Original Investigations

The efficacy of dydrogesterone use to suppress premature luteinizing hormone surge on cycle outcomes in controlled ovarian stimulation
Doğan Durdağ et al. Dydrogesterone to suppress premature LH surge

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Abstract
Objective: Progestins are used as an alternative to GnRH antagonists to suppress premature LH surge and flexible protocol has been defined recently. The aim of this study is to compare the efficacy of flexible protocols with dydrogesterone and GnRH antagonist in suppressing LH surge.
Material and Methods: This retrospective case-control study, involving 105 patients, was conducted in an infertility unit of a tertiary referral university hospital, to compare a daily dose of 40 mg dydrogesterone with GnRH antagonist to suppress premature LH surge in controlled ovarian hyperstimulation cycles between July 2018 and July 2019. Dydrogesterone was started when the leading follicle was 12 mm or serum estradiol was over 300 pg/ml. A subgroup analysis of poor responder patients was also performed.
Results: Duration of pituitary suppression was longer in dydrogesterone group. Premature ovulation before scheduled oocyte pick up was observed in 11.5% (6/52) and 0% of the patients receiving dydrogesterone and GnRH antagonist respectively. However, collected oocyte counts and MII oocyte counts were found to be similar between the groups. All of the six patients who had premature ovulation in dydrogesterone group were in poor responder subgroup.
Conclusion: Dydrogesterone can be used as an alternative to antagonist regimen in patients where embryo transfer is not planned in the same cycle. However, flexible regimen may not be appropriate in patients with diminished ovarian reserve as advanced follicular maturation

and delayed suppressive effect of oral progesterone may cause premature ovulation. Randomized controlled trials in particular patient groups are required to determine the most effective minimum dose and time of application to ensure treatment success.
Keywords: Controlled ovarian hyperstimulation, dydrogesterone, luteinizing hormone surge, progestin-primed ovarian stimulation

Introduction

In controlled ovarian hyperstimulation (COH) cycles, it is aimed to develop numerous follicles to obtain ideal number and quality of oocytes. Premature luteinizing hormone (LH) surge and premature ovulation during the treatment is one of the major causes of cycle cancellation [1]. In GnRH antagonist protocol, GnRH antagonists suppress endogenous gonadotropins in minutes, however new stimulation regimens with lower costs without compromising success rates are under investigation [2, 3].

Studies have demonstrated that progesterone is an important regulator on timing of ovulation, and it can be used instead of GnRH antagonists to prevent early luteinization. In the protocol, which is defined as progestin-primed ovarian stimulation (PPOS), progestins are used as an alternative to GnRH antagonists to suppress LH surge. For this purpose, various progesterone forms and doses are reported [4]. Application of progesterone controls oocyte development and timing of ovulation, however, owing to disruption of synchronization between embryo development and endometrial receptivity due to untimely progesterone exposure, embryos obtained from these oocytes cannot be transferred in the same cycle [5]. Nevertheless, improvements in cryopreservation and vitrification techniques enable to freeze all oocytes or embryos to be transferred in the following cycles [2, 6].

Few studies have shown that the application of this protocol does not adversely affect oocyte development and the number of oocytes obtained, compared to antagonist protocol [1, 7, 8]. Besides, flexible PPOS protocol has been defined recently [9].

The aim of this study is to investigate whether a synthetic progesterone, dydrogesterone, when used in flexible protocol, is as effective as GnRH antagonists in suppressing LH surge and also we aimed to determine its effects on other cycle parameters.

Material and Methods

This retrospective case-control study was conducted in an infertility unit of a tertiary referral university hospital, involving 105 patients, for whom GnRH antagonist or oral dydrogesterone was used to block premature LH surge in COH cycles between July 2018 and July 2019. Patients, aged between 23 and 41, who applied for fertility preservation due to advanced age or malignancy, or who underwent controlled ovarian stimulation due to diminished ovarian reserve, unexplained infertility, endometriosis or male factor were included in the study.

In dydrogesterone group including 52 patients, starting from the third day of the cycle, 150-225 IU gonadotropin (human menopausal gonadotropin (hMG) or recombinant follicle stimulating hormone (rFSH)) was administered. Dydrogesterone (Duphaston® 10 mg, Abbott Farma, Netherlands) 2x20 mg/day was started when dominant follicle reached 12 mm in diameter or serum estradiol was over 300 pg/ml. Gonadotropin dose was adjusted according to the response of the ovary 5 days later and it was applied until trigger day, while dydrogesterone was continued 2x20 mg until trigger day. When two or more follicles reached 18 mm diameter, final oocyte maturation was triggered with 250µg choriogonadotropin alpha (Ovitrelle® 250 mcg, Merck - Serono, Madrid, Spain) and GnRH agonist (Decapeptyl® 0.1 mg, Ipsen Pharma or Lucrin® 5 mg/ml, Abbott). Regular and flexible PPOS protocols are shown in Figure 1a and 1b.

Control group consisted of age matched 53 patients, who received GnRH antagonist

Cetrorelix (Cetrotide® 0.25 mg, Merck - Serono) by antagonist protocol. This group was given 150-225 IU gonadotropin (hMG or rFSH) starting on the third day of the cycle. When the dominant follicle reached 13 mm in diameter, 0.25 mg cetrorelix was started and continued until trigger day. Gonadotropin dose was also adjusted according to ovarian response and it was continued until trigger day. When two or more follicles reached 18 mm in diameter, final oocyte maturation was triggered with 250 □g choriogonadotropin alpha (Ovitrelle® 250 mcg, Merck - Serono, Madrid, Spain) and GnRH agonist (Decapeptyl® 0.1 mg, Ipsen Pharma or Lucrin® 5 mg/ml, Abbott). In both groups oocyte retrieval was performed 36 hours after trigger application. Cryopreservation of the oocytes was performed using vitrification technique.

Files and computer records of the patients were examined. Age, body mass index (BMI), cause of infertility, type of COH protocol, duration and total dose of gonadotropins, duration of antagonist (cetrorelix) / dydrogesterone use, basal hormone levels, the suppression of premature LH surge, premature ovulation, and total and mature oocyte counts were evaluated. Premature LH surge was defined as serum LH level >15 mIU/mL on trigger day [8]. Premature ovulation was defined as rupture of the dominant follicle before oocyte retrieval and elevation of serum progesterone >3 ng/ml [8]. Efficacy in suppressing premature LH surge was compared between oral dydrogesterone and GnRH antagonist.

A subgroup analysis of poor responder patients between the study and control groups was further performed. This subgroup included patients belonging to Group 3 and 4 according to Poseidon classification (with AMH <1.2 ng/mL or antral follicle count <5) [10].

Statistical analysis

Data analyses were performed using SPSS Version 21.0 (IBM Corporation, Armonk, NYC, USA). The variables were investigated using visual (histograms and probability plots) and analytical methods (Shapiro-Wilk test) to determine whether or not they are normally distributed. According to the results, non-parametric tests were preferred. Descriptive statistics of continuous variables were compared between groups using Mann-Whitney U test. The Chi-square test or Fisher's exact test (when chi-square test assumptions do not hold due to low expected cell counts) were used to compare categorical variables between groups. Continuous variables were presented as median (25^{th}-75^{th} percentiles) values, whereas categorical variables were presented as number and percentage. A *P* value of <0.05 was considered statistically significant.

Results

A total of 52 patients, who were given dydrogesterone, were compared with an age matched control group of 53 patients who were administered GnRH antagonist protocol. Demographic features, total duration and dose of gonadotropins, number of total oocytes and MII oocytes collected were similar between the two groups, however, total duration of dydrogesterone/cetrorelix administration was found to be significantly different (p<0.001). Trigger day estradiol was lower, while trigger day progesterone and maximum LH levels were higher in dydrogesterone group. It was also remarkable that AMH (anti mullerian hormon) levels were low in both groups [0.80 (0.38-2.31) and 0.42 (0.30-4.0) in dydrogesterone and antagonist groups respectively, p:0.188] (Table 1).

Indications for COH were fertility preservation due to advanced age in 28 (26.7%) patients, fertility preservation due to malignancy in 12 (11.4%) patients, diminished ovarian reserve in 29 (27.6%) patients, unexplained infertility in 3 (2.9%) patients, endometriosis in 14 (13.3%) patients, and male factor in 19 (18.1%) patients (Table 2). Significant difference was not found between dydrogesterone and GnRH antagonist groups in terms of indications (p=0.215).

It was observed that dual trigger was used in all patients except five patients whose estradiol was > 4000 pg/mL on trigger day, where analog trigger was applied. Two groups were similar with respect to application of trigger agents.

Premature LH surge was 13.5% in dydrogesterone group and 9.4% in antagonist group. Significant difference was not found between the two groups (p=0.517). It was also observed that premature ovulation before the scheduled oocyte pick up day was encountered in 6 (11.5%) patients in dydrogesterone group, whereas it did not occur in antagonist group (p=0.013). In four of all six patients oocytes could be collected from the other follicles, while oocyte retrieval could not be achieved from two patients due to diminished ovarian reserve.

The subgroup of poor responder patients included 40 patients, of whom 25 were in the dydrogesterone group and 15 were in the antagonist group. Clinical outcomes were similar between dydrogesterone and antagonist groups, however, all of the six patients who had premature ovulation were in the dydrogesterone group (Table 3).

Discussion

This study demonstrated that dydrogesterone, used in flexible PPOS protocol, partly provided similar results with antagonist protocol in preventing premature LH surge, with favorable results including total number and quality of oocytes collected. However, high incidence of premature ovulation in patients receiving dydrogesterone suggested that flexible regimen might not be suitable in all patients.

Transient but quick LH suppression provided by GnRH antagonist is associated with competitive blockade of GnRH receptor [8, 11], while progestins suppress GnRH secretion at hypothalamus when they are administered in the early phase of the cycle prior to estrogen elevation [8, 12]. It has been stated that serum LH levels are more stable with PPOS and oocyte retrieval can be planned more precisely [8]. Furthermore, ease of oral use instead of daily injections and lower cost of treatment are advantageous [7, 9, 13]. However, as the main limitation of these protocols is the inability to perform transfer in the same cycle, progestins may be more suitable for planned freeze-all cycles, preimplantation genetic testing cycles, elective oocyte cryopreservation and oocyte donor stimulation [14].

Progesterone is known to inhibit estradiol induced LH surge both in early follicular phase and early luteal phase [1]. Although there is much about endogenous LH surge and the role of progesterone to be elucidated [15], it has been reported that progesterone should be administered at the right time to be effective [1]. Recently, multiple follicle selection waves and random start protocols have brought attention to flexible PPOS programs, and in a study, including donor cycles, it is shown that flexible PPOS protocol can effectively suppress premature ovulation as well [9].

In our study, cycle parameters other than the incidence of early ovulation were mostly similar between the groups. Notably, total duration of pituitary suppression was longer in dydrogesterone group, since we started to use dydrogesterone 1 day earlier as opposed to GnRH antagonist administration protocols. This result is partly similar with previous studies. In the report of Kuang et al., while hMG dose and duration were higher in the study group, collected oocyte counts and other cycle parameters were similar [1]. In the study of Xiao et al., while dose and duration of gonadotropins were higher in PPOS group, other characteristics were similar [7]. Cycle parameters were similar in the study of Chen et al. [8], and were also similar in the study of Wang et al., with the exception of hMG dose being higher in PPOS group [16]. Lower trigger day estradiol level in dydrogesterone group in our study was probably caused by higher number of poor responder patients in this group. Also, difference between LH levels, which were <10 mIU/mL in both groups, was not considered as clinically significant. Though, higher trigger day progesterone levels in dydrogesterone group were consistent with the finding of premature ovulation.

Patients who underwent COH with several indications were included in our study. Data regarding different patient groups using PPOS protocols are available in the literature. PPOS is reported to be successful in polycystic ovary syndrome (PCOS) patients as an alternative to the antagonist protocol, as it reduces the risk of ovarian hyperstimulation syndrome, suppresses premature LH surge, and uses freeze-all strategy [7, 16]. It has been suggested that higher total gonadotropin dose and duration with PPOS are caused by decreased follicle sensitivity due to high progesterone and pituitary suppression [7]. On the other hand, there are also studies, which report that PPOS suppresses LH surge better than GnRH antagonists, with similar oocyte counts, in poor responder patients [8, 17, 18]. Among our patients who received treatment for fertility preservation due to malignancy, PPOS protocol was not administered to patients with breast cancer, while two of the patients in our cetrorelix group had breast cancer. These two patients received letrozole 5 mg/day (Femara®, Novartis, Switzerland), starting from the third day of the menstrual cycle along with gonadotropin, until trigger day.

Synthetic progesterones are preferred in studies as natural micronized progesterones can affect serum values, and medroxyprogesterone acetate (MPA) is the most commonly used agent for this purpose. Kuang et al. compared 10 mg/day MPA with standard antagonist protocol for the first time, and found similar results in terms of hMG dose and duration as well as oocyte and embryo counts [1]. It was previously reported that MPA could not inhibit ovulation at a dose of 5 mg/day [19]. However, Dong et al., who investigated the minimum dose to suppress LH surge, concluded that 4 mg MPA was similar to 10 mg in terms of the number of oocytes collected and was sufficient to prevent premature LH surge [20]. Yu et al. compared MPA and dydrogesterone to suppress premature LH surge, and reported that premature LH surge was not seen in either group, and similar oocyte counts and cycle characteristics were observed between the groups [4]. Nevertheless, there are few studies using dydrogesterone, and no exact protocol in terms of dose and duration has been specified. There are reports that dydrogesterone does not prevent ovulation at recommended doses (10-20 mg/day) for MPA, and a minimum dose of 30 mg dydrogesterone is required for this purpose [21, 22]. Study of Yu et al. also concluded that dydrogesterone is weaker than MPA in suppressing GnRH, and a minimum 20 mg dose is needed to be effective [4]. Based on these reports, while 30 mg/day is considered as the proper dose for dydrogesterone, in order to provide patient compliance, 40 mg/day (2x2 tablets) dydrogesterone was preferred in our study.

Rates of premature LH surge were 13.5% and 9.4% in dydrogesterone and cetrorelix groups respectively, while the difference was not found to be significant. In the study of Kuang et al., premature LH surge was not observed in both groups (1 in 150 patients in the study group) [1]. In the study of Chen et al. in poor responder group, the rate of premature LH surge was significantly lower in PPOS group than antagonist group, however, the number of obtained oocytes and embryos were similar [8]. In the study of Wang et al. in PCOS group, premature LH surge and premature ovulation were not reported, and the cycle parameters were similar with the exception of higher hMG doses in the MPA group [16]. However, there are also studies reporting higher rates of premature LH surge. Although the suppressive effect of GnRH antagonists on LH is rapid and reversible, premature LH surge is reported to be seen at 0.34%-38% of the patients [23, 24]. When compared to the prompt effect of GnRH antagonists in minutes, dydrogesterone acts even slower as its peak plasma level is achieved at 1 hour [21].

Collection of oocytes before ovulation in some of our patients with premature LH surge was accomplished by changing the oocyte aspiration time according to LH monitorization. This positive effect of LH monitoring has also been reported in previous studies. Chen et al., in their study with poor responders, observed that, at least one mature oocyte could be collected

from 9 of 10 patients who had premature LH surge in antagonist group by changing the oocyte retrieval time [8]. LH monitoring was not performed in the flexible PPOS protocol study of Yildiz et al, however, premature ovulation was not reported for either group, though this study included donor cycles and not poor responders [9].

In our study, dual trigger was used for completion of final maturation, in line with the results of previous studies [1, 16, 25].

While premature ovulation was not observed in our cetrorelix group, this rate was significantly higher in dydrogesterone group. It was formerly reported that, rise in serum progesterone level after the increase in serum estradiol concentrations results in earlier LH surge [26, 27]. Therefore, higher premature LH surge and premature ovulation rates in our dydrogesterone group may be related to the late administration of dydrogesterone in our study, when compared to above-mentioned studies, in which progesterone administration was started at the third day of the cycle [1, 4, 8]. It is also reported that diminished ovarian reserve increases the risk of premature LH surge in antagonist cycles [24]. Although we classified our cohort due to COH indications, 48.1% and 28.3% of the patients were poor responders in dydrogesterone and GnRH antagonist groups respectively. It has been demonstrated in some studies that follicular phase may be shortened in older ovulatory women due to earlier dominant follicle selection. Moreover, low response may also be associated with accelerated luteinization of mature follicles [28, 29]. The relatively high prevalence of poor responder patients may be a potential reason of advanced follicular maturation, and possibly premature ovulation. Therefore, particularly in patients with diminished ovarian reserve, flexible protocol may not be suitable, and early administration of dydrogesterone may be necessary to prevent premature ovulation. Though, Turkgeldi et al. recently reported that flexible PPOS protocol might be used as an alternative to the flexible GnRH-antagonist protocol in patients with diminished ovarian reserve [18]. In this study, pituitary suppression by medroxyprogesterone acetate was commenced as the estradiol level was ≥200 ng/L in contrast to the 300 ng/L threshold of estradiol in our study (similar threshold level with our accustomed flexible GnRH antagonist protocol was used in our study since there is not a clear cut for flexible PPOS protocol), and only one premature ovulation was encountered in the study group, which consisted of 27 patients. These findings may suggest that dydrogesterone should be administered earlier.

Furthermore, oocytes could be retrieved from 4 of 6 patients who had premature ovulation in our study. It was also reported in previous studies that fertilization and live birth could be achieved from the oocytes of the smaller follicles as well as the oocytes collected from cul-de sac after premature ovulation [30].

Main limitation of this study is its retrospective nature. However, lack of difference between the demographic characteristics of both groups may decrease the risk of bias that may occur in this sense. Besides, while live birth rate is an important parameter in evaluating cycle success, pregnancy outcomes could not be assessed due to freeze-all strategy, and in particular, cryopreservation of the oocytes for fertility preservation in an important part of the patients.

Conclusion

Dydrogesterone can be used as an alternative to antagonist regimen in patients, where embryo transfer is not planned to be performed in the same cycle. However, particularly in patients with diminished ovarian reserve, early start of progesterone may be appropriate owing to advanced and accelerated follicular maturation, along with oral absorbtion pharmacokinetics of dydrogesterone. However, randomized controlled trials in particular populations are required to determine the most effective minimum dose and time of application to ensure treatment success.

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This study was approved by Institutional Review Board and Ethics Committee of Ankara University Faculty of Medicine (Decision number: 20-1364-18).

References

1. Kuang Y, Chen Q, Fu Y, Wang Y, Hong Q, Lyu Q, et al. Medroxyprogesterone acetate is an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for in vitro fertilization. Fertility and sterility. 2015;104:62-70. e3.
2. Massin N. New stimulation regimens: endogenous and exogenous progesterone use to block the LH surge during ovarian stimulation for IVF. Human reproduction update. 2017;23:211-20.
3. Wang Y, Kuang Y, Chen Q, Cai R. Gonadotropin-releasing hormone antagonist versus progestin for the prevention of premature luteinising hormone surges in poor responders undergoing in vitro fertilisation treatment: study protocol for a randomised controlled trial. Trials. 2018;19:1-6.
4. Yu S, Long H, Chang HY-n, Liu Y, Gao H, Zhu J, et al. 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. Human Reproduction. 2018;33:229-37.
5. Chen Y-m, Qi Q-r, Xie Q-z, Yang Y-f, Xia Y, Zhou X-d. Effect of progestin-primed ovarian stimulation protocol on outcomes of aged infertile women who failed to get pregnant in the first IVF/ICSI cycle: a self-controlled study. Current medical science. 2018;38:513-8.
6. Cobo A, Kuwayama M, Pérez S, Ruiz A, Pellicer A, Remohí J. Comparison of concomitant outcome achieved with fresh and cryopreserved donor oocytes vitrified by the Cryotop method. Fertility and sterility. 2008;89:1657-64.
7. Xiao Z-n, Peng J-l, Yang J, Xu W-m. Flexible GnRH Antagonist Protocol versus Progestin-primed Ovarian Stimulation (PPOS) Protocol in Patients with Polycystic Ovary Syndrome: Comparison of Clinical Outcomes and Ovarian Response. Current medical science. 2019;39:431-6.
8. Chen Q, Chai W, Wang Y, Cai R, Zhang S, Lu X, et al. Progestin versus gonadotropin-releasing hormone antagonist for the prevention of premature luteinizing hormone surges in poor responders undergoing in vitro fertilization treatment: a randomized controlled trial. Frontiers in Endocrinology. 2019;10:796.
9. Yildiz S, Turkgeldi E, Angun B, Eraslan A, Urman B, Ata B. Comparison of a novel flexible progestin primed ovarian stimulation protocol and the flexible gonadotropin-releasing hormone antagonist protocol for assisted reproductive technology. Fertility and sterility. 2019;112:677-83.
10. Grisendi V, Mastellari E, La Marca A. Ovarian reserve markers to identify poor responders in the context of Poseidon classification. Frontiers in Endocrinology. 2019;10:281.
11. Inaudi P, Barra V, Vellucci FL, Regini C, Luisi S. GnRH antagonist does not prevent premature luteinization and ovulation in stimulated cycles with gonadotropins for IVF: two case reports. Gynecological Endocrinology. 2018;34:189-91.
12. Attardi B, Scott R, Pfaff D, Fink G. Facilitation or Inhibition of the Oestradiol‐Induced Gonadotrophin Surge in the Immature Female Rat by Progesterone: Effects

on Pituitary Responsiveness to Gonadotrophin‐Releasing Hormone (GnRH), GnRH Self‐Priming and Pituitary mRNAs for the Progesterone Receptor A and B Isoforms. Journal of neuroendocrinology. 2007;19:988-1000.
13. Evans MB, Parikh T, DeCherney AH, Csokmay JM, Healy MW, Hill MJ. Evaluation of the cost-effectiveness of ovulation suppression with progestins compared with GnRH analogs in assisted reproduction cycles. Reproductive biomedicine online. 2019;38:691-8.
14. Beguería R, García D, Vassena R, Rodríguez A. Medroxyprogesterone acetate versus ganirelix in oocyte donation: a randomized controlled trial. Human Reproduction. 2019;34:872-80.
15. Ata B, Capuzzo M, Turkgeldi E, Yildiz S, La Marca A. Progestins for pituitary suppression during ovarian stimulation for ART: a comprehensive and systematic review including meta-analyses. Human Reproduction Update. 2020.
16. Wang Y, Chen Q, Wang N, Chen H, Lyu Q, Kuang Y. Controlled ovarian stimulation using medroxyprogesterone acetate and hMG in patients with polycystic ovary syndrome treated for IVF: a double-blind randomized crossover clinical trial. Medicine. 2016;95.
17. Huang P, Tang M, Qin A. 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. Journal of gynecology obstetrics and human reproduction. 2019;48:99-102.
18. Turkgeldi E, Yildiz S, Cekic SG, Shakerian B, Keles I, Ata B. Effectiveness of the flexible progestin primed ovarian stimulation protocol compared to the flexible GnRH antagonist protocol in women with decreased ovarian reserve. Human Fertility. 2020:1-7.
19. Wikström A, Green B, Johansson ED. The plasma concentration of medroxyprogesterone acetate and ovarian function during treatment with medroxyprogesterone acetate in 5 and 10 mg doses. Acta obstetricia et gynecologica Scandinavica. 1984;63:163-8.
20. Dong J, Wang Y, Chai W, Hong Q, Wang N, Sun L, et al. The pregnancy outcome of progestin‐primed ovarian stimulation using 4 versus 10 mg of medroxyprogesterone acetate per day in infertile women undergoing in vitro fertilisation: a randomised controlled trial. BJOG: An International Journal of Obstetrics & Gynaecology. 2017;124:1048-55.
21. Schindler AE, Campagnoli C, Druckmann R, Huber J, Pasqualini JR, Schweppe KW, et al. Reprint of classification and pharmacology of progestins. Maturitas. 2008;61:171-80.
22. Rižner TL, Brožič P, Doucette C, Turek-Etienne T, Müller-Vieira U, Sonneveld E, et al. Selectivity and potency of the retroprogesterone dydrogesterone in vitro. Steroids. 2011;76:607-15.
23. Bosch E, Valencia I, Escudero E, Crespo J, Simon C, Remohi J, et al. Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome. Fertility and sterility. 2003;80:1444-9.
24. Reichman DE, Zakarin L, Chao K, Meyer L, Davis OK, Rosenwaks Z. 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. Fertility and sterility. 2014;102:99-102.
25. Lu X, Hong Q, Sun L, Chen Q, Fu Y, Ai A, et al. Dual trigger for final oocyte maturation improves the oocyte retrieval rate of suboptimal responders to gonadotropin-releasing hormone agonist. Fertility and sterility. 2016;106:1356-62.

26. Helmond F, Simons P, Hein P. The effects of progesterone on estrogen-induced luteinizing hormone and follicle-stimulating hormone release in the female rhesus monkey. Endocrinology. 1980;107:478-85.
27. Helmond F, Simons P, Hein P. Strength and duration characteristics of the facilitory and inhibitory effects of progesterone on the estrogen-induced gonadotropin surge in the female rhesus monkey. Endocrinology. 1981;108:1837-42.
28. Klein NA, Harper AJ, Houmard BS, Sluss PM, Soules MR. Is the short follicular phase in older women secondary to advanced or accelerated dominant follicle development? The Journal of Clinical Endocrinology & Metabolism. 2002;87:5746-50.
29. Luborsky J, Thiruppathi P, Rivnay B, Roussev R, Coulam C, Radwanska E. Evidence for different aetiologies of low estradiol response to FSH: age-related accelerated luteinization of follicles or presence of ovarian autoantibodies. Human reproduction. 2002;17:2641-9.
30. Wu FS-Y, Lee RK-K, Hwu Y-M. Encountering premature ovulation during controlled ovarian hyperstimulation in IVF/ICSI cycles. Taiwanese Journal of Obstetrics and Gynecology. 2012;51:256-9.

Table 1. Demographic and clinical features of the groups			
	Dydrogesteron (n=52)	**Cetrorelix (n=53)**	**p**
Age (years) (Median (25^{th}-75^{th} percentiles)	33 (25-38)	32 (30-36)	0.527
BMI (Median (25^{th}-75^{th} percentiles)	24.1 (19.7-25.4)	25.8 (23.3-28.6)	0.103
Parity (Median (25^{th}-75^{th} percentiles)	0 (0-0)	0 (0-0)	0.476
AMH (ng/mL) [Median (25^{th}-75^{th} percentiles)]	0.80 (0.38-2.31)	0.42 (0.30-4.0)	0.188
Duration of pituitary suppression (day) [Median (25^{th}-75^{th} percentiles)]	6 (4-7)	4 (3-6)	**<0.001**
Duration of gonadotropins (day) (Median (25^{th}-75^{th} percentiles))	10 (8-11)	9 (8-11)	0.110
Total dose of gonadotropins (IU) (Median (25^{th}-75^{th} percentiles))	2025 (1800-2475)	1950 (1560-2712)	0.809
Trigger day E2 (pg/mL) (Median (25^{th}-75^{th} percentiles))	748 (150-1060)	1395 (550-2382)	**0.007**
Trigger day P (ng/mL) (Median (25^{th}-75^{th} percentiles))	1.27 (1.0-2.29)	1 (0.80-7.75)	**0.004**
Maximum LH (mIU/mL) (Median (25^{th}-75^{th} percentiles))	6 (5.0-10.47)	4 (2.5-16)	**0.005**
Number of oocytes (Median (25^{th}-75^{th} percentiles))	8 (2-12)	8 (2-13)	0.669
Number of M2 oocytes (Median (25^{th}-75^{th} percentiles))	6 (1-10)	7 (1-11)	0.399
Premature ovulation (n (%))	6 (11.5)	0(0)	**0.013**
(BMI: Body mass index, AMH: anti müllerian hormon, E2: estradiol, P: progesterone, LH: luteinizing hormon)			

Table 2. Indications of controlled ovarian hyperstimulation			
	Dydrogesterone n (%)	**Cetrorelix n (%)**	**Total number of patients**
Fertility preservation due to advanced age	12 (42.9%)	16 (57.1%)	28
Fertility preservation due to malignancy	9 (75.0%)	3 (25.0%)	12
Diminished Ovarian Reserve	16 (55.2%)	13 (44.8%)	29
Unexplained Infertility	1 (33.3%)	2 (66.7%)	3
Endometriosis	8 (57.1%)	6 (42.9%)	14
Male factor	6 (31.6%)	13 (68.4%)	19

Table 3. Demographic and clinical features of the patients in poor responder subgroup			
	Dydrogesteron (n=25) (48.1%)	**Cetrorelix (n=15) (28.3%)**	**p**
Age (years) (Median (25^{th}-75^{th} percentiles))	32 (25-38)	35 (32-37)	0.595
BMI (Median (25^{th}-75^{th} percentiles))	24.7 (19.6-30.1)	26.6 (23.4-29.9)	0.199
Parity (Median (25^{th}-75^{th} percentiles))	0 (0-0)	0 (0-0)	0.289
AMH (ng/mL) (Median (25^{th}-75^{th} percentiles))	0.34 (0.09-0.74)	0.42 (0.22-0.58)	0.903
Duration of pituitary suppression (day) (Median (25^{th}-75^{th} percentiles))	5 (4-6)	4 (3-6)	0.397
Duration of gonadotropins (day) (Median (25^{th}-75^{th} percentiles))	8 (6-9)	10 (8-12)	0.820
Total dose of gonadotropins (IU) (Median (25^{th}-75^{th} percentiles))	1800 (1425-2025)	2213 (1631-3600)	0.345
Trigger day E2 (pg/mL) (Median (25^{th}-75^{th} percentiles))	157 (78-724)	408 (335-1132)	0.108
Trigger day P (ng/mL) (Median (25^{th}-75^{th} percentiles))	1.0 (0.6-1.5)	5.0 (1.0-9.5)	0.054
Maximum LH (mIU/mL) (Median (25^{th}-75^{th} percentiles))	9.0 (6.3-14.3)	11.5 (7.5-17.0)	0.897
Number of oocytes (Median (25^{th}-75^{th} percentiles))	2.0 (0.5-5.0)	2.0 (1.0-3.3)	0.283
Number of M2 oocytes (Median (25^{th}-75^{th} percentiles))	2.0 (0.5-4.0)	1.5 (1.0-2.3)	0.377
Premature ovulation (n(%))	6 (24)	0(0)	***0.046***
(BMI: Body mass index, AMH: anti müllerian hormon, E2: estradiol, P: progesterone, LH: luteinizing hormon)			

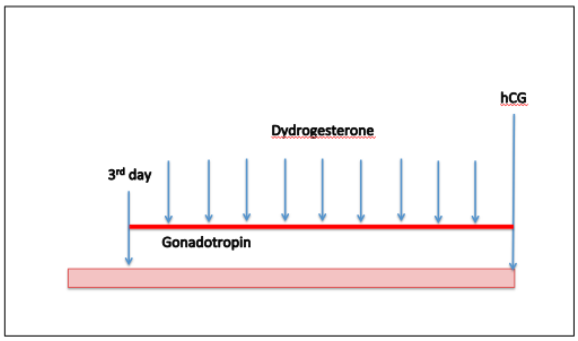

Figure 1a. Regular PPOS protocol

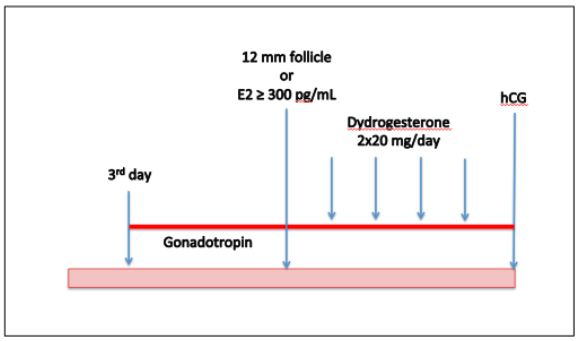

Figure 1b. Flexible PPOS protocol