome (PCOS) is one of the common ovarian factors responsible for primary or secondary infertility.[3] With advancements in assisted reproductive technology (ART), many couples with primary or secondary infertility can conceive successfully.[4] Common methods of stimulating the ovaries include administration of exogenous gonadotropins and administration of gonadotropin-releasing hormone (GnRH) antagonist such as cetrorelix.[5] Controlled ovarian stimulation is one of the most important as well as crucial steps in this context.[6] However, premature surge of luteinizing hormone (LH) during this process can lead to cycle cancellation. Numerous methods have been tried to address this concern including desensitization by GnRH agonists, which could increase follicular synchronization along with rapid and reversible LH suppression. However, the need for higher dosages and longer duration of treatment is associated with higher medication costs along with the risk of ovarian hyperstimulation syndrome (OHSS).[7]

Medroxyprogesterone acetate (MPA) has been suggested as an alternative approach owing to the ease of use, lower cost, and easy availability. Further, the oral form of MPA is considered to have better acceptance compared to GnRH injections. However, concerns about the need for embryo freezing and embryo transferring during next cycles do exist.[7]

Therefore, this study was conducted to assess the benefits of MPA in comparison to GnRH agonists in terms of LH surge

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Date of Submission: 14-04-2021 | Date of Acceptance: 25-05-2021

prevention, number of mature oocytes and viable embryos obtained, and clinical pregnancy from frozen-thawed embryo transfer (FET) cycle, among women undergoing in-vitro fertilization (IVF).

Materials and Methods

This was a retrospective, comparative study where data related to patients who underwent treatment for infertility at two centers over a period of one year were screened to compare the outcomes of MPA and GnRH agonist therapy. Data related to infertile women aged 25–30 years with primary or secondary infertility, antral follicle count (AFC) of 8–10, and anti-Müllerian hormone (AMH) level of 2–3.2 ng/mL, were included in the study. The exclusion criteria were as follows: evidence of ovarian failure, follicular antral count <8, patients with endometriosis, patients with polycystic ovaries, severe male factors for infertility, and severe congenital uterine anomalies excluding the possibility of embryo transfer.

Following a detailed evaluation, data related to 150 patients who had received GnRH antagonists and a same number of patients who received MPA therapy (total 300 patients) were included in this study. Details related to estradiol (E2), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and progesterone (P4) levels before treatment initiation and during followup were evaluated. The data of the patients was categorized into two groups (A and B) based on the treatment followed.

Patients who had received GnRH antagonist were categorized as Group A. They had received cetrorelix 0.25 mg daily when the follicular diameter reached 14 mm (variable protocol). Stimulation was started with recombinant FSH at a dose of 150 IU to 225 IU based on AMH and AFC levels. Follicular monitoring was initiated on the fifth day following stimulation using transvaginal ultrasound and had been repeated every alternate day. Trigger was given with recombinant hCG 250 IU when the leading follicles reached 18–20 mm.

Patients who received MPA were categorized into Group B. These patients had received MPA 10 mg once a day on the second day of the cycle. It was started from day 2 of menses at a dose of 10 mg twice daily, till day of trigger. The stimulation drug used was recombinant FSH 150–225 IU, according to AMH and AFC levels. Follicular monitoring was started on the fifth day of stimulation using transvaginal ultrasound and had been repeated every alternate day. The trigger was given with recombinant hCG 250 IU when the leading follicles reached 18–20 mm. The Cummins criteria[8] were used for the evaluation of embryos.

The primary outcome was a comparison of the incidence of premature LH surge between both groups. The secondary outcomes included, the number of mature oocytes and viable embryos obtained, and the number of clinical pregnancies from frozen-thawed embryo transfer (FET) cycle.

Parameters evaluated included the number of blastomeres, the regularity of blastomeres, and embryonic fragmentation grade. Suitable embryos (8-cell grades 1 and 2) were frozen using the vitrification mechanism. The number of oocytes retrieved, the number of mature oocytes, and the number of viable embryos were compared between the two groups. Endometrial preparation had been carried out in a similar manner in both the groups for the FET cycle. On day 2 of menstruation, both groups were started on 6 mg E2, which was continued till the endometrial thickness was >7 mm. This was followed by the daily administration of progesterone (100 mg/IM [intramuscular]) for six days, and embryos in the blastocyst stage were transferred. Cetrorelix was administered when the follicular diameter reached 14 mm (variable protocol). Estradiol and P4 had been continued until 12 weeks of pregnancy.

SPSS 16.0 software was used for statistical analysis. A p-value <0.05 was considered statistically significant. Microsoft Office was used for the preparation of charts and graphs.

Results

A total of 300 patients were included in this study. The patient demographics including age, body mass index (BMI), and duration of infertility is given in table 1. There was no significant difference between the mean age in both groups (27.12 ± 1.12 years vs. 27.32 ± 1.64 years; p=0.128).

Table 1 Demographics of the study subjects

Parameter	Group A	Group B	P value
Age (years), Mean±SD	27.12 ± 1.12	27.32 ± 1.64	0.218
BMI (kg/m^2), Mean±SD	24.12 ± 3.48	23.78 ± 2.98	0.364
Duration of infertility, years (Mean±SD)	6.88 ± 0.74	7.02 ± 0.92	0.147

The mean BMI of both groups was found to be comparable with no statistically significant difference. The minimum duration of infertility was 16 months while the maximum duration was eight years and three months. The mean duration of infertility was comparable in both groups, with no statistically significant differences noted between the groups (p=0.147).

As shown in Figure 1, in Group A, out of 150 patients, three patients had >3 previous IVF failures, whereas one or two and no previous IVF failures were seen in 58 and 89 patients, respectively. Similarly, in Group B, out of 150 patients five patients had >3 previous IVF failures, whereas one or two and no previous IVF failures were seen in 35 and 110 patients, respectively.

In Group A, out of 150 cases, 112 (74.66%) cases were of primary infertility, whereas 38 (25.33%) cases were of secondary infertility. In Group B, 122 cases (81.33%) were of primary infertility, while the remaining 28 (18.66%) were of secondary infertility (Figure 2).

After treatment, the number of oocytes retrieved, the number of mature oocytes, and the number of viable embryos were compared between the two groups. Analysis of oocytes above the size of 15 mm showed that, in Group A, the number of mean mature oocytes was 11.92 ± 0.98, whereas

in Group B, the number of mean mature oocytes was 14.02 ± 0.74 (Table 2). The mean number of mature oocytes was found to be higher in Group B, and the difference was found to be statistically significant (p<0.0001).

Table 2 Comparison of cycle characteristics of controlled ovarian stimulation between both groups

Parameter	Group A	Group B	P value
Number of mature oocytes, Mean±SD	11.92 ± 0.98	14.02 ± 0.74	<0.0001
Number of retrieved oocytes, Mean±SD	8.98 ± 0.78	9.12 ± 0.81	0.128
Number of embryos Mean±SD	5.98 ± 0.68	6.14 ± 0.70	0.45

Statistically significant

There was no statistically significant difference noted in the number of retrieved oocytes and embryos between both groups (Table 2).

Estimation of serum LH at the time of trigger showed that the mean serum LH in Group A was 1.42 ± 0.38, whereas in Group B, the mean serum LH was 1.72 ± 0.46 (Table 3). The mean LH in both groups was comparable, and the difference was not significant (p=0.10).

Furthermore, the gonadotropin required in both groups was evaluated (Table 3); in Group A, the mean amount of gonadotropin required was 1370 ± 88 IU, whereas in Group B, it was 1354 ± 76 IU. There was no statistically significant difference in the gonadotropin requirement between both groups (p=0.09).

Table 3 Serum LH at the time of trigger and gonadotropin requirement

Parameter	Group A	Group B	p-value
Serum LH, Mean±SD	1.42 ± 0.38	1.72 ± 0.46	0.10
Gonadotropin requirement, Mean±SD	1370 ± 88	1354 ± 76	0.09

Analysis of the clinical pregnancy rate revealed that, in Group A, out of 150 patients, 56 patients (37.33%) conceived. In Group B, the percentage of clinical pregnancy was 30.66% (Figure 3). The clinical pregnancy rate was comparable in both groups with no statistically significant difference (p=0.27).

Discussion

This comparative study was undertaken to compare the use of MPA and GnRH antagonists for the prevention of premature LH surge in patients undergoing IVF with stimulation protocol. The patients were divided into two groups, depending on whether they had received GnRH antagonist or MPA (Groups A and B, respectively). The number of oocytes was found to be comparable in both groups. Mature oocytes were found to be higher in Group B, which was statistically significant (p<0.0001). The number of retrieved oocytes, and the mean number of embryos, was found to be comparable in both groups, and there was no statistically significant difference in any of these parameters in both studied groups.

Hamdi *et al.* conducted a prospective controlled study to investigate the role of MPA in the prevention of LH surge during controlled ovarian hyperstimulation. Characteristics of the cycle and pregnancy outcomes were compared in subsequent FET cycles. The authors found that the number of oocytes retrieved in both the case and control groups was equal. Luteinizing hormone suppression persisted during ovarian stimulation in the case group, and there was no incidence of premature LH surge. There was no significant difference between the number of follicles, mature follicles, oocytes resumed, and obtained embryos between the two groups. Based on these findings, the authors concluded that MPA as an oral drug is effective for the prevention of premature LH surge.[7] Similar effectiveness has been reported by Wikstrom *et al.*[9] and Zhu *et al.* for MPA.[10]

Kuang *et al*. conducted a prospective controlled study to investigate the use of MPA to prevent LH surge during controlled ovarian hyperstimulation and to compare cycle characteristics and pregnancy outcomes in FET cycles. In the study group, human menopausal gonadotropin (hMG) and MPA were administered simultaneously beginning on cycle day 3. Ovulation was induced with a GnRH agonist or co-triggered by a GnRH agonist and hCG when dominant follicles matured. A short protocol was used in the control group. Viable embryos were cryopreserved for later transfer in both protocols. The authors found that the number of oocytes retrieved in the study group was similar to that in controls (9.9 ± 6.7 vs. 9.0 ± 6.0), and therefore, higher doses of hMG were administered to the study group. In the study group, LH suppression persisted during ovarian stimulation, and the incidence of premature LH surge was 0.7% (1/150). No statistically significant differences were found in the clinical pregnancy rates (47.8% vs. 43.3%), implantation rates (31.9% vs. 27.7%), and live birth rates (42.6% vs. 35.5%) between the study group and controls. The authors concluded that MPA is an effective oral alternative to GnRH agonists for the prevention of premature LH surge.[11]

The structure of MPA is similar to that of the naturally occurring progesterone. It binds to the progesterone receptor located in the hypothalamus, female reproductive tract, and the pituitary, and inhibits the secretion of GnRH. Medroxyprogesterone acetate blunts the midcycle LH surge by decreasing the frequency of GnRH release.[12] It has been reported that MPA has moderate to strong progestin action with fewer androgenic properties and does not interfere with endogenous progestin production.[11] While embryo freezing is necessary in progesterone treatment, patients often request for embryo freezing due to occupational or familial reasons. Further, progesterone therapy was considered advantageous in patients with inappropriate conditions of the endometrium and oocyst donation.[7] Hence, the need and the cost associated for embryo freezing cannot be

considered as a hindrance for adopting this protocol.

Dong *et al.* conducted a study to investigate the clinical outcomes and endocrinological characteristics of progestin-primed ovarian stimulation (PPOS) using MPA 4 mg vs. 10 mg daily in infertile women with normal ovarian reserve. Ovulation was induced with hCG (1000 IU) and co-triggered by GnRH agonist (0.1 mg) after the maturation of the dominant follicles. Viable embryos were cryopreserved for later FET cycles in both groups. The authors found that the number of oocytes retrieved, and viable embryos was similar between the two groups (9.8 ± 6.3 vs. 9.6±5.9; 4.2 ± 2.6 vs. 3.7±3.0; p>0.05). No significant difference was found in the clinical pregnancy rate (58.0% vs. 48.7%) and live birth rate per participant (48.7% vs. 42.0%) (p>0.05).[13] One of the main advantages of MPA is that it can be administered orally and has better patient compliance.[11] The other advantages, as reported in various studies, include better control of the LH level and lower risk of ovarian hyperstimulation syndrome. Guo *et al.* reported that MPA might be a better choice in women with endometriosis undergoing controlled ovarian hyperstimulation for IVF.[14] The outcomes noted in the current study are in line with those noted in other studies. The study group consisted of young women who may not ovulate early. This may be considered as one of the limitations of the study. Further studies to evaluate the benefits in older age group are required to substantiate the benefits noted in the current study.

Conclusion

Medroxyprogesterone acetate, when used in ovarian stimulation protocol, is a good alternative to GnRH antagonist. It yields a good number of mature oocytes—leading to good-quality embryos, hence reducing the cost and dose of gonadotropins required. When used in carefully selected patients, the outcomes are comparable to any standard gonadotropin stimulation cycle.

Acknowledgements: We would like to thank BioQuest Solutions for Editorial support

Source of Fund: Nil

Conflict of Interest: None

How to cite this article: Kale RA, Kale AA. Medroxyprogesterone Acetate Versus GnRH Antagonist for Prevention of Premature Luteinizing Hormone Surge in Primary and Secondary Infertility Patients Undergoing IVF/ICSI Cycles: A Multicentric Study. *Bangladesh J Fertil Steril*; 2021;1(2): 84-87

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