Archives of Gynecology and Obstetrics (2023) 308:579–586
https://doi.org/10.1007/s00404-023-07071-z

GYNECOLOGIC ENDOCRINOLOGY AND REPRODUCTIVE MEDICINE

Comparison of fixed and flexible progestin-primed ovarian stimulation protocols to prevent premature luteinization in patients with diminished ovarian reserve

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Received: 11 January 2023 / Accepted: 2 May 2023 / Published online: 13 May 2023

Abstract

Purpose Flexible progestin-primed ovarian stimulation (PPOS) protocol is demonstrated to be effective in suppressing premature luteinization in few studies. We aimed to compare fixed and flexible PPOS protocols in preventing premature luteinization in patients with diminished ovarian reserve.

Methods This retrospective cohort study included patients with a diminished ovarian reserve who were administered PPOS protocols for pituitary suppression during ovarian stimulation in a tertiary center in between January 2019 and June 2022. At fixed protocol, 20 mg/day dydrogesterone was started in cycle day two or three along with gonadotropins and continued until trigger day. In contrast, at flexible protocol, 20 mg/day dydrogesterone was commenced when the leading follicle reached 12 mm or serum estradiol (E2) level was > 200 pg/mL.

Results A total of 125 patients, of whom 83 were administered fixed PPOS protocol and 42 were administered flexible PPOS protocol, were included in the analysis. Both groups had similar baseline characteristics and cycle parameters, including total days of gonadotropin administration and total gonadotropin dose ($p > 0.05$). Premature luteinization occurred at 7.2% and 11.9% of patients in fixed and flexible PPOS protocols, respectively ($p = 0.505$). Retrieved oocytes numbers, metaphase II oocyte numbers, and 2PN numbers were also similar ($p > 0.05$). Clinical pregnancy rates per transfer were 52.5% in fixed and 36.4% in flexible protocols ($p = 0.499$).

Conclusion Both fixed and flexible PPOS protocols had statistically similar outcomes in preventing premature luteinization and other cycle parameters. The flexible PPOS protocol seems to be as effective as the fixed PPOS protocol for patients with diminished ovarian reserve; however, further prospective studies should be conducted to validate the results of our research.

Keywords Progestin-primed ovarian stimulation (PPOS) · Diminished ovarian reserve · Dydrogesterone · Flexible protocol · Premature luteinization

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What does this study add to the clinical work

Flexible progestin-primed ovarian stimulation (PPOS) protocol is recently used for pituitary suppression. Efficacy of fixed and flexible PPOS protocols in preventing premature luteinization in patients with diminished ovarian reserve are found to be similar. This study contributes to literature in a field where few data is present.

Introduction

Progestin-primed ovarian stimulation (PPOS) protocols are used as an alternative to Gonadotropin Releasing Hormone (GnRH) antagonists for pituitary suppression for the last few years. Oral administration and lower costs of progestins are advantageous, while fresh embryo transfer is precluded due to high progesterone exposure and impaired endometrial receptivity. However, the PPOS protocol is effective at planned all-freeze cycles in different patient populations [1]. In the former studies, progestins are commenced along with gonadotropins at the beginning of the cycle [2, 3]. Recently, progestins are also demonstrated to prevent Luteinizing Hormone (LH) surge and premature ovulation when administered in the later phase of the cycle [4]. Namely, in flexible protocols, the initiation time of progestins is based on the follicle size and/or hormone values during the cycle [4]. While a few studies compared flexible PPOS protocols with GnRH antagonist protocols and reported similar outcomes, only one study reports the effectiveness of flexible PPOS protocol in patients with diminished ovarian reserve [5]. Since flexible PPOS protocol has been introduced recently, further studies are needed to demonstrate the efficacy of this protocol, particularly in subgroups such as patients with low ovarian reserve.

This study aims to compare the effect of fixed and flexible PPOS protocols on cycle outcomes of patients with a diminished ovarian reserve and to evaluate the efficacy of the flexible protocol in this patient group, regarding the few data that already exists.

Materials and methods

Study population and participants

Data of controlled ovarian stimulation cycles of patients with diminished ovarian reserve, where progestin was used for pituitary suppression, in a tertiary center in between January 2019 and June 2022 were analyzed retrospectively. Two subgroups utilizing fixed and flexible PPOS protocols were formed, and cycle outcomes of these two groups were compared.

All patients, who had diminished ovarian reserve and were administered PPOS protocols for pituitary suppression during this time interval, were included in the study. The progestin used for this purpose in our center is dydrogesterone. Diminished ovarian reserve is defined as anti-mullerian hormone (AMH) < 1.1 ng/mL or antral follicle count < 7 [6].

Patients aged > 45 years, undergoing oocyte cryopreservation for medical reasons, using progestins other than dydrogesterone, and patients with uterine anomalies were excluded. Only one cycle of each patient was included in the study. As for patients with more than one cycle, chronologically the first cycle was included.

Protocol

In our fixed PPOS protocol, 150–300 IU/day gonadotropin (human menopausal gonadotropin (HMG) (Merional®, IBSA Institut, Switzerland) and/or recombinant follicle stimulating hormone (rFSH) (Gonal-f®, Merck-Serono, Switzerland)), along with dydrogesterone (Duphaston®, Abbott, Türkiye) 10 mg twice daily are administered starting from day 2 or day 3 of the menstrual cycle. The gonadotropin dose is adjusted according to the ovarian response, and the gonadotropin is continued with dydrogesterone until trigger day.

In our flexible PPOS protocol, 150–300 IU/day gonadotropin is administered starting from day 2 or day 3 of the menstrual cycle. When the dominant follicle reaches 12 mm or serum estradiol (E2) is measured > 200 pg/mL, dydrogesterone (Duphaston®, Abbott, Türkiye) 10 mg twice daily is commenced and is continued along with gonadotropin until trigger day. In both groups, when one or more follicles reach 18 mm in size, final oocyte maturation is triggered with 250 µg choriogonadotropin alfa (Ovitrelle® 250 mcg, Merck-Serono, Italy) and GnRH agonist (Decapeptyl® 0.1 mg, Ferring, Germany or Lucrin® 5 mg/mL, Abbott, Spain) (Fig. 1). Premature luteinization is defined as a progesterone value > 1.2 ng/mL at or before the trigger day [7].

Oocytes are collected under transvaginal ultrasound guidance 36 h after the trigger, oocyte maturity is evaluated following denudation, and all metaphase II (MII) oocytes are fertilized by intracytoplasmic sperm injection (ICSI), using appropriate fertilization medium (G-TL®, Vitrolife, Sweden). The fertilization rate is evaluated according to the ratio of embryos with two pronuclei (2 PN), assessed 16–18 h after ICSI, to the number of MII oocytes. Following daily morphological assessment, according to embryo quality, embryos are vitrified on the 3rd or 5th day using

a vitrification medium (MediCult Vitrification Cooling® Medium, Origio, Denmark).

Embryos are thawed and transferred at a suitable time for the patient. Frozen embryo transfer (FET) cycles included only artificially prepared cycles. Accordingly, estradiol hemihydrate (Estrofem® 2 mg, Novo Nordisk, Türkiye) 6 mg/day is administered for at least 12 days starting from the 2nd or 3rd day of the menstrual cycle, and vaginal progesterone (Progestan® 200 mg, Koçak Farma, Türkiye) 600 mg/day + subcutaneous progesterone (Prolutex® 25 mg, IBSA, Türkiye) 25 mg/day are administered provided that the endometrial thickness is ≥ 7 mm. Day 3 embryos are transferred on the 4th day and Day 5 blasts are transferred on the 6th day of progesterone administration. In the case of thin endometrium, the duration of estradiol administration is increased up to 36 days [8]. Embryos are thawed using a warming medium (MediCult Vitrification Warming® Medium, Origio, Denmark) and transferred at the appropriate time due to their developmental stage.

Luteal phase support is provided with vaginal and subcutaneous progestins in combination. Pregnancy is determined by the serum beta-human chorionic gonadotropin (ß-hCG) value measured 11 days after the transfer. Luteal support is continued until a negative ß-hCG test or until the 10th week of pregnancy. Clinical pregnancy is determined by the presence of a fetal heartbeat. This study only included FET cycles, in which embryos obtained from the specified PPOS cycles were used.

Outcome variables

Descriptive features of the patients, including age, body mass index (BMI), antral follicle counts, AMH values, infertility periods, and cycle characteristics, including total gonadotropin and dydrogesterone administration times, total gonadotropin amounts administered, progesterone and estradiol values on trigger day, endometrial thickness, presence of premature luteinization, which was demonstrated by progesterone value higher than 1.2 ng/mL on trigger day, number of collected and MII oocytes, fertilization rates, and clinical pregnancy rates were analyzed and the results of the two groups were compared.

The primary outcome measure of the study was premature luteinization rates, and secondary outcome measures were the length of stimulation, gonadotropin dose administered, total number of oocytes and number of MII oocytes, fertilization rates, and clinical pregnancy rates.

Statistical analyses

SPSS statistical package (Version 26.0, SPSS Inc., Chicago, IL, USA) was used for data analysis. Categorical measurements were summarized with numbers and percentages, while continuous measurements were demonstrated by mean and standard deviation or median and range. In the comparison of continuous measurements in the two groups, distributions were controlled, and Student's t test was used for variables with parametric distribution, while Mann–Whitney U test was used for non-parametric variables. In all tests, $p < 0.05$ was considered statistically significant.

Results

Progestin-primed ovarian stimulation protocols were observed to be applied to 152 patients with diminished ovarian reserve during the study period, and a number of the total cycles were 193. After excluding repeat cycles of the same patients, oocyte cryopreservation cycles, and cycles, in which progestins other than dydrogesterone were used, 125 patients were included in the study. Of these patients, 83 were administered fixed, and 42 were administered flexible PPOS protocols (Fig. 2). Baseline characteristics, including age, BMI, antral follicle count,

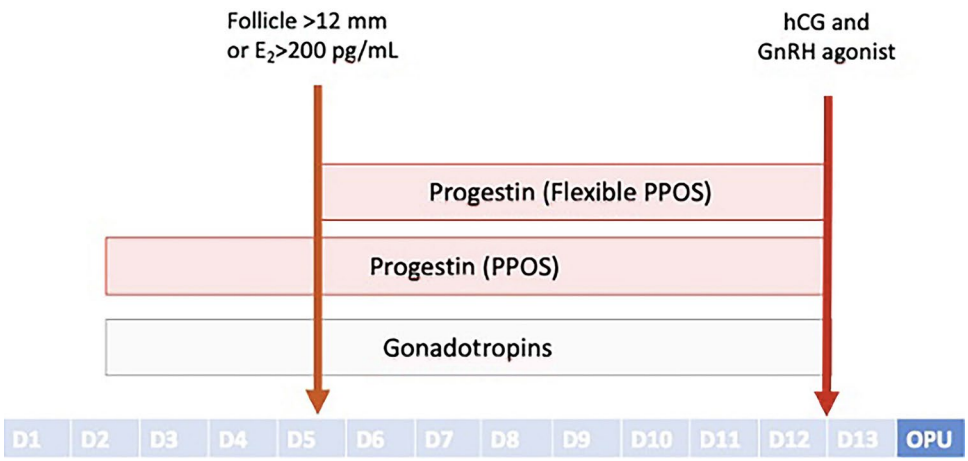

Fig. 1 Fixed and flexible PPOS protocols. PPOS progestin-primed ovarian stimulation

AMH levels, and infertility period, were similar for both groups ($p > 0.05$) (Table 1). Cycle parameters, including total days of gonadotropin administration and total gonadotropin doses, were similar; progesterone and estradiol values and endometrial thickness at trigger day were also similar ($p > 0.05$). Premature luteinization occured in 6 (7.2%) and 5 (11.9%) patients in fixed and flexible PPOS protocols, respectively ($p = 0.505$). Since the PPOS protocol inherently necessitated freezing of all cycles, premature luteinization was not a cause for cycle cancelation; however, cycle cancel rates due to the absence of oocytes, fertilization failure, or low-quality embryos were similar between fixed and flexible protocol groups ($p = 0.114$). The number of oocytes and MII oocytes was similar in both groups ($p > 0.05$). At four patients in the fixed PPOS group (4.8%) and three patients in the flexible PPOS group (7.1%), no oocytes were encountered at oocyte retrieval (p: 0.687). Furthermore, no statistical difference was found between the 2PN numbers and fertilization rates of the two groups ($p = 0.725$ and $p = 0.762$, respectively). Frozen embryo transfer was applied to 40 patients in the fixed protocol and 11 in the flexible protocol. Clinical pregnancy rates of patients who underwent FET cycles were 52.5% in fixed protocol and 36.4% in flexible protocol groups ($p = 0.499$) (Table 2). Demographics and cycle outcomes of the patients who had premature luteinization were statistically similar in fixed and flexible protocols ($p > 0.05$ for all parameters) (Table 3). Furthermore, the same parameters of 11 patients who had premature luteinization were not statistically different from the whole population ($p > 0.05$ for age, antral follicle count, AMH levels, retrieved oocytes, MII oocyte, and 2 PN numbers).

Discussion

This study compared the efficacy of fixed and flexible PPOS protocols in preventing premature luteinization in patients with diminished ovarian reserve. Stimulation time and total gonadotropin doses, premature luteinization rates, the total number of oocytes and the MII oocytes, and fertilization rates were statistically similar in both protocols. Clinical pregnancy rates were also similar.

Kuang et al. (2015) were the first to publish the comparison of PPOS protocol, which was applied using medroxyprogesterone acetate (MPA), with GnRH agonist protocol, and they reported premature LH surge at only 1 in 150 of the study group. Although the stimulation time and the total HMG dose used are higher in the MPA arm in their study, MII counts, embryo qualities, implantation, and pregnancy rates are similar in both protocols. It is emphasized that progestin administration should be commenced at E2 values < 50–70 pg/mL to be sufficiently effective [2]. It has been demonstrated that progestins other than MPA are also effective in suppressing LH surges in the fixed protocols [9, 10]. Although progestins cannot be used in fresh cycles due to the negative effects of progestins on endometrium and implantation, their usage in planned all-freeze cycles has potential benefits owing to their ease of application and cost advantage. Regarding diminished ovarian reserve cycles, PPOS might have some additional benefits in patients presumed to have preimplantation genetic screening and patients necessitating additional gynecological surgery before embryo transfer.

One of the most critical parameters in evaluating the protocol's effectiveness, as in other controlled ovarian stimulation protocols, is the efficacy of suppressing premature luteinization and ovulation. Since premature luteinization is the indirect preliminary indicator

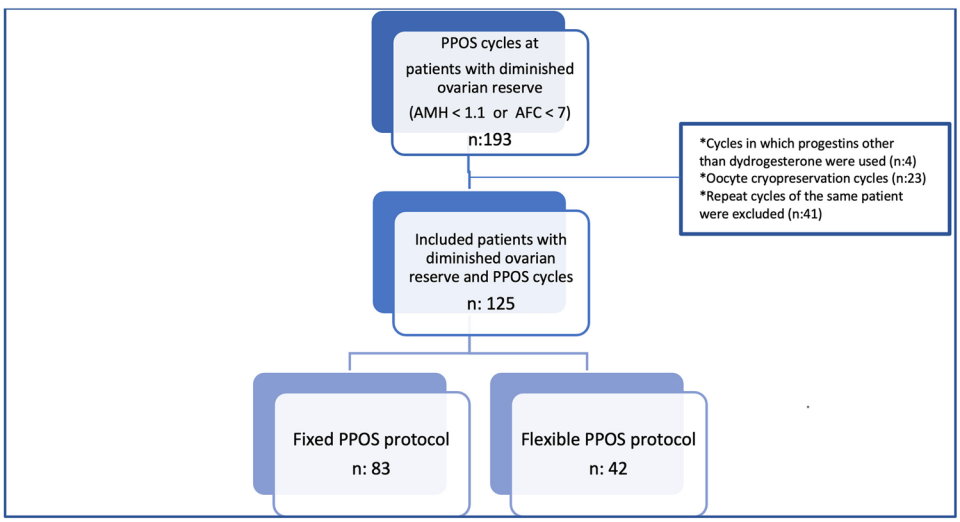

Fig. 2 Flowchart demonstrating the criteria used for diagnosing diminished ovarian reserve and other exclusion criteria. PPOS progestin-primed ovarian stimulation, AMH anti-mullerian hormone, AFC antral follicle count

of premature ovulation in most cases, the efficiency of PPOS protocols is evaluated by comparing their effect on preventing premature luteinization. It has previously been demonstrated that premature luteinization is particularly more frequent in women with diminished ovarian reserve than normo-responder patients, both in GnRH agonist and GnRH antagonist protocols [7, 11, 12]. One reason may be the acceleration of dominant follicle selection and the shortening of the early follicular phase, especially in advanced-aged patients [13]. In a previous study, where we examined the efficacy of flexible PPOS protocol, most patients with premature LH surge had decreased ovarian

Table 1 Baseline characteristics of the groups

	Fixed PPOS (n:83) median (range)	Flexible PPOS (n:42) median (range)	*p*
Total days of dydrogesterone administration	8 (4–13)	6 (2–10)	***0.000***
Total days of gonadotropin administration	9 (5–15)	9 (5–14)	0.080
Total gonadotropin dose (IU)	2700 (1200–5100)	3075 (1500–4875)	0.142
Progesterone at trigger day (ng/mL)	0.4 (0.1–4.7)	0.4 (0.1–4.8)	0.746
Estradiol at trigger day (pg/mL)	695 (151–3021)	552 (131–7610)	0.179
Endometrial thickness (mm)	8.6 (2.0–15.5)	7.9 (4.8–13.0)	0.967
Premature luteinization (*n*, %)	6 (7.2)	5 (11.9)	0.505
Premature ovulation (*n*, %)	4 (4.8)	3 (7.1)	0.687
Number of retrieved oocytes	4 (0–14)	3 (0–11)	0.541
Number of MII oocytes	3 (0–9)	3 (0–11)	0.620
Number of 2 PN	2 (0–6)	2 (0–7)	0.725
Total motile sperm count ($\times 10^6$)	33.465 (0–149.000)	33.840 (0–115.440)	0.810
Cycle cancelation rate (*n*, (%))	25/83 (30.1)	19/42 (45.2)	0.114
Fertilization rate (%)	62.5 (0–100)	66.6 (0–100)	0.762
Clinical pregnancy (*n*, (%))	21/40 (52.5)	4/11 (36.4)	0.499

PPOS progestin-primed ovarian stimulation

Table 2 Cycle characteristics of the groups

Data availability (data are available upon request)	Fixed PPOS (n:83) mean ± SD or median (range)	Flexible PPOS (n:42) mean ± SD or median (range)	*p*
Age	36.8 ± 4.1	39.6 ± 4.75	0.899
Body mass index (kg/m^2)	24.6 ± 4.7	25.5 ± 4.3	0.327
Antral follicle count	4 (0–14)	4 (0–11)	0.981
Anti-Mullerian hormone (ng/mL)	0.59 (0.06–1.37)	0.65 (0.05–1.46)	0.194
Infertility period (year)	3 (1–21)	3 (1–22)	0.614

PPOS progestin-primed ovarian stimulation

Table 3 Demographics and cycle parameters of patients with premature luteinization in fixed and flexible PPOS groups

	Premature luteinization fixed PPOS (n:6; 7.2%) median (range)	Premature luteinization flexible PPOS (n:5; 11.9%) median (range)	*p*
Age	39.5 (31–41)	38 (31–43)	0.854
Anti-Mullerian hormone (ng/mL)	0.38 (0.10–1.20)	0.81(0.31–1.23)	0.456
Antral follicle count	4 (2–8)	4 (0–7)	0.707
Number of retrieved oocytes	6 (0–9)	8 (2–11)	0.358
Number of MII oocytes	5.5 (0–6)	6 (2–8)	0.303
Number of 2 PN	2.5 (0–5)	3 (1–5)	0.516

PPOS progestin-primed ovarian stimulation

reserve [14]. Nonetheless, in our current study, the demographics of the 11 patients with premature luteinization were statistically similar to those of the entire group. In the randomized-controlled study of Chen et al. in 340 patients with poor ovarian response, it is reported that premature LH surge is observed at a lower rate in the PPOS group compared to the antagonist protocol, while the number of oocytes and embryos obtained are similar [15]. In the study of Huang et al., in which they compared PPOS and antagonist protocol in patients with poor response, it is stated that MII rate, fertilization rate, and good-quality embryo rates are significantly higher in the PPOS group, with significantly higher rates of clinical pregnancy and live birth in subsequent FET. It is concluded that the PPOS protocol may improve outcomes in patients with poor response [16]. Peng et al. compared the outcomes of PPOS and mild stimulation in patients over 40. Although the amount of gonadotropin used was higher in the PPOS group, stimulation duration, the total number of oocytes and MII oocytes, fertilization, and cleavage rates were similar. The rate of good-quality embryos was higher in the PPOS group. However, clinical pregnancy rates were found to be similar [17]. In their study, the role of progesterone in oocyte nuclear and cytoplasmic maturation is emphasized, and it is stated that better embryo quality in the PPOS group may be due to the interaction between progesterone and receptors [17]. Previous studies comparing PPOS and GnRH analogs denoted that longer stimulation duration and higher gonadotropin use may be required due to pituitary suppression by the progestins [2, 17]. However, there are also reports in the poor prognosis group, where no significant difference is observed in these parameters in comparing PPOS and antagonist protocol [18]. Similar stimulation duration and total gonadotropin doses in our study indicate similar efficacy of pituitary suppression for both fixed and flexible protocols.

Flexible PPOS protocol, where progestins are commenced later in the cycle, has been introduced more recently. In the few studies conducted by this protocol, progestin is administered when the leading follicle diameter is ≥ 14 mm or serum E2 level is ≥ 200 ng/mL [4, 5]. In the study of Turkgeldi et al., in which flexible PPOS protocol is compared with the antagonist protocol in patients with decreased ovarian reserve, stimulation duration, cumulus–oocyte complexes, and the number of MII oocytes are similar between the two groups. Premature LH surge is reported in 4 (14.8%) and 2 (3.7%) patients in the flexible PPOS and antagonist groups, respectively, while premature ovulation occurred only in one patient in the flexible PPOS group [5]. Kalafat et al. recently compared the efficacy of fixed and flexible PPOS protocols in patients at risk of premature ovarian insufficiency. They reported that the MII oocyte rates and premature LH surge rates (13.3% and 20.0% in fixed and flexible groups, respectively, p = 0.5) were similar, with similar duration of stimulation and total gonadotropin consumption, between the two groups [19]. Also, in our study, premature luteinization rates (7.2% and 11.9% in fixed and flexible PPOS protocols, respectively) and other cycle outcomes were similar in both groups. In flexible GnRH antagonist protocols, the antagonist is commenced when the leading follicle diameter is 12–14 mm [20, 21]. The negative effect of premature ovulation would be more pronounced in the diminished ovarian reserve group. Progestins were started when the diameter of the leading follicle was 12 mm in our flexible PPOS protocol to prevent premature ovulation in this group of patients. While progestins are demonstrated to avoid premature luteinization in poor responders effectively [15], the clinically important result of premature luteinization in PPOS cycles is particularly premature ovulation resulting in scarce/no oocytes at oocyte retrieval. Although premature luteinization does not necessarily end up with premature ovulation, patients with low ovarian reserve are more prone to premature luteinization, and encountering scarce/no oocytes is a potential risk in this group. Nonetheless, neither premature luteinization nor cancel rates due to the absence of oocytes differed in our groups. Premature luteinization can be evaluated by LH or progesterone level measured at or before the trigger day. In our center, progesterone value is utilized in routine follow-ups for premature luteinization. Although different values have been suggested in the literature, progesterone value > 1.2 ng/mL measured at trigger day is considered as the cut-off value for premature luteinization according to our clinical experience (unpublished data) [7, 22].

Many studies conducted in patients with a diminished ovarian reserve are based on cycle parameters, such as duration of stimulation, total gonadotropin dose, retrieved oocytes and MII oocyte counts. Since clinical pregnancy and live birth rates are relatively lower in the diminished ovarian reserve group, a large population is needed to demonstrate the effectiveness of specific protocols. However, there are studies evaluating the cumulative live birth rates of PPOS protocols in patients with poor prognosis, and different results have been reported. In the study of Zhang et al., it is stated that live birth rates are significantly higher in the GnRH antagonist protocol compared to the PPOS regimen, especially at ≥ 35-year-old patients with diminished ovarian reserve (cumulative pregnancy rates 46.8% vs 35.1%, cumulative live birth rates 35.3% vs 25.2%, at antagonist and PPOS protocols, respectively, $p < 0.001$) [23]. Du et al., on the other hand, reported similar cumulative live birth rates with both treatment protocols in patients with poor prognosis [18]. In FET protocols, time to thawing cycle varies due to patients' requests or medical conditions. In our study, all included cycles did not end up with embryo transfer during the study period. Nevertheless, clinical pregnancy rates

were found to be similar after the inclusion of all cycles with thawing and transfer following PPOS cycles.

Although the retrospective nature and the small sample size are the main limitations of this study, our study population was a relatively uniform group of patients with a diminished ovarian reserve in a single center. Another limitation is the low rates of transferred embryos in fixed and flexible progestin groups. While a significant difference was not found between the results of the two groups during the study period, the small sample size may compromise the accuracy of the outcomes regarding pregnancy rates in particular. Thus, the possibility of false-negative findings necessitates studies with larger populations.

In conclusion, progestin-primed suppression of ovulation is relatively new and has yet to be studied extensively in the literature. Furthermore, there are almost no data for flexible application of progestin as a substitute for GnRH antagonists in patients with diminished ovarian reserve. Therefore, our study is noteworthy as it reveals the results of the diminished ovarian reserve patients who may be prone to premature ovulation. Postponement of commencing progestins in the cycle does not seem to impair cycle outcomes and clinical pregnancy rates. However, prospective randomized studies might provide new insights into the effectiveness of delayed onset (flexible) progestin application for prevention of premature luteinization in patients with diminished ovarian reserve.

Acknowledgements This study's preliminary data were presented as a poster at the 38th Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), Milan, 3–6 July 2022.

Author contributions GDD, PÇA, and EŞ designed the study, drafted and revised the manuscript. PÇA, EŞ, and TÇ enrolled patients and assigned participants to interventions. GDD, DAY, and SY contributed to data collection. PÇA and GDD were involved in statistical analysis, interpretation of data, and critical discussion. EŞ and TÇ supervised and revised the manuscript.

Funding No funding was received for conducting this study.

Data availability Data are available upon request.

Declarations

Conflict of interest The authors declare no conflicts of interest.

Ethical approval This study was approved by Başkent University Institutional Review Board (Project No. KA22/333).

This study was performed in accordance with Declaration of Helsinki.

Consent to participate Informed consent to participate the study was obtained from all patients prior to their treatment.

Consent for publication Informed consent for publication of the data was obtained from all patients prior to their treatment.

References

1. Ata B, Capuzzo M, Turkgeldi E, Yildiz S, La Marca A (2021) Progestins for pituitary suppression during ovarian stimulation for ART: a comprehensive and systematic review including meta-analyses. Hum Reprod Update 27(1):48–66. https://doi.org/10.1093/humupd/dmaa040
2. Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q et al (2015) Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertil Steril 104(1):62-70.e3. https://doi.org/10.1016/j.fertnstert/2015.03.022
3. Iwami N, Kawamata M, Ozawa N, Yamamoto T, Watanabe E, Moriwaka O et al (2018) New trial of progestin-primed ovarian stimulation using dydrogesterone versus a typical GnRH antagonist regimen in assisted reproductive technology. Arch Gynecol Obstet 298(3):663–671. https://doi.org/10.1007/s-00404-018-4856-8
4. Yildiz S, Turkgeldi E, Angun B, Eraslan A, Urman B, Ata B (2019) Comparison of a novel flexible progestin primed ovarian stimulation protocol and the flexible gonadotropin-releasing hormone antagonist protocol for assisted reproductive technology. Fertil Steril 112(4):677–683. https://doi.org/10.1016/j.fertnstert/2019.06.009
5. Turkgeldi E, Yildiz S, Cekic SG, Shakerian B, Keles I, Ata B (2022) Effectiveness of the flexible progestin primed ovarian stimulation protocol compared to the flexible GnRH antagonist protocol in women with decreased ovarian reserve. Hum Fertil (Camb) 25:306–312. https://doi.org/10.1080/14647273.2020.1794060
6. Cohen J, Chabbert-Buffet N, Darai E (2015) Diminished ovarian reserve, premature ovarian failure, poor ovarian responder—a plea for universal definitions. J Assist Reprod Genet 32(12):1709–1712. https://doi.org/10.1007/s10815-015-0595-y
7. Bosch E, Valencia I, Escudero E, Crespo J, Simón C, Remohí J et al (2003) Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertil Steril 80(6):1444–1449. https://doi.org/10.1016/j.fertnstert.2003.07.002
8. Mumusoglu S, Polat M, Ozbek IY, Bozdag G, Papanikolaou EG, Esteves SC et al (2021) Preparation of the endometrium for frozen embryo transfer: a systematic review. Front Endocrinol. https://doi.org/10.3389/fendo.2021.688237
9. Massin N (2017) New stimulation regimens: endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. Hum Reprod Update 23(2):211–220. https://doi.org/10.1093/humupd/dmw047
10. Yu S, Long H, Chang HY-N, Liu Y, Gao H, Zhu J et al (2018) New application of dydrogesterone as a part of a progestin-primed ovarian stimulation protocol for IVF: a randomized controlled trial including 516 first IVF/ICSI cycles. Hum Reprod 33(2):229–237. https://doi.org/10.1093/humrep/dex367
11. Reichman DE, Zakarin L, Chao K, Meyer L, Davis OK, Rosenwaks Z (2014) Diminished ovarian reserve is the predominant risk factor for gonadotropin-releasing hormone antagonist failure resulting in breakthrough luteinizing hormone surges in in vitro fertilization cycles. Fertil Steril 102(1):99–102. https://doi.org/10.1016/j.fertnstert.2014.04.010
12. Kochhar PK, Ghosh P (2020) Diminished ovarian reserve predisposes to premature luteinizing hormone surges in gonadotropin-releasing hormone antagonist cycles in in vitro fertilization. J Hum Reprod Sci 13(3):191. https://doi.org/10.4103/jhrs.JHRS_133_19

13. Klein NA, Harper AJ, Houmard BS, Sluss PM, Soules MR (2002) Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? J Clin Endocrinol Metab 87(12):5746–5750. https://doi.org/10.1210/jc.2002-020622
14. Durdağ GD, Bektaş G, Türkyılmaz E, Göktepe H, Sönmezer M, Şükür YE et al (2021) The efficacy of dydrogesterone use to suppress premature luteinizing hormone surge on cycle outcomes in controlled ovarian stimulation. J Turk Ger Gynecol Assoc 22(4):293. https://doi.org/10.4274/jtgga.galenos.2020.2020.0110
15. Chen Q, Chai W, Wang Y, Cai R, Zhang S, Lu X et al (2019) Progestin vs gonadotropin-releasing hormone antagonist for the prevention of premature luteinizing hormone surges in poor responders undergoing in vitro fertilization treatment: a randomized controlled trial. Front Endocrinol (Lausanne) 10:796. https://doi.org/10.3389/fendo.2019.00796
16. Huang P, Tang M, Qin A (2019) Progestin-primed ovarian stimulation is a feasible method for poor ovarian responders undergoing in IVF/ICSI compared to a GnRH antagonist protocol: a retrospective study. J Gynecol Obstet Hum Reprod 48(2):99–102. https://doi.org/10.1016/j.jogoh.2018.10.008
17. Peng Q, Cao X, Wang J, Wang L, Xu J, Ji X et al (2019) Progestin-primed ovarian stimulation vs mild stimulation in women with advanced age above 40: a retrospective cohort study. Reprod Biol Endocrinol 17(1):1–7. https://doi.org/10.1186/s12958-019-0518-3
18. Du M, Zhang J, Li Z, Liu X, Li J, Liu W et al (2021) Comparison of the cumulative live birth rates of progestin-primed ovarian stimulation and flexible GnRH antagonist protocols in patients with low prognosis. Front Endocrinol (Lausanne) 12:705264. https://doi.org/10.3389/fendo.2021.705264
19. Kalafat E, Dizdar M, Turkgeldi E, Yildiz S, Keles I, Ata B (2022) The comparison of fixed and flexible progestin primed ovarian stimulation on mature oocyte yield in women at risk of premature ovarian insufficiency. Front Endocrinol (Lausanne) 12:797227. https://doi.org/10.3389/fendo.2021.797227
20. Kolibianakis EM, Venetis CA, Kalogeropoulou L, Papanikolaou E, Tarlatzis BC (2011) Fixed versus flexible gonadotropin-releasing hormone antagonist administration in in vitro fertilization: a randomized controlled trial. Fertil Steril 95(2):558–562. https://doi.org/10.1016/j.fertnstert.2010.05.052
21. Kahyaoglu I, Dogru HY, Kaplanoglu I, Ozgu-Erdinc AS, Dilbaz S, Mollamahmutoglu L (2021) Effect of antagonist start day on cycle outcomes in poor responders. J Hum Reprod Sci 14(4):400–405. https://doi.org/10.4103/jhrs.jhrs_75_21
22. Kiliçdag EB, Haydardedeoglu B, Cok T, Haciveliogl SO, Bagis T (2010) Premature progesterone elevation impairs implantation and live birth rates in GnRH-agonist IVF/ICSI cycles. Arch Gynecol Obstet 281(4):747–752. https://doi.org/10.1007/s00404-009-1248-0
23. Zhang S, Yin Y, Li Q, Zhang C (2021) Comparison of cumulative live birth rates between GnRH-A and PPOS in low-prognosis patients according to POSEIDON criteria: a cohort study. Front Endocrinol (Lausanne) 12:644456. https://doi.org/10.3389/fendo.2021.644456