International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

An Overview on Ovarian Response in Dydrogesterone-Primed Ovarian Stimulation and Gonadotropin-Releasing Hormone Antagonist Protocols

Mustapha Amin Fahmy EL-Sayed, Mohamad Mohamad Al Bakry, Tarek Mohamed Elbeheidy, Khaled Fathy Helal

Obstetrics and Gynecology Department, Faculty of Medicine, Zagazig University, Egypt

Abstract

The ovarian stimulation protocol is a vital step in assisted reproductive technology. Increased estrogen levels associated with the use of gonadotropins may lead to a luteinizing hormone (LH) peak. Unless preventive measures are taken, an LH surge occurs in 20–25% of stimulated cycles.1 Detection of an LH peak prior to the scheduled time is among the major reasons for cancellation of in vitro fertilization (IVF) treatment. Recently, progesterone was suggested as an alternative agent for preventing the LH surge in ovarian stimulation cycles. Progesterone was demonstrated to reduce GnRH pulsatility from the hypothalamus and to inhibit LH release associated with increased estradiol levels. Therefore, no spontaneous LH surge occurred during ovarian stimulation in the luteal phase in some studies. These findings led to a progesterone-primed ovarian stimulation (PPOS) protocol. Subsequent studies confirmed the blocking effect of progesterone on LH elevation during ovarian stimulation, with optimal pregnancy outcomes in FET cycles. The requirement for the freeze-all strategy in the PPOS protocol due to endometrium desynchronization seems to be a disadvantage. However, PPOS may be the best option for conditions in which fresh embryo transfer is not appropriate, such as donor cycles, preimplantation genetic testing cycles, fertility preservation, and hyper-responsive patients with high risk of OHSS.

Keywords: ovarian stimulation, in vitro fertilization, Dydrogesterone-primed ovarian stimulation.

Mini review article **Corresponding Author*, e-mail: *mafahmy21@gmail.com*

1. Introduction

Progestins-primed ovarian stimulation (PPOS) were employed to inhibit the premature release LH during COS in PCOS ladies and found that orally administered progestin consistently suppressed LH levels in the bloodstream, effectively preventing an LH surge through the process of OS, improved rates of continued pregnancy (58.67%) and live-birth (54.67%) compared to 40% observed in PCOS ladies having IVF/ICSI therapy with GnRHan regimens [1]. Cuello-Garcia et al. [2] suggested that the progestin protocol stimulates the production of endogenous progestin, which effectively inhibits luteinizing hormone (LH) and prevents OHSS, based on rat granulosa cells. However, Oktem et al. [3] showed that follicle-stimulating hormone (FSH) may increase the expression of 3B-HSD, leading to increased production of endogenous progestin without luteinization. In PCOS patients, hypersecretion of LH during follicular phase can cause abnormal granulosa cell function, oocyte arrest or immaturity, and hinder developmental potential of oocytes, resulting in decreased quality of oocytes and embryos [4]. Administering progestin during follicular phase can slow LH pulse frequency, block estrogen-induced LH surges, and promote oocyte health and cytoplasmic maturation.

Additionally, the high proportion of progesterone to estrogen in the follicular fluid may lead to better embryo development [5]. PPOS needed a higher total dose of Gn stimulation with PCOS than the GnRH analogue protocols. The possible theory is that the high progesterone milieu during PPOS leads to deeper pituitary suppression, which will make follicles less sensitive to gonadotropin stimulation [6]. La Marca et al. [7] have shown no significant difference in the blastocyst euploidy rate, neonatal outcomes, or the risk of congenital malformations between PPOS and conventional GnRH analogue protocols. Another potential issue hindering the PPOS protocol's application is its cost. Evans et al. [8] found that, compared to conventional GnRH analogue protocols for fresh embryo transplantation, the PPOS protocol resulted in a significantly higher cost per live birth, compared to short agonist and antagonist protocols, respectively. However, the PPOS protocol is actually more cost-effective than other COS protocols for patients requiring the "freezing-all" strategy, indicating the extra cost is mainly

from embryo freezing and subsequent frozen-thawed embryo transfer (FET) [9]. What's more, it is noted that PCOS patients undergoing FET have a lower risk of OHSS and a higher LBR than fresh cycles.

Thus, given the high risk of OHSS and the potential benefit of FET for PCOS patients, the choice between the protocols may depend more on the patient's condition and preference. For example, PPOS may be a better option if the patient plans to use a freezing strategy, like in preimplantation genetic testing or fertility preservation cycles [10]. Eftekhar et al. [11] evaluated the cycle characteristics and pregnancy outcome of individuals with PPOS and compare them with conventional antagonist. They showed that PPOS is not appropriate for women with PCOS, Tahoun et al. [12] investigated the effectiveness of PPOS and compared it with the standard PCOS antagonist regimen. They showed that fixed PPOS in PCOS patients receiving IVF/ICSI therapies is a safe, efficient procedure. Yang et al. [13] investigated the efficacy of PPOS in patients with PCOS during in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI). PPOS leads to no significant difference in the risk ofOHSS, the number of metaphase II oocytes, or rate of live birth when compared to GnRH analogue protocols.

Additionally, PPOS required a higher dose of Gn and tended to improve the implantation rate, clinical pregnancy rate, and ongoing pregnancy rate. The higher implantation rate, clinical pregnancy rate, and ongoing pregnancy rate were found in PPOS compared to the GnRH agonist short protocol. However, the certainty of evidence for outcomes was generally low. There is no evidence to support that PPOS reduces risk of OHSS or improves pregnancy outcomes in PCOS patients undergoing IVF/ICSI compared to GnRH analogue protocols. Still, protocol may be a viable alternative, especially for frozen-thawed embryo transfer, due to its efficiency and safety. Darwish et al. [14] evaluated outcomes of Fixed Progestin-Primed Ovarian Stimulation (FPPOS) and Flexible GnRH Antagonist Protocol (FGnRHan) on OSR and pregnancy outcomes in PCOS ladies undergone intracytoplasmic sperm injection-frozen embryo transfer (ICSI-FET). The FPPOS protocol proves to be a powerful, practical, user-friendly, economical, and clinically equivalent alternative to standard FGnRHan protocol.

2. Dydrogesterone-primed ovarian stimulation protocol

Dydrogesterone is a derivative of natural progestin and has high bioavailability, while Utrogestan is microparticle progesterone with lower bioavailability in the human body after oral administration. As a result, different types of oral progestins may lead to varying degrees of pituitary suppression in COS cycles and differences in the total dose of Gn stimulation [15]. Biological effects of progesterone at the cellular level are mediated by intracellular progesterone receptors (PR). The ability of any progestin to bind to the PGR varies between different compounds and thus their biological effect differs. In the circulation, relative binding affinity of DYG to PR is lower than that of MPA [16]. Since the PPOS protocol does not cause pituitary desensitization, the use of a GnRHa for ovulation trigger is applicable. However, a trigger with GnRHa alone is accompanied by the risk of a low response of the HPO axis ($LH \leq 15$ IU/L), resulting in lower oocyte retrieval rates [17]. Wang et al. **[1]** demonstrated that a double trigger, including GnRHa and a low dose of hCG (1000 IU), could avoid a low response of the HPO axis and does not increase risk of OHSS. DYG has been extensively used worldwide for the treatment of threatened miscarriage and recurrent miscarriage, as well as for luteal phase support in the setting of infertility [18]. Yu et al. [19] investigated cycle characteristics and endocrinological profiles of patients taking gonadotrophin while using DYG co-treatment. They showed that DYG, which exhibits no or weak inhibition of ovulation at a normal dosage, can serve as an hMG adjuvant during ovarian stimulation. This finding suggests the possibility of a new application of DYG: as an appropriate alternative progestin for the PPOS protocol in IVF.

3. Ovarian response in PPOS and GnRH analogue protocols

In-vitro fertilization (IVF) with the gonadotropin-releasing hormone (GnRH) antagonist protocol is the treatment of choice for patients with PCOS. Compared to GnRH agonist protocol, GnRH-antagonist protocol can significantly reduce the incidence of OHSS without interfering with rates of clinical pregnancy and live birth [20]. Progestin-primed ovarian stimulation (PPOS) protocol is a new ovarian stimulation regimen based on a freeze-all strategy that uses progestin as an alternative to a GnRH analog for suppressing a premature LH surge during the follicular phase. This new regimen of ovarian stimulation has been proved to effectively prevent a premature LH surge and does not compromise oocyte competence in cycles followed by embryo cryopreservation. It has been widely used in patients undergoing IVF since 2016 and showed good IVF outcomes [21**]**. Yildiz et al. [22] suggested that PPOS yields a similar number of oocytes with similar reproductive potential, i.e. fertilization, blastulation and euploidy rates, to GnRH analogues. Notable differences are that the duration of stimulation is significantly shorter with PPOS than with the long GnRH agonist protocol (by a mean of 2.4 days), and that PPOS requires less gonadotrophin (647 IU on average), whereas the opposite is observed in comparison to the short GnRH agonist protocol, which takes 0.5 days less and requires 433 IU less of gonadotrophins on average [23].

These differences are too small to be clinically significant, and are explained by the different endocrine characteristics of these protocols: i.e. the profound pituitary suppression by the long agonist protocol prolongs the cycle and the initial flare effect of the short agonist protocol shortens it. There are no significant differences between PPOS and GnRH antagonists regarding ovarian response and stimulation characteristics. It should be noted that most studies are non-randomized and comprise low- to moderate-quality evidence. However, the consistency of the findings across different studies from different centres provides assurance in effect estimates [24]. The most important characteristic of PPOS cycles is the mandatory omission of a fresh embryo transfer. Obviously, endometrial exposure to progesterone before oocyte retrieval in an ovarian stimulation cycle causes earlier decidualization, and the window of implantation would be closed long before a blastocyst would develop and reach the endometrium. Perhaps the window of implantation may even never 'open' in conventional PPOS cycles, as progestin is started simultaneously with gonadotrophins and there is no oestrogen exposure to prime the endometrium for the progesterone effect. Clearly, PPOS is only an alternative option when a fresh embryo transfer is

not intended. The mandatory freeze-all approach for PPOS has multiple implications including cost-effectiveness.

It is intuitive to think that a PPOS cycle would cost less than a GnRH antagonist cycle, because progestins are much cheaper than antagonists. However, if a fresh transfer, which would have been carried out in a GnRH analogue cycle, would be cancelled just because PPOS was employed, the additional costs of cycle monitoring for the first frozen transfer, medication, embryo thawing/warming and indirect costs associated with additional clinic visits and loss of working time would exceed the cost savings in the stimulation cycle [8]. Overall, PPOS is clearly a more cost-effective option if a fresh embryo transfer is not considered possible or is not preferred, which includes all fertility preservation (except for progesterone receptor-positive breast cancer patients), preimplantation genetic testing (PGT) and planned freeze-all cycles. When a fresh embryo transfer is an option, the only available cost-effectiveness study so far is based on US prices, which are usually higher than those of other countries, and local costs should be considered when making a decision [8]. PPOS protocol is effective and feasible, without deteriorating the pregnancy outcomes. In addition, the total amount of gonadotrophin and the duration of gonadotrophin usage were significantly higher in the PPOS protocol group than in the GnRH antagonist group.

One possible reason for this is that follicle becomes less sensitive to gonadotropin stimulation in the high progesterone and the pituitary suppression during the ovarian hyperstimulation in PPOS protocol [25]**.** Wang et al. [1] compared cycle characteristics and endocrinological profiles using PPOS and GnRH-agonist short protocol for PCOS patients and found that PPOS protocol overcame premature ovulation and decreased the incidence of OHSS for patients with PCOS. Xiao et al. [26] compared the effects of these two protocols on the ovarian response and clinical outcomes in patients with PCOS undergoing IVF or ICSI. A total of 157 patients undergoing in-vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) were recruited into this study. The patients were divided into two groups by the stimulation protocols: the GnRH antagonist protocol group and the PPOS protocol group. There was no significant difference in clinical characteristics between the two groups. Dose and duration of gonadotropin were higher in the PPOS protocol group. Estradiol levels on day of human chorionic gonadotropin (hCG) administration were significantly lower in PPOS protocol group. Fertilization rates and number of good quality embryos were similar between two groups. Remarkably, we found 6 patients with moderate ovarian hyperstimulation syndrome (OHSS) in the GnRH antagonist protocol group but 0 in PPOS protocol group. A total of 127 women completed their frozen embryo transfer (FET) cycles.

There were no significant differences b/w two groups in terms of clinical pregnancy rate per transfer, implantation rate, first-trimester miscarriage rate and on-going pregnancy rate per transfer. They demonstrated PPOS protocol decreased incidence of OHSS without adversely affecting pregnancy outcomes for patients with PCOS undergoing IVF. Gurbuz and Gode [27] compared effects of progestin-primed ovarian stimulation using dydrogesterone (DYD) and gonadotropin-releasing hormone (GnRH) antagonist protocol on cycle characteristics and pregnancy rates in freeze-all cycles in patients with polycystic ovary syndrome (PCOS). They concluded that dydrogesterone-primed ovarian stimulation seems to be an effective alternative to GnRH antagonist protocol for freeze-all cycles in PCOS patients. Zhu et al. [28] explored differences between progestins and gonadotropin-releasing hormone antagonists (GnRH-ant) during ovarian stimulation in PCOS patients. They showed progesterone protocol is comparable with GnRH-ant protocol regarding oocytes/embryo yields and probability of clinical pregnancy, but the two regimens are distinct in regulation of pituitary LH secretion. Huang et al. [29] investigated whether this regimen (corifollitropin alfa/PPOS protocol) could effectively reduce GnRHant injections and prevent premature LH surge in PCOS patients undergoing IVF/ICSI cycles. This is a retrospective cohort study recruiting 333 women with PCOS, with body weight b/w 50 and 70 kg, undergoing first IVF/ICSI cycle.

We used corifollitropin alfa/GnRHant protocol prior to Jan 2017 (n = 160), then changed to corifollitropin alfa/PPOS protocol (n = 173). All patients received corifollitropin alfa 100 μg on menstruation day 2/3 (S1). Additional rFSH was administered daily from S8. In corifollitropin alfa/ GnRHant group, cetrorelix 0.25 mg/day was administered from S5 till trigger day. In corifollitropin alfa/PPOS group, dydrogesterone 20 mg/day was given from S1 till trigger day. GnRH agonist was used to trigger maturation of oocyte. All good quality day 5/6 embryos were frozen, and frozenthawed embryo transfer (FET) performed on subsequent cycle. Dydrogesterone successfully replace GnRHant to block LH surge while an average of 6.8 days of GnRHant injections needed in corifollitropin alfa/GnRHant group. No patients suffered from ovarian hyperstimulation syndrome (OHSS). The other clinical outcomes including additional duration/dose of daily gonadotropin administration, number of oocytes retrieved, and fertilization rate were similar between two groups. The implantation rate, clinical pregnancy rate, and live birth rate in first FET cycle were also similar between two groups. In women with PCOS undergoing IVF/ICSI treatment, corifollitropin alfa/PPOS protocol could minimize injections burden with comparable outcomes to corifollitropin alfa/GnRHant protocol.

References

[1] Y. Wang, Q. Chen, N. Wang, H. Chen, Q. Lyu, Y. Kuang. (2016). 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. 95(9): e2939.

[2] C.A. Cuello-Garcia, N. Santesso, R.L. Morgan, J. Verbeek, K. Thayer, M.T. Ansari, J. Meerpohl, L. Schwingshackl, S.V. Katikireddi, J.L. Brozek. (2022). GRADE guidance 24 optimizing the integration of randomized and non-randomized studies of interventions in evidence syntheses and health guidelines. Journal of Clinical Epidemiology. 142: 200-208.

[3] O. Oktem, N. Akin, G. Bildik, K. Yakin, E. Alper, B. Balaban, B. Urman. (2017). FSH Stimulation promotes progesterone synthesis and output from human granulosa cells without luteinization. Human Reproduction. 32(3): 643-652.

[4] J. Qiao, H.L. Feng. (2011). Extra-and intra-ovarian factors in polycystic ovary syndrome: impact on

oocyte maturation and embryo developmental competence. Human Reproduction Update. 17(1): 17-33.

[5] S.M. Borman, C.L. Chaffin, K.M. Schwinof, R.L. Stouffer, M.B. Zelinski-Wooten. (2004). Progesterone promotes oocyte maturation, but not ovulation, in nonhuman primate follicles without a gonadotropin surge. Biology of Reproduction. 71(1): 366-373.

[6] S. Kadoura, M. Alhalabi, A.H. Nattouf. (2022). Conventional GnRH antagonist protocols versus long GnRH agonist protocol in IVF/ICSI cycles of polycystic ovary syndrome women: a systematic review and meta-analysis. Scientific Reports. 12(1): 4456.

[7] A. La Marca, M. Capuzzo, S. Sacchi, M.G. Imbrogno, F. Spinella, M.T. Varricchio, M.G. Minasi, P. Greco, F. Fiorentino, E. Greco. (2020). Comparison of euploidy rates of blastocysts in women treated with progestins or GnRH antagonist to prevent the luteinizing hormone surge during ovarian stimulation. Human Reproduction. 35(6): 1325-1331.

[8] M.B. Evans, T. Parikh, A.H. DeCherney, J.M. Csokmay, M.W. Healy, M.J. Hill. (2019). Evaluation of the cost-effectiveness of ovulation suppression with progestins compared with GnRH analogs in assisted reproduction cycles. Reproductive BioMedicine Online. 38(5): 691-698.

[9] J. Huang, Q. Xie, J. Lin, X. Lu, N. Wang, H. Gao, R. Cai, Y. Kuang. (2019). Neonatal outcomes and congenital malformations in children born after dydrogesterone application in progestin-primed ovarian stimulation protocol for IVF: a retrospective cohort study. Drug Design, Development and Therapy. 2553-2563.

[10] S. Guan, Y. Feng, Y. Huang, J. Huang. (2021). Progestin-primed ovarian stimulation protocol for patients in assisted reproductive technology: A meta-analysis of randomized controlled trials. Frontiers in endocrinology. 12: 702558.

[11] M. Eftekhar, M. Hoseini, L. Saeed. (2019). Progesterone-primed ovarian stimulation in polycystic ovarian syndrome: An RCT. International Journal of Reproductive BioMedicine. 17(9): 671-676.

[12] A. Tahoun, M. Elgazzar, A. Shedid, A. Rezk. (2021). Fixed Progesterone-primed ovarian stimulation in polycystic ovarian syndrome: RCT. Benha Journal of Applied Sciences. 6(5): 109-115.

[13] L. Yang, F. Liang, Y. Yuan, X. Luo, Q. Wang, L. Yao, X. Zhang. (2023). Efficacy of progestin-primed ovarian stimulation in women with polycystic ovary syndrome undergoing in vitro fertilization: a systematic review and meta-analysis. Frontiers in endocrinology. 14: 1224858.

[14] F.F.I. Darwish, A.N. Elmantwe, H. Elbanhawy, A.K.E. Abbas, E. Noury, M. Anwar, A.M.B. Ahmed. (2023). Progestin-Primed Ovarian Stimulation (PPOS) Versus Flexible GnRH Antagonist Protocol (FGnRHan) In Women with Polycystic Ovary Syndrome (PCOS): A Retrospective Analysis of Clinical Outcomes and Ovarian Response of a Substantial Cohort. Benha medical journal. 41(1): 1-6.

[15] T. Levy, Y. Yairi, I. Bar–Hava, J. Shalev, R. Orvieto, Z. Ben–Rafael. (2000). Pharmacokinetics of the progesterone-containing vaginal tablet and its use in assisted reproduction. Steroids. 65(10-11): 645-649.

[16] A.E. Schindler, C. Campagnoli, R. Druckmann, J. Huber, J.R. Pasqualini, K.W. Schweppe, J.H. Thijssen. (2008). Reprint of classification and pharmacology of progestins. Maturitas. 61(1-2): 171-180.

[17] X. Lu, Q. Hong, L. Sun, Q. Chen, Y. Fu, A. Ai, Q. Lyu, Y. Kuang. (2016). Dual trigger for final oocyte maturation improves the oocyte retrieval rate of suboptimal responders to gonadotropin-releasing hormone agonist. Fertility and sterility. 106(6): 1356-1362.

[18] F.G. Mirza, A. Patki, C. Pexman-Fieth. (2016). Dydrogesterone use in early pregnancy. Gynecological endocrinology. 32(2): 97-106.

[19] S. Yu, H. Long, H.Y.-n. Chang, Y. Liu, H. Gao, J. Zhu, X. Quan, Q. Lyu, Y. Kuang, A. Ai. (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. Human Reproduction. 33(2): 229-237.

[20] A.H. Balen, L.C. Morley, M. Misso, S. Franks, R.S. Legro, C.N. Wijeyaratne, E. Stener-Victorin, B.C. Fauser, R.J. Norman, H. Teede. (2016). The management of anovulatory infertility in women with polycystic ovary syndrome: an analysis of the evidence to support the development of global WHO guidance. Human Reproduction Update. 22(6): 687-708.

[21] I. Crha, P. Ventruba, E. Filipinská, M. Dziakova, J. Žáková, M. Ješeta, E. Lousová, Z. Papíková. (2018). Medroxyprogesteron acetate use to block LH surge in oocyte donor stimulation. Ceska gynekologie. 83(1): 11-16.

[22] S. Yildiz, E. Turkgeldi, B. Ata. (2022). Role and effectiveness of progestins in pituitary suppression during ovarian stimulation for assisted reproductive technology: a systematic review and a meta-analysis. Minerva Obstetrics and Gynecology.

[23] B. Ata, M. Capuzzo, E. Turkgeldi, S. Yildiz, A. La Marca. (2021). Progestins for pituitary suppression during ovarian stimulation for ART: a comprehensive and systematic review including meta-analyses. Human Reproduction Update. 27(1): 48-66.

[24] S. Yildiz, E. Turkgeldi, B. Angun, A. Eraslan, B. Urman, B. Ata. (2019). 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. 112(4): 677-683.

[25] G. Griesinger, C.A. Venetis, T. Marx, K. Diedrich, B.C. Tarlatzis, E.M. Kolibianakis. (2008). Oral contraceptive pill pretreatment in ovarian stimulation with GnRH antagonists for IVF: a

systematic review and meta-analysis. Fertility and sterility. 90(4): 1055-1063.

[26] Z.-n. Xiao, J.-l. Peng, J. Yang, W.-m. Xu. (2019). 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. 39(3): 431-436.

[27] A.S. Gurbuz, F. Gode. (2020). Dydrogesterone-primed ovarian stimulation is an effective alternative to gonadotropin-releasing hormone antagonist protocol for freeze-all cycles in polycystic ovary syndrome. Journal of Obstetrics and Gynaecology Research. 46(8): 1403-1411.

[28] X. Zhu, H. Ye, J. Ye, Y. Fu. (2021). Progesterone protocol versus gonadotropin-releasing hormone antagonist protocol in women with polycystic ovarian syndrome undergoing in vitro fertilization treatments with frozen-thawed embryo transfer: a prospective randomized controlled trial. Annals of Translational Medicine. 9(5): 387.

[29] T.-C. Huang, M.-Z. Huang, K.-M. Seow, I.-J. Yang, S.-P. Pan, M.-J. Chen, J.-L. Hwang, S.-U. Chen. (2021). Progestin primed ovarian stimulation using corifollitropin alfa in PCOS women effectively prevents LH surge and reduces injection burden compared to GnRH antagonist protocol. Scientific Reports. 11(1): 22732.