Original Article

Progestin Primed Ovarian Stimulation with Dydrogesterone as an Oral Alternative to the Conventional GnRH Antagonist Protocol in Infertile PCOS Women Undergoing IVF: A Retrospective Study in Egypt

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ABSTRACT

Objective: To determine whether the progestin primed ovarian stimulation (PPOS) protocol using dydrogesterone (DYG) is comparable to the gonadotropin antagonist (GnRH ant) protocol in regards to effectiveness and safety, when used in infertile polycystic ovarian syndrome (PCOS) patients undergoing IVF.

Study Design: A retrospective cohort study consisting of 60 infertile women with PCOS who underwent IVF or ICSI, with equal numbers using the PPOS or GnRH ant protocols followed by cryopreservation of all embryos from April 2021 to May 2022. Primary outcome was the number of oocytes retrieved. Other outcomes included the duration and total dose of gonadotropins used, the mature metaphase II oocyte counts retrieved, fertilisation rates and viable embryo rates in both groups. The rate of OHSS in both groups were also compared.

Results: Both groups were comparable in terms of age, body mass index (BMI), duration of infertility and baseline levels of anti-mullerian hormone (AMH). Both groups were also comparable in terms of the number oocytes retrieved (27.37 ± 5.37 for PPOS vs 28.87 ± 5.91 for GnRH-ant protocol). Although the number of 2PN fertilized oocyte was significantly less in the PPOS group than the GnRH ant group (14.07±3.17 vs 16.67±3.24, P <0.005), the 2PN fertilization rate and the high-quality embryos cryopreserved (8.67 ± 2.99 for PPOS vs 9.3± 2.89 for GnRH-ant protocol) were similar between the two groups. The number of women that experienced mild and moderate OHSS were comparable in both groups.

Conclusion: In comparison to the conventional GnRH ant protocol, PPOS protocol using DYG provides an effective management option with similar clinical outcomes and a good safety profile.

Key Words: Dydrogesterone (DYG), in *vitro* fertilization (IVF) GnRH antagonist protocol (GnRH ant), ovarian hyperstimulation syndrome (OHSS), polycystic ovary syndrome (PCOS), progestin-primed ovarian stimulation (PPOS).

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INTRODUCTION

Polycystic ovary syndrome (PCOS) accounts for an average of eighty percent of anovulatory infertility cases[1,2]. The European Society of Human Reproduction and Embryology (ESHRE), has recommended that those that do not respond to first- and second-line ovulation therapies, would benefit from invitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI)[3]. Although an increased number of oocytes are normally produced in PCOS women undergoing IVF treatment, they are frequently of low quality, resulting in a lower fertilization rate and a raised miscarriage rate[4]. A higher risk of moderate and severe ovarian hyperstimulation syndrome (OHSS) is also witnessed[5,6].

The 2016 World Health Organization (WHO) guidelines, have recommended the use of the gonadotropin-releasing hormone (GnRH) antagonist protocol as the treatment of choice for patients with PCOS undergoing IVF [2]. GnRH antagonists (GnRHant), unlike GnRH agonists (GnRHa), avoids the flare effect by producing an abrupt decline in luteinising hormone (LH) and follicle stimulating hormone (FSH) by competitively inhibiting endogenous GnRH. Daily subcutaneous injections in the late follicular phase prevents the LH surge[7,8].

Recent large prospective studies have reported improved perinatal and pregnancy outcomes, and lower frequency of OHSS and pregnancy loss, following the transfer of frozen thawed IVF embryos, when compared to fresh embryo transfer, among infertile patients with PCOS. With progress in embryo vitrification techniques, combining a GnRHant cycle with a GnRHa trigger, followed by freezing all embryos for a subsequent cycle is encouraged and considered an ideal protocol for infertile

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patients with PCOS undergoing IVF[9-13]. GnRHant remains, however, to be expensive and inconveniently requires daily injections[14].

Progestin primed ovarian stimulation (PPOS) protocol has been recently proposed, by Kuang *et al*., as an effective alternative to GnRHa and GnRHant protocols in infertile women with PCOS undergoing IVF. Daily administration of oral progestin in the follicular phase, during controlled ovarian stimulation (COS), has been reported to effectively block LH surge[15]. All embryos, however, are cryopreserved for a subsequent cycle transfer, since early progestin exposure results in desynchronisation between development of the embryo and endometrial receptivity[16]. Exogenous progestins are conveniently administered orally, and are cheaper than GnRH ant, and thus when both protocols follow a freeze all approach, PPOS is considered an attractive protocol for all infertile PCOS patients undergoing IVF[15].

The selection of the suitable progestin is crucial to an effective PPOS protocol. Medroxyprogesterone acetate (MPA), micronized progesterone (MIP), and dydrogesterone (DYG), have all been reported to effectively block LH surge during COS[17,18]. MPA has been researched more extensively than other progestins, with larger studies showing similar pregnancy outcomes,[19-23] and a few studies showing improved oocyte quality, when compared to standard GnRH agonist and antagonsist protocols[15,24,25]. Few studies on limited population groups, are available on DYG, with results showing less profound pituitary suppression when compared to MPA[26,27].

Egypt has experienced a shortage of the only, once available, widely used GnRH antagonist drug Cetrotide (CET) since February 2022, and to date. Fertility specialists have since reverted to the novel PPOS protocol, however, with a shortage of the more researched MPA drug, DYG has now been the drug used for infertile PCOS patients undergoing IVF.

We have conducted this retrospective study in our fertility centre in Egypt to compare the effectiveness and safety of PPOS protocol using DYG to the GnRH ant protocol used in infertile PCOS patients. We hope that this study could provide statistical evidence, which together with the limited research available, would allow fertility specialists to counsel patients more confidently and allow patients to make more informed choices regarding their fertility plan.

METHODS

A retrospective case control study between April 2021 and May 2022 at the Mis Reproductive Centre (MRC), after approval from the ethics committee. The study population, consisted of 60 eligible infertile women with PCOS who underwent an IVF or ICSI cycle using the GnRH ant or PPOS protocol followed by the cryopreservation of all embryos.

The novel PPOS protocol, using DYG to block premature LH surge in COS, was implemented in our centre, in February 2022 and was used in 30 infertile women with PCOS. These were matched and compared with an equal number of women (control group) that were stimulated using the routinely used, flexible GnRH ant protocol, prior to that date. February 2022 was the start of the shortage of GnRH antagonist drug, CET in the Egyptian market. Efforts were made to match cases and controls by age, body mass index (BMI), duration of infertility, and attempts of IVF. Women with PCOS eligible to be analysed in this study were required to be between 20 and 35 years of age, not exceeding a BMI of 35 (class II) and with a history of infertility lasting more than one year. The diagnosis of PCOS was made according to the revised 2003 Rotterdam consensus[28]. Two of three of the following criteria were met: I - oligo- and/or anovulation; II - clinical and/or biochemical evidence of hyperandrogenism; or III - polycystic ovarian morphology on ultrasound, with other aetiologies of ovulatory dysfunction and hyperandrogenism excluded. Exclusion criteria included endometriosis grade 3 or higher, use of hormonal contraceptives before the study cycle, documented history of ovarian surgery, previous diagnosis of congenital or acquired uterine anomalies, history of recurrent spontaneous abortion or abnormal chromosomal karyotype in either of the partners.

A documented baseline scan on the second or third day of the menstrual period is routinely performed to exclude any follicles >12 mm or ovarian pathology that would prohibit ovarian stimulation. The PPOS protocol was administered by starting 150 – 225 IU of gonadotropin daily, (human menopausal gonadotropin (hMG) (Menopure® 75IU, Ferring) and/ or recombinant follicle stimulating hormone (rFSH) (Gonal-f® 300IU, Merck-Serono) in addition to oral DYG (Duphaston® 10 mg, Abbott Farma, Netherlands) 30mg daily from day two of menstruation until trigger day. Women with a high antral follicular count above twenty, or with an elevated basal FSH (above 7IU/L) would be started on a daily HMG dose of 150IU/day. A daily dose of 225 IU/day of HMG was used for all other patients. According to the ovarian response the dose of gonadotropin was adjusted after day five of stimulation as assessed by transvaginal ultrasonography and serum hormone levels.

In the control group (flexible GnRHant protocol), 150-225IU daily dose of gonadotropin was administered daily from day two of the menstrual cycle, as in the PPOS group, however daily subcutaneous (sc) doses of CET (Cetrotide® 0.25 mg, MerckSerono) was initiated when the dominant follicle reached 13mm, until trigger day.

In both protocols, final oocyte maturation was triggered, after serum estrogen (E2) was checked, when two or more follicles had reached 18 mm diameter, using sc 0.1 mg triptorelin (Decapeptyl; Ferring, Germany or Triptofem; IBSA) and / or intramuscular 5000 IU human chorionic gonadotropin (hCG) (Choriomone; IBSA). Oocyte retrieval was performed 34-36 hours after trigger, guided by transvaginal ultrasound using a single lumen aspiration needle. Follicles over 10mm in diameter were all aspirated and assessed for oocyte maturation after denudation. All metaphase II oocytes were fertilised four to six hours later, by either standard IVF or ICSI according to semen quality. Embryos were cultured and scored on day three according to Cummins's criteria[29]. Grade I and II high quality embryos were cryopreserved by vitrification, while grade III and IV embryos were subjected to extended culture until day five. Good blastocysts morphologically (grade 3BC or above) were frozen, based on the Gardner and Schoolcraft system[30].

Patients were monitored for symptoms and signs of OHSS, three- and six-days following oocyte retrieval with the severity graded according to the guideline issued by the Practice Committee of the American Society for Reproductive Medicine in 2016[31].

The primary study outcome was the number of oocytes retrieved. Other outcomes analysed in this study were the comparison of the duration and total dose of gonadotropins used, the mature metaphase II oocyte counts retrieved, in addition to the fertilisation rates and viable embryo rates in both groups. Fertilisation rate was defined as the number of fertilised oocytes divided by the number of total retrieved oocytes retrieved. The embryo rate per oocyte retrieved was defined as the number of embryos divided by the number of oocytes retrieved. Cycle cancelation rates, and rate of OHSS in both groups were also compared. The definition of cycle cancelation referred to the completion of oocyte retrieval but without viable embryos.

Sample size calculation was not made for this retrospective study, but all cycles that have met the inclusion criteria since the beginning of using PPOS and the matched cycles using the GnRH ant protocol prior to those, were included in the analysis.

RESULTS

A total of 60 infertile women with PCOS that underwent IVF/ICSI followed by cryopreservation, were included in this study as two equal groups. Baseline characteristics of the studied participants are presented in (Table 1). There was no significant difference between the PPOS group and the GnRH ant group in terms of age, body mass index (BMI), duration of infertility or the baseline levels of anti-Mullerian hormone (AMH).

Table 1: Baseline characteristics of study population

	PPOS group (n= 30)	GnRH ant control group (n=30)	*P value*
Age (y)	28.0±4.05	27.57 ±4.73	0.683
BMI	30.24 ±3.24	30.21 ±3.55	0.973
Infertility duration (y)	3.71 ±1.59	4.13 ±1.78	0.331
Baseline AMH level	5.29±1.09	5.41±1.25	0.685

Data are presented as mean ± standard deviation or n (%). $P > .05$ for all comparisons.

Further sub analyses of the demographic data were conducted in (Table 2). The two groups were found to be similar regarding the proportion of women in different age groups, different BMI groups, types of infertility and number of previous trials.

Table 2: Sub analyses of demographic data

		PPOS group (n= 30)	GnRH ant control group (n=30)	*P value*
Age (y)	<30	18 (60%)	18 (60%)	1.0
	30 or more	12 (40%)	12 (40%)	
BMI	< 30kg/m^2	12 (40%)	12 (40%)	1.0
	30kg/m^2 or more	18 (60%)	18 (60%)	
Previous trials	0	23(76.7%)	19 (63.3%)	0.501
	1	5 (16.7%)	7 (23.3%)	
	2	2 (6.7%)	4 (13.3%)	
Infertility type	1ry	28 (93.3%)	24 (80%)	0.254
	2ry	2 (6.7%)	6 (20%)	

Data are presented as n (%). $P > .05$ for all comparisons.

The cycle characteristics of COS for the two groups are shown in (Table 3). The PPOS group had used a shorter gonadotropin duration and used a lower dose of gonadotrophin than the GnRH-antagonist group for COS, which did not reach statistical significance. Compared with the GnRH-antagonist group, the estradiol levels on the day of trigger were lower, the number of oocytes retrieved were less and the number of MII oocytes were less in the PPOS group, however, these findings did not also reach statistical significance. Although the number of 2PN fertilized oocyte was significantly less in the PPOS group than the GnRH ant group (14.07±3.17 vs 16.67±3.24, P <0.005), the 2PN fertilization rate were similar between the two groups. In addition, there was no significant difference in the number of good-quality embryos cryopreserved between the two groups. The number of women that experienced mild and moderate OHSS were comparable in both groups.

Table 3: The cycle characteristics of COS

	PPOS group (n= 30)	GnRH ant control group (n=30)	*P value*
Gonadotropin total doses (IU)	2,817.50 ±716.32	2,972.50 ±889.7	0.46
Stimulation duration (days)	11.1 ±0.96	11.37 ±1.03	0.181
E2 pg/ml	5159.9 ±960.32	5478.07 ±855.7	0.331
No. of oocytes retrieved(n)	27.37±5.37	28.87±5.91	0.308
MII	18.37±2.94	19.8±3.58	0.095
Maturity %	68.23	69.7	0.573
2PN	14.07±3.17	16.67±3.24	0.003
2PN Fertility Rate	52.24	59.05	0.024
Cryopreserved	8.67±2.99	9.3±2.89	0.408
Embryo Rate	32.05	32.7	0.797
OHSS – mild	10 (33.3%)	11 (36.7%)	0.92
OHSS - moderate	4 (13.3%)	5 (16.7%)	

Data are presented as mean ± standard deviation or n (%). $P > .05$ for all comparisons.

Table 4: Sub analyses of tigger agent application between the groups

		PPOS group (n= 30)	GnRH ant control group (n=30)	*P value*
Trigger type	Agonist	15(50%)	15 (50%)	0.924
	HCG	5 (16.7%)	4 (13.3%)	
	Dual	10 (33.3%)	11 (36.7%)	

Different ovulation trigger agents were used according to estimated risk of OHSS and drug availability in the Egyptian market. Comparing the proportion of women using the different ovulation trigger agents, the two groups were found to be similar.

DISCUSSION

This retrospective cohort study supports the hypothesis that the clinical efficiency of DYG, used in the PPOS protocol for infertile PCOS women, is comparable to the conventional GnRH ant protocol using CET. Poor oocyte quality resulting in decreased fertilisation rates, and OHSS are two major complications that face fertility experts when dealing with infertile PCOS women[32]. In regards to the ovarian response, the mature oocyte retrieval counts, maturity rate, in addition to the dose and duration of gonadotropins used in the PPOS group were found to be comparable, albeit slightly, but insignificantly less than that in the GnRH ant group. The clinical outcomes such as fertilisation rates, good quality embryos cryopreserved and embryo rates were comparable in both groups. Regards to safety, there were no cases of severe OHSS in either group, in addition, mild and moderate cases were comparable in both groups.

Sub analyses of the demographic data was carried out, to account for any potential age, BMI and infertility type and duration differences between the groups, that could affect the interpretation of our results. By matching the PPOS and GnRH ant groups we were able to select two groups with similar proportions of women in the various subtypes.

The PPOS protocol has been proven to be effective and safe[15,33-36]. A number of different studies have explored the relationship between PPOS and the GnRH agonist and antagonist protocols[22], in different patient populations. Few studies have compared the different types of progesterone used in PPOS with each other[26,37-39], but only two studies[40,41], to our knowledge, has focused their attention and compared the clinical efficacy and safety of DYG used during PPOS protocol to the widely recommended CET in GnRH antagonist protocols in infertile PCOS women.

Gurbuz *et al*. retrospectively analysed 525 patients with PCOS, (258 using 20mg DYG and 267 using CET). The numbers of mature and fertilized oocytes were similar in both groups, in agreement to our findings. In addition, there was no significant difference in clinical pregnancy rate of the first frozen embryo transfer cycle, biochemical pregnancy rates, implantation rates, miscarriage rates and ongoing pregnancy rates between both groups[40]. A randomised controlled study of 120 infertile women with PCO, was conducted by Eftekhar *et al*., with half receiving 20mg DYG and the other half using CET. In this study, the trigger day serum E2 levels, the number of MII oocytes and the fertilized oocytes, were significantly lower in the PPOS group than in GnRHant group ($p = 0.019$, $p = 0.035$, $p = 0.032$, $p = 0.030$ respectively), in agreement to our study. Despite these results, the difference in chemical and clinical pregnancy rates, was not statistically significant between the groups. In addition, mild and moderate OHSS was significantly less in the PPOS group (p=0.001)[41].

Three studies compared cycle and clinical outcomes following PPOS using MPA, rather than DYG, with GnRH ant protocols, in infertile women with PCOS undergoing IVF. Zhuno-mi XIAO *et al*., randomised 157 PCO patients to two groups, and concluded that the PPOS protocol decreased the incidence of OHSS without adversely affecting clinical outcomes. Estradiol levels on the day of trigger were significantly lower than the PPOS group and thus a significantly reduced number of oocytes were retrieved, however the number of 2PN fertilized oocyte, cleaved embryo, 2PN fertilization rate, and cleavage rate were similar between the two groups. In addition, there was no significant difference in the number of good-quality embryos between the two groups[32]. Wang N *et al*., randomised 392 patients with PCOS to one of the two protocols and concluded a similar outcome[42]. Wang Y *et al*., also randomised 120 women with PCO equally to two groups and although the fertilisation rates were higher in the PPOS group, the clinical outcomes were

comparable, as was the incidence of OHSS[24]. The amount of HCG used in triggering oocyte maturation is strongly associated with the incidence of OHSS and thus results in this study need to be interpreted with caution due to different triggering regimens used for each group. Other studies compared PPOS using MPA or micronized P with the GnRH ant protocol in normally ovulating women and reported similar outcomes[15,24,43].

Several studies have compared IVF outcome data among different progestin formulations undergoing the PPOS protocol[26,37-39]. A recent systemic review including meta-analysis, importantly reported similar clinical outcomes and safety profiles in PPOS protocols using MPA, MIP and DYG[44]. The minimum effective dosage for each progestin remains to be determined, and with the few studies using DYG, no exact protocol has been specified regarding the recommended dose of DYG[45]. Interestingly though, DYG was found to be weaker than MPA in pituitary inhibition, resulting in higher circulating LH levels in the follicular phase of ovarian stimulation, with less profound LH suppression[37]. All studies are consistent regarding a documented comparable or lower gonadotropin consumption in cycles using DYG when compared to MPA or to the conventional GnRH ant protocol[15,24].

Due to a higher ovarian response to gonadotropins and with multiple follicular development resulting in higher estradiol concentrations, women with PCOS are at increased risk for OHSS[2,46]. In theory, moderate and severe OHSS can be avoided by using a dual trigger to partially replace the long acting hCG for a short acting GnRH agonist[47]. A freeze all policy to transfer embryos into a more physiological intrauterine environment during FET cycles would also contribute to a reduced risk[9-13]. The use of the PPOS protocol in women with PCOS has been reported in studies, to reduce the incidence of OHSS, although the mechanism is not yet clear[15,47-49]. In our study, none of the women experienced severe OHSS, with mild and moderate OHSS comparable in both groups. With shortages of medication in Egypt, it had been necessary, at times, to revert to the use of the more available hCG trigger solely, while saving the use of dual triggers to very high-risk patients. HCG dose available in the Egyptian market is 5000IU, significantly higher than the recommended and widely used dose of 1000IU in PCOS patients. The dose of HCG is strongly linked to an increased risk of OHSS[50], which could explain the larger proportion of cases of moderate OHSS in our study compared to other similar studies.

The extensive worldwide use of DYG for the treatment of threatened and recurrent miscarriage, as well as for the luteal phase support in infertile patients, suggests its long-term safety[26]. The safety of DYG on neonates has been proven by the Lotus I and II Phase III studies[51,52]. There have been reported concerns regarding prolonged exposure of the developing follicles to progesterone. Until now, relatively few studies have investigated this aspect, and although most that have done have been reassuring, they provide low quality evidence in that regard[53-55]. Huang el al., and Vanni *et al*., have challenged this concept and reported a significant reduction in the rate of top quality blastocycts with elevated progesterone concentrations on the day of oocyte maturation induction[56,57]. Uncertainty about the impact of PPOS on oocytes and embryos still exists. Thus, further well-designed studies are required to achieve confirmation.

This retrospective study has limitations. The power of the statistical analysis could be questioned due to a limited sample size, in addition to possible confounders, owing to the retrospective nature of this single centred study. A lack of difference between the demographic characteristics of both groups, as seen in this study however, should decrease the risk of bias. Due to a limited number of studies that explore the effect of different gonadotropin starting doses on patients at high risk of OHSS[58], the starting dose of gonadotropins has been tailored, in this study, according to our centres experience. Furthermore, the low reserves of drugs needed for dual triggering in the Egyptian market, has resulted in three different triggering regimens in our study. Although some studies have recommended a freeze all regimen when using the GnRH ant protocol with women with PCOS, in clinical practice there still remains a proportional use of fresh embryo transfer, if during the treatment cycle, the patient is not found to be at a very high risk for OHSS. In this study we have compared the clinical outcomes of the PPOS protocol to the GnRH ant protocol undergoing freeze all embryo transfers only. DYG use in PPOS protocol appears to be more cost-effective based on its fewer gonadotropin consumption, and lower cost of medication. This, however, could be offset by the additional cost of a frozen embryo transfer, if a fresh transfer would have been feasible in that stimulation cycle. The cost-effectiveness of progestins compared with GnRH antagonists has been highlighted in a recent article by Evans and colleagues[59], limited to planned freeze-only cycles and to high-responder patients for whom a ‘freeze only’ is likely and the risk of OHSS is high. To thoroughly compare the clinical effectiveness and also the potential economic advantage between both protocols, data from both fresh and freeze all embryo transfer GnRH ant cycles need to be included.

CONCLUSION

This study was initiated following an abrupt shortage of CEX and MPA in the Egyptian market, which had resulted in the use of the less researched PPOS protocol using DYG for women with PCOS. Based on the results of our study, PPOS using DYG provides an appealing management option with comparable clinical outcomes and a good safety profile, with the advantage of the use of an oral agent instead of daily injections. A high-quality meta-analysis including more well-designed RCTs

comparing PPOS using DYG to conventional protocols in women with PCOS is required to increase the strength of our hypothesis-generating findings.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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