Repeated application of luteal phase oestradiol/GnRH antagonist priming increases IVF success for poor ovarian reserve patients

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ABSTRACT
We aimed to compare repeated LPP (luteal phase oestradiol LPP/GnRH antagonists protocol) treatment with different protocol results with poor ovarian response (POR) patients. Two hundred and ninety-three cycles with poor ovarian reserve who underwent LPP, microdose flare up protocol and antagonist protocol were included in the study. Of these, 38 patients were applied LPP in the first cycle and LPP in the second cycle. After the microdose or antagonist protocol applied in the first cycle, LPP was applied to 29 patients in the second cycle. There are 128 patients who received LPP only once and 31 patients who received microdose flare up only once. The clinical pregnancy rate was monitored higher in LPP application group in the second cycle than the patients who received only LPP and patients who received LPP after different protocols (p = .035). b-hCG positivity per embryo and clinical pregnancy rate were found to be significantly higher with the LPP application in the second protocol (p = .000, p = .001). Repeated LPP may be the first choice protocol for low ovarian reserve patients.

IMPACT STATEMENT
- What is already known on this subject? There is no standard treatment protocol applied to patients with low ovarian reserve. In this patient group, the rate of lack of response to stimulation and cycle cancellation is high. Increasing FSH level in patients with poor ovarian reserve causes the formation of larger follicles by increasing the sensitisation of follicles in the late luteal phase.
- What do the results of this study add? Our study was conducted for the first time in the literature. We compared the results of second cycle LPP (luteal phase oestradiol LPP/GnRH antagonists protocol) application in patients with low ovarian reserve who resulted in failed IVF after commonly used LPP, microdose flare up protocol and antagonist protocols.
- What are the implications of these findings for clinical practice and/or further research? Luteal phase oestrogen LPP/GnRH antagonist may be the first choice in patients with poor ovarian reserve patients. In unsuccessful cases, the LPP protocol should be considered in the retreatment for the second time.

Introduction
Poor ovarian reserve is observed at a rate of approximately 9–24% in the whole infertile population. Increasing FSH level in patients with poor ovarian reserve causes the formation of larger follicles by increasing the sensitisation of follicles in the late luteal phase. Due to this situation, asynchronisation develops. With oestradiol and antagonist in luteal phase, pregnancy rates can be increased by preventing the asynchronisation in priming follicles.

The first study in the literature on this subject was conducted by Dragisic et al. (2005), initially based on the studies conducted by Fanchin et al. (2003a, 2003b) on adding antagonist in the luteal phase after the first luteal phase oestradiol priming application, thought that the success could be increased by adding both oestradiol and antagonist to suppress FSH in the luteal phase and increase the number of mature oocytes (Fanchin et al. 2003a, 2003b). As a result of the study, they found that the number of mature oocytes and the rate of embryo transfer (ET) were significantly higher (Dragisic et al. 2005).

Other commonly used ovarian stimulation protocols in patients with low ovarian response are the initiation of gonadotropins and a GnRH-a in the follicular phase or the use of a microdose flare up protocol after treatment with oral contraceptives (Demirogul and Gurgan 2009).

Treatment with COCs in one cycle in microdose flare up protocols results in lower FSH levels at the beginning of the next menstrual cycle, potentially enabling synchronisation of early antral follicles and an increase in the number of oocytes present during oocyte retrieval.
GnRH antagonist treatment regimens, on the other hand, allow a more natural retrieval of follicles during the follicular phase without suppressing FSH and LH caused by a GnRH-a (Demirol and Gurgan 2009).

We planned this study considering that the application of LPP for the second time after the applications of the LPP protocol, microdose flare up protocol and antagonist protocol applied in patients with poor ovarian reserve, resulting in unsuccessful IVF, may increase the success results. Our study was conducted for the first time in the literature.

Materials and methods

Our study was designed retrospectively, 293 cycles and 226 patients between the 24 and 46 age group, who applied between January 2013 and March 2019 and had a bad ovarian response (<4 oocytes) in the previous cycle, had a bad ovarian reserve test (low AMH ≤1.1, low AFC ≤7) or FSH 10 with poor ovarian response (POR) and underwent LPP, microdose flare up protocol and antagonist protocol were included in the study. Patients were excluded if they had pathological sperogram and/or endocrine or other medical abnormalities requiring medical treatment and were high or normoresponder patients (Medenica 2022). LPP was applied only once to 128 patients with low ovarian reserve, and microdose flare up was applied only once to 31 patients. Apart from these patients, 38 patients who underwent LPP protocol in the first cycle were applied LPP protocol again in the second cycle. The LPP protocol was applied in second cycle to 29 patients who received microdose or antagonist protocol in the first cycle. In our study, the results of the treatment protocols applied to patients with low ovarian response were shared. LPP + LPP protocol application results and different protocol + LPP application results were compared. Patients between ≤23 and ≥46 years of age, were not made fresh ET and cycles with frozen ET are not included in the study. The study received approval from the ethics committee of Health Sciences University Gulhane Training and Research Hospital.

LPP group patients: 10 days after ovulation confirmation with LH peak and transvaginal ultrasonography (TV USG) in patients whose LH peak was followed on the 8th, 10th and 12th days of the cycle before starting treatment, Estrofem TB (2 mg oestradiol hemihydrate, Novo Nordisk, Istanbul, Turkey) usage of 1 in the morning and 2th in the evening was started. One day later, Cetrotide (cetrorelix 0.25 mg Sc., Merck Serono, Istanbul, Turkey) 0.25 mg/day was applied for three days. 300 IU FSH (Gonal-F; Merck Serono, Istanbul, Turkey), 300 IU hMG (Merional; IBSA, Istanbul, Turkey) was started on the second day of the menstruation. Follicular development was followed by serial TV USG and serum E2 levels. Cetrorelix (Cetrotide; Merck Serono, Istanbul, Turkey) 0.25 mg/day subcutaneously leading follicle >12 mm or E2 >300 pg/mL human chorionic gonadotropin (hCG) was administered until the day of injection.

On the first and second day of the cycle, 1 mg/0.2 mL subcutaneous leuprolide acetate (Lucrin; Abbott, Rungis Cedex, France) was administered once a day to patients who underwent microdose flare up protocol. Leuprolide acid was then administered 0.5 mg/0.1 mL per day. On the 2nd day of the cycle, gonadotropin stimulation 200–450 IU (randomly randomised by Gonal F; Merck Serono, Genf, Switzerland or Puregon; MSD, Oss, Netherlands) and/or 75–150 IU hMG (Menogon; Ferring, Kiel, Germany) was administered simultaneously with leuprolide.

Gonadotropin stimulation 200–450 IU and/or 75–150 IU hMG was applied on the second day of spontaneous menstruation to patients who underwent antagonist protocol. When the dominant follicle reached 14 mm in size or on the 6th day of the cycle, randomised subcutaneous cetrorelix/ganirelix 0.25/day (Cetrotide; Merck Serono, Genf, Switzerland or Orgalutran; MSD, Oss, Netherlands) was administered.

The cycle was cancelled in patients who did not show a follicular growth response to ovarian induction and had a peak E2 < 100 pg/mL.

When one or more follicles grow to 17 mm or more, hCG (Ovitrelle 250 µg; Merck Serono, Genf, Switzerland), hCG (10,000 IU IM, Profasi 5000 IU, Serono, Istanbul, Turkey), was given for final oocyte maturation. Endometrial thickness was recorded by TV-USG on the day of hCG administration. Oocytes were collected with a cook, echo type, double lumen aspiration needle with TV-USG guide 36 hours after hCG. ICSI was performed on all patients. According to the quality of the embryos formed after ICSI, 1 or 2 embryos were transferred according to the age of the patient with abdominal USG after 48–120 h (one ET for under 35, two ET for over 35 years old).

For luteal support, after oocyte collection, one prostaglandin depot 500 mg/2 mL per week (Bayer, Istanbul, Turkey), 600 mg daily of progesteran capsule (Koçak Farma, İstanbul, Turkey) is given intravaginally. Six milligrams daily of oestradiol hemihydrate (Estrofem 2 mg, Novo Nordisk, Istanbul, Turkey) is administered orally. Pregnancy test was performed 12 days after ET and if it was positive, it was accepted as b-hCG positivity. Gestational sac positivity was accepted as the clinical pregnancy rate. Pregnancies over 24 weeks were accepted as live births.

Among the patients included in the study, who were unsuccessful after applying the LPP protocol, 38 patients who were re-applied LPP for the second time were included in the study. Re-applied LPP was started immediately from the previous cycle. Along with the demographic data of 38 patients, the duration of stimulation, the gonadotropin dose used, the number of oocytes collected, the MII number, and the cycle cancellation rates were evaluated. The number of embryos of 38 patients, embryo implantation rate per patient and ET, clinical pregnancy rate per patient and ET, live birth rate per patient and ET were evaluated.

Our first LPP results and our second LPP results were compared. The results of LPP + LPP application and different protocol + LPP application results were compared. In our study, Kolmogorov–Smirnov’s test was used to check whether the data conformed to the normal distribution or not. Independent Student’s t-test was applied to patients with normal distribution. Mann–Whitney’s U-test was applied to patients who did not conform with normal distribution. Chi-square test was used for categorical data. p < .05 was considered to be significant.
Results

According to the data of our study, patients with low ovarian response were divided into groups according to their first cycle, with the second cycle being LPP. Patients who received only one cycle of treatment were divided into groups as those who received LPP and microdose flare up.

After LPP, 38 patients were re-applied LPP for the second time. The first LPP results were compared with the second LPP results. No difference was observed between the groups in terms of the number of oocytes collected, metaphase II oocyte count, number of embryos obtained, and embryo quality (Table 1).

Patients with unsuccessful IVF application, those who underwent LPP + LPP and those who underwent different protocols + LPP were compared. b-hCG positivity per embryo and clinical pregnancy rate were found to be significantly higher in the LPP + LPP group. There was no significant difference between the two groups in terms of live birth rate. No significant difference was observed between the groups in terms of the number of oocytes collected, metaphase II oocyte count, number of embryos obtained, embryo quality and number of transferred embryo (Table 1).

One hundred and twenty-eight patients who only underwent LPP and 38 patients in the LPP + LPP group who were applied LPP for the first time (totally 166 LPP) were compared with 31 patients who received only microdose flare up and 19 patients who received microdose flare up for the first time in the different protocol + LPP group (50 microdose flare up in total). While the collected oocyte count, MII oocyte count and embryo count were significantly higher in the microdose flare up group, interestingly, the live birth rate was significantly higher in the LPP group. (Note: The FSH value of the patients in the microdose flare up group was significantly lower, this difference may be due to the better FSH value in the microdose flare up group.) The live birth rate was 12% in the LPP group and 2% in the microdose flare up group (Table 3).

Our results of LPP protocol application in the second cycle in patients with low ovarian response, which resulted with failed IVF once, and clinical pregnancy rate were found to be significantly higher than the patients who received only LPP and patients who received LPP after different protocols ($p = .035$).

Discussion

Infertility is the most stressful problem for couples and fertility treatments negatively affect their lives (Gullo et al. 2021). Starting in vitro fertilisation therapy requires an important psychological preparation and a state of wellness. To achieve this, measures to increase IVF success are critically important (Burgio et al. 2022).

There are many studies on interventions to increase the success rates in IVF. In one of these studies, the injection of the supernatant fluids of embryo cultures into the endometrial cavity has been studied. But this has not shown to have any positive effects (Prapas et al. 2012). On the other side, there are studies on the effectiveness of the inositol supplement in the treatment (Espinola et al. 2021). A relationship between myo-inositol concentration within the follicular fluid and the oocyte quality is known. Culturing embryos in media enriched with myo-inositol have a more number of expanded blastocyst formed (Gullo et al. 2015).

There is growing acceptance that nutrition may be related to fertility, and specifically to ART success, in women. However, there is still no specific official dietary guidance. Vitamin D is a steroid hormone that appears to play a critical role on oocytes development and embryo quality. Vitamin D supplementation promotes oocyte development and improves embryo quality (Menichini et al. 2022).

There is no standard treatment protocol applied to patients with low ovarian reserve. In this patient group, the rate of lack of response to stimulation and cycle cancellation is high. In this study, we compared the results of second cycle LPP application in patients with low ovarian reserve who resulted in failed IVF after commonly used LPP, microdose flare up protocol and antagonist protocols. b-hCG positivity and clinical pregnancy rate were found to be

| Table 1. The first LPP results were compared with the second LPP results. |
|------------------|------------------|------------------|---|
|                  | LPP              | LPP + LPP        | $p$  |
| Age              | 35.7 ± 4.7       | 36 ± 4.7         | .709 |
| FSH              | 11 ± 4.2         | 11.2 ± 4.6       | .971 |
| AMH              | 0.6 ± 0.7        | 0.6 ± 0.7        | .819 |
| Stimulation time | 10.1 ± 2.1       | 10.2 ± 2         | .435 |
| Dose             | 5784.6 ± 1291.1  | 6000 ± 1210      | .342 |
| Number of oocytes collected | 3.5 ± 2.9       | 4.5 ± 3.3        | .149 |
| MII oocytes count | 2.4 ± 2.1        | 3.1 ± 2.5        | .181 |
| Number of embryo | 1.7 ± 1.7        | 2.0 ± 1.7        | .335 |

| Table 2. LPP + LPP and those who underwent different protocols + LPP were compared. |
|------------------|------------------|------------------|---|
|                  | LPP + LPP        | Other protocols + LPP | $p$  |
| Age              | 36 ± 4.7         | 35.4 ± 5.4       | .666 |
| FSH              | 11.2 ± 4.6       | 9.2 ± 3.7        | .510 |
| AMH              | 0.6 ± 0.7        | 0.6 ± 0.5        | .664 |
| Stimulation time | 10.5 ± 2         | 10.3 ± 2.3       | .699 |
| Dose             | 6000 ± 1210.3    | 5710.3 ± 7       | .363 |
| Number of oocytes collected | 4.5 ± 3.3       | 6.5 ± 4.6        | .080 |
| MII oocytes count | 3.1 ± 2.5        | 4.6 ± 3.5        | .090 |
| Number of embryo | 2.0 ± 1.7        | 2.7 ± 2          | .137 |
| On going pregnancy per embryo transferred | 3              | 2               | .296 |
| b-hCG positivity per embryo transferred    | 7              | 2               | .000 |
| Clinical pregnancy per embryo transferred   | 6              | 2               | .001 |
applied to 28 patients, and it was shown that LPG protocol applied to 26 patients, microdose flare up protocol was applied to 28 patients with poor response to IVF (DiLuigi et al. 2011). LPP protocol was significantly higher in the LPP + LPP group. There was no significant difference between the two groups in terms of live birth rate. No significant difference was observed between the groups in terms of the number of oocytes collected, metaphase II oocyte count, number of embryos obtained, embryo quality and number of transferred embryos. Similarly, an increase in the number of oocytes collected was not shown with LPA when compared to MD in the study performed by Ata et al. (2011). However, a tendency towards higher embryo implantation and clinical pregnancy rates has been observed, but the differences are not statistically significant (Ata et al. 2011).

In the study conducted by Schmidt et al. (2005), the GnRH antagonist protocol (ganirelix protocol) was compared with the microdose leuprolide protocol in weak ovarian responders. As a result of the clinical study in poor responders, no significant difference was observed in terms of mature follicle count, mean oocyte count, mature oocyte count, fertilisation rates, implantation rates or clinical pregnancy rates. The use of ganirelix for GnRH antagonist protocols has been suggested to be as effective as the traditional microdose protocol in treating poor responders (Schmidt et al. 2005).

In our study, in the group where only LPP was applied and only microdose flare was examined, the collected oocyte count, MII oocyte count and embryo count were significantly higher in the microdose flare up group, while the live birth rate was higher in the LPP group (12–2%, respectively).

Also, in the study of DiLuigi et al. (2011), LPP protocol was applied to 26 patients, microdose flare up protocol was applied to 28 patients, and it was shown that LPG protocol was seen as effective as microdose flare up protocol in patients with poor response to IVF (DiLuigi et al. 2011).

As a result of their study, Demiroi and Gurgan (2009) suggested that the microdose flare up protocol was superior to the multiple dose antagonist protocol in terms of the total gonadotropin dose used, the number of mature oocytes collected and the implantation rate (Demiroi and Gurgan 2009).

In a study in which 45 patients in the LPP group and 76 patients in the microdose flare up group were compared, no difference was observed between implantation rate, clinical pregnancy rate and spontaneous abortion rate. However, an important difference between the two protocols is that the gonadotropin was administered in the LPG protocol for a longer time (days). This is due to increased pituitary suppression and increased E2 levels in the LPG protocol and delayed FSH elevation with exposure to GnRH antagonist in the late luteal phase, which delays FSH elevation (Weitzman et al. 2009).

Controlled ovarian hyperstimulation (COH) protocols for patients with POR are designed to prevent early follicle selection in the luteal phase and to optimise the follicular hormonal environment and antral follicle response. The use of the E2 LPP/GnRH-antagonist protocol appears to increase ovarian response during COH for IVF, and may result in smoother follicular development, more oocytes, more ETs, and a better pregnancy rate (Dragisic et al. 2005).

In our study, we found that repeated LPP applications in low ovarian reserve were associated with higher b-hCG positivity and clinical pregnancy rate.

Chang et al. (2012) retrospectively examined the PORs stimulated with the luteal oestradiol protocol and the standard GnRH antagonist protocol, and found that the luteal oestradiol protocol had significantly higher peak oestradiol levels, oocyte count, pregnancy rates and lower cancellation rates (Chang et al. 2012).

These results may be a result of the heterogeneity in the luteal oestradiol group, where most patients used oestradiol during the day of hCG administration. Oestrogen is known to induce FSH receptor proliferation in granulosa cells and stimulate follicular growth and granulosa cell proliferation. Long-term use of oestradiol may result in higher peak oestradiol levels and obtained oocyte count (Mutlu et al. 2017).

In our study, the collected oocyte count, MII oocyte count and embryo count were found to be significantly lower in patients who underwent LPP compared to the microdose flare up group, while the live birth rate was found to be higher (12% vs. 2%).

In a study involving 180 patients < 35 years younger with POR, the luteal phase oestrogen LPP/GnRH antagonist protocol

Table 3. LPP for the first time were compared with patients who received only microdose flare up.

|                      | LPP (166) | Microdose flare up (50) | p   |
|----------------------|-----------|-------------------------|-----|
|                      | Ort ± SD  | Ort ± SD                |     |
| Age                  | 36.4 ± 4.6| 36 ± 4.4                | .444|
| FSH                  | 11.4 ± 5.2| 9.3 ± 3.3               | .029|
| AMH                  | 0.6 ± 0.6 | 0.6 ± 0.4               | .593|
| Stimulation time     | 10.7 ± 1.9| 9.1 ± 1.6               | .265|
| Number of oocytes collected | 4.1 ± 3.3 | 5.8 ± 3.9 | .034 |
| MII oocytes count    | 2.9 ± 2.4 | 4.1 ± 3.2               | .000|
| Number of embryo     | 1.9 ± 1.7 | 3.0 ± 2.5               | .000|
| On going pregnancy per embryo transferred | 20 (12%) | 2 (2%) | .020 |
| Clinical pregnancy per embryo transferred | 29 (29.3%) | 11 (33.3%) | .663 |
| b-hCG positivity per embryo transferred | 30 (30.3%) | 11 (33.3%) | .746 |
| Embryo quality       |           |                         |     |
| Grade I              | 70 (42.2%)| 30 (60%)                | .085|
| Grade II             | 36 (21.7%)| 5 (10%)                 |     |
| Grade III            | 3 (1.8%)  | 0                       |     |
| TFF                  | 35 (22%)  | 10 (20%)                |     |
| EKK                  | 22 (13.2%)| 5 (10%)                 |     |
| Number of transferred embryo |          |                         |     |
| 0                    | 67 (40.4%)| 17 (34%)                | .112|
| 1                    | 61 (36.8%)| 14 (28%)                |     |
| 2                    | 38 (22.8%)| 19 (38%)                |     |
and the microdose flare up protocol were compared. Patients undergoing stimulation with LPP showed a tendency of increase in the implantation rate and the pregnancy rate per cycle. Cycle cancellation rate was found to be higher in the OCP-MDL group, but no statistically significant difference was found (Shastri et al. 2011).

In our literature review, there is no previous study on this subject and our study is the first one to be done. The low number of our cases is a limitation of our study, and larger studies are needed on this subject.

Conclusions

Luteal phase oestrogen LPP/GnRH antagonist may be the first choice in patients with DOR. In unsuccessful cases, the LPP protocol should be considered in the retreatment for the second time.

Disclosure statement

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