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Original article

Dydrogestrone-Primed Stimulation Protocol versus Conventional Antagonist Protocol in Polycystic Ovarian Syndrome Cases Undergoing ICSI

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Abstract

Background: Ovarian stimulation protocols significantly impact in vitro fertilization (IVF) outcomes, with concerns of luteinizing hormone (LH) surges and ovarian hyperstimulation syndrome (OHSS). Progesterone-primed ovarian stimulation (PPOS) protocols, including the use of synthetic progestin like dydrogesterone, have shown promise as LH surge prevention alternatives. **This study aimed to** compare Dydrogesterone and GnRH Antagonist treatments by assessing the incidence of premature LH surges and the total number of mature oocytes retrieved in PCOS patients. **Methods:** This prospective comparative study was conducted at Benha University Hospital, involving 60 PCOS patients who met the inclusion criteria. Patients were divided into two groups: DYD group (received dydrogesterone medication) and CET group (received cetrorelix medication). Ovarian stimulation was initiated with recombinant FSH. Oocyte maturation was triggered using a GnRH agonist. Embryos were evaluated, vitrified, and warmed. Endometrial preparation and frozen embryo transfer (FET) were performed as per protocol. **Results**: There was no statistically significant difference in the number of mature oocytes between the CET and DYD groups (p-value = 0.620). The LH levels on trigger day are comparable between the groups (p-value = 0.191). **Conclusion:** Both protocols are effective in terms of achieving a similar number of mature oocytes, fertilization rates, and low incidences of OHSS. However, the Dydrogestrone protocol demonstrated a shorter duration of ovarian stimulation and a lower total gonadotropin dose compared to the Antagonist Protocol.

Keywords: Dydrogestrone-Primed Stimulation; Conventional Antagonist Protocol; Polycystic Ovarian Syndrome; ICSI.

Introduction

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, 2).

Detection of an LH peak prior to the scheduled time is among the major reasons for cancellation of in vitro fertilization (IVF) treatment. For many years, gonadotropin-releasing hormone (GnRh) analogs were the first choice in IVF treatments to down regulate GnRh receptor and prevent early LH surge (3).

However, the use of GnRh analogs had the disadvantages of large numbers of injections and the risk of ovarian hyperstimulation syndrome (OHSS). Subsequent utilization of GnRh antagonists yielded shorter treatment times and fewer gonadotropin injections. Although OHSS occurred less frequently in antagonist than in agonist cycles, the risk was not eliminated completely (4).

To prevent OHSS, a freeze-all strategy involves using a GnRH analog trigger, freezing embryos, and transferring them post-endometrial preparation. Elevated steroid levels in fresh cycles lead to gene expression changes and lower pregnancy rates compared to FET. Therefore, freeze-all and FET are recommended for hyper-responsive patients to enhance pregnancy rates and avoid OHSS (5).

Progesterone serves as an alternative for preventing the LH surge in ovarian stimulation cycles by reducing GnRH pulsatility and inhibiting LH release tied to elevated estradiol levels. This led to the progesterone-primed ovarian stimulation (PPOS) protocol, with studies, such as one by Kuang, showing comparable pregnancy rates between medroxyprogesterone acetate (MPA) and a short agonist protocol (6).

Progesterone blocks LH elevation during ovarian stimulation, ensuring optimal pregnancy outcomes in FET cycles. Despite the need for a freeze-all strategy in PPOS due to endometrial desynchronization, it remains a preferred option for situations where fresh embryo transfer is unsuitable, like donor cycles, preimplantation genetic testing, fertility preservation, and high-risk OHSS cases (7).

MPA was also suggested to lead to stronger pituitary suppression, and gonadotropin usage for longer periods and at higher dosages. Therefore, the appropriate progestin type for the PPOS protocol has not been confirmed. Dydrogesterone (DYD) is a synthetic progestin with a similar molecular structure to natural progesterone, with a long history of extensive use for luteal support in pregnancy and threatened miscarriage (8).

Administration of DYD during controlled ovarian hyperstimulation

(COH) was like administration of natural progesterone in the prevention of LH surge, embryonic characteristics, and pregnancy outcomes. However, DYD was better tolerated, had fewer adverse effects and was more stable for follow-up of blood hormone levels than natural progesterone (9).

Huang and Eftekhar showed that the application of DYD in PPOS protocol could achieve comparable oocyte retrieval and pregnancy outcomes in two different studies (10-12). Therefore, in the present study, we compared the efficacy of Dydrogesterone and the GnRH antagonist cetrorelix (CET) in the prevention of LH peak in hyper-responsive patients undergoing freeze-all IVF.

The purpose of this study was to compare Dydrogesterone and GnRH Antagonist treatments by assessing the incidence of premature LH surges and the total number of mature oocytes retrieved in PCOS patients.

Patients and methods

This prospective comparative study was done at Benha University Hospital, Obstetrics & Gynecology Department and private centers of ICSI during the period from January 2022 to January 2023. Among patients attending the outpatient clinic, sixty polycystic ovarian syndrome (PCOS) patients who underwent freeze-all in (ICSI) cycles were enrolled in this study.

Written informed consent from every patient included in this study. The consent was proved by the medical ethical committee of Benha University Hospital (MS.11-4-2022).

Inclusion criteria were patients aged between 20–30 years, patients with body mass index (BMI) > 25 kg\m^2 and diagnosed with PCOS according to the Rotterdam classification.

Exclusion criteria were patients with severe male factor, Severe endometriosis (grade 3 or higher), uterine or ovarian abnormalities and endocrinological abnormalities (as Hypothyroidism).

The 60 patients were divided into two groups; each group consists of 30 patients: **First group (CET group):** Thirty women received daily subcutaneous injections of 0.25 mg of Cetrorelix (Cetrotide®), starting on stimulation day 6 or when the leading follicle reached a diameter of ≥ 14 mm. **Second group (DYD group):** Thirty women were administered Dydrogesterone (Duphaston® 10 mg) orally twice daily, starting from day 2 of menstruation until the trigger day.

All patients were subjected to the following:

Full history taking including past medical history, gynecological history, obstetric history, surgical history, medication history, family history of reproductive or endocrine disorders, lifestyle factors, including smoking, alcohol consumption, and exercise habits

and any known allergies or sensitivities to medications or substances relevant to the study.

Treatment: Patients underwent comprehensive assessment, including measuring estradiol, progesterone, LH, FSH, and TSH levels, along with transvaginal ultrasound on day 2 or 3 of menstruation. Antral follicle count (AFC), age, and body mass index (BMI) were also considered. Ovarian stimulation began with subcutaneous injection of highly purified FSH (Fostimone®, IBSA, Switzerland) on day 2 or 3 of the follicular phase. The dose of recombinant FSH was determined based on the baseline evaluation of clinical findings. The treatment protocol was tailored according to the patient's preference. The antagonist protocol (CET group) included daily subcutaneous injections of 0.25 mg of cetrorelix (Cetrotide, Merck) from stimulation day 6 or when the leading follicle was >14 mm in diameter. Meanwhile, 20 mg of oral DYD (Duphaston; Abbott Healthcare) was administered in the study group (DYD group) from day 2 or 3 of menstruation until the trigger day.

For both groups, oocyte maturation was triggered with a single subcutaneous injection of 0.2 mg of the GnRH agonist, triptorelin (Gonapeptyl; Ferring Pharmaceuticals), when transvaginal ultrasound indicated at least three follicles >17 mm in diameter. Oocyte pick-up was carried out approximately 35–37 h later. The retrieved cumulus-oocyte complexes were counted, denuded and the number of mature oocytes was assessed (13, 14).

Primary outcome measure was the incidence of premature LH surge (the cutoff level of premature LH surge was 10 IU/L or twofold above this level in cases where basal LH was >10 IU/L).

Secondary outcome measures were the total number of mature oocytes retrieved after ovarian stimulation, fertilization rate and viable embryos, endocrine profile in both treatment groups, duration of ovarian stimulation, number of days of GnRH antagonist use, and total gonadotropin dose.

Pregnancy outcomes: Chemical pregnancy was determined by serum β hCG > 50 IU/L two wk after ET. In addition, clinical pregnancy was confirmed by detecting fetal heartbeats 2 wk following the positive β hCG. Miscarriage was defined as losing pregnancy prior to 20 wk of gestation. The implantation rate was considered as percentage of gestational sacs/ transferred embryos.

Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences) version 25 (IBM Inc., Chicago, IL, USA). Shapiro-Wilks normality test and histograms were used to test the distribution of quantitative variables to select accordingly the type of statistical testing: parametric or nonparametric. Parametric variables

(e.g., age) were expressed as mean and standard deviation (SD) and comparison between two variables within the same group was compared by paired T test. Non- parametric variables were expressed as median and interquartile range (IQR) and comparison between two variables within the same group was compared by Wilcoxon test. Categorial variables (e.g., sex) were expressed as frequency and percentage and were statistically analyzed by Chi-square test. A two-tailed P value ≤ 0.05 was considered statistically significant.

Results

This prospective study was conducted in a private IVF center over 60 patients classified into two groups: CET group: Thirty women received daily subcutaneous injections of 0.25 mg of Cetrorelix (Cetrotide®,) starting on stimulation day 6 or when the leading follicle reached a diameter of ≥ 14 mm. DYD group: Thirty women were administered Dydrogesterone (Duphaston® 10 mg) orally twice daily, starting from day 2 of menstruation until the trigger day.

There was no statistically significant difference between the studied groups as regard baseline data. **Table 1**

The distribution of primary and secondary infertility cases is comparable between the two groups, with 73.3% and 70.0% of primary cases in the CET and DYD groups, respectively. Secondary infertility cases account for 26.7% and 30.0% in the CET and DYD groups, respectively. The mean duration of infertility is similar in both groups, with 2.97 ± 1.71 years for the CET group and 3.13 ± 1.7 years for the DYD group. In both groups, all participants (100.0%) have Polycystic Ovary Syndrome (PCOS) as the indication for in Vitro Fertilization (IVF). **Table 2**

FSH levels in both groups showed similar ranges, with a mean of 3.77 ± 0.8 IU/L in the CET group and 4.13 ± 1.14 IU/L in the DYD group. Similarly, the LH levels in both groups fall within comparable ranges, with a mean of 8.48 ± 1.59 IU/L in the CET group and 8.67 ± 1.61 IU/L in the DYD group. There was no statistically significant difference between the studied groups as regards day 3 (FSH, LH and FSH/LH ratio). **Table 3**

Estradiol (E2) levels also showed similar ranges, with a mean of 44.31 ± 24.65 Pg/mL in the CET group and 40.1 ± 19.07 Pg/mL in the DYD group. There was no statistically significant difference between the studied groups as regard day 3 (E2, progesterone and AFC). **Table 4**

The DYD group experienced a longer duration of ovarian stimulation compared to the CET group. The stimulation duration in the CET group ranges from 8 to 11 days, with a mean of 9.57 ± 1.07 days, while in the DYD group, it ranges from 9 to 12 days, with a mean of 10.67 ± 1.12 days. **Table 5**

The CET group received a higher average dose of gonadotropins compared to the DYD group. The range of gonadotropin doses administered to participants in the CET group is 1100 to 2600, with a mean of 1853.33 ± 448.36 units, while in the DYD group, it ranges from 1150 to 2100 units, with a mean of 1615 ± 273.59 units. **Table 5**

In terms of Endometrial Thickening on Trigger Day, there was a statically significant difference between the studied groups as the CET group showed a thicker endometrium on average (P-value =0.005). Also, there was no statistically significant difference in the number of mature oocytes between the CET and DYD groups, with a range of 7–17 in both groups (p-value = 0.620). The number of fertilized oocytes was comparable between the groups, with a range of 4–13 in the CET group and 4–15 in the DYD group (p-value = 0.931). **Table 6**

Regarding the incidence of Moderate or Severe OHSS: CET group had a higher incidence (10%) compared to DYD group (3.3%) with insignificant difference (p<0.05). The incidence of premature luteinization is 2.5% in the CET group and 0% in the DYD group. The LH levels on trigger day are comparable between the groups, with ranges of 0.7–5.1 IU/L in the CET group and 0.9–5.4 IU/L in the DYD group (p-value = 0.191). **Table 6**

Table 1: Comparison between studied cases according to baseline data

	CET group (n = 30)		DYD group (n = 30)		Test of Sig.	p
Age (years)						
Range.	23 – 35		23 – 35		t=	0.646
Mean ± SD.	29.5 ± 4		29.03 ± 3.82		0.462	
Parity	No.	%	No.	%		
0	22	73.3	21	70.0	χ^2=	0.424
1	5	16.7	8	26.7	1.716	
>1	3	10.0	1	3.3		
BMI (kg/m^2)						
Range.	25 – 31		25 – 33		t=	0.204
Mean ± SD.	27.38 ± 1.84		28.08 ± 2.37		1.283	

SD: Standard deviation, χ2: Chi square test, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$

Table 2. Comparison between studied cases according to infertility data

	CET group (n = 30)		DYD group (n = 30)		Test of Sig.	p
Type of infertility	No.	%	No.	%		
primary	22	73.3	21	70.0	χ^2=	0.774
secondary	8	26.7	9	30.0	0.082	
Duration of infertility per years						
Range.	1 – 6		1 – 6		t=	0.706
Mean ± SD.	2.97 ± 1.71		3.13 ± 1.7		0.379	
Indication of IVF						
PCOS only	30	100.0	30	100.0	χ^2= 0.0	1.0

SD: Standard deviation, χ2: Chi square test, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$

Table 3: Comparison between studied cases according to FSH,LH and FSH/LH ratio in day 3

	CET group (n = 30)	DYD group (n = 30)	Test of Sig.	p
FSH (IU/L)				
Range.	2.2 – 5.4	2.1 – 6.5	t=	0.168
Mean ± SD.	3.77 ± 0.8	4.13 ± 1.14	1.397	
LH (IU/L)				
Range.	5 – 11.2	5.3 – 12	t=	0.647
Mean ± SD.	8.48 ± 1.59	8.67 ± 1.61	0.461	
LH:FSH ratio				
Range.	1.79 – 3.34	1.45 – 3.45	t=	0.647
Mean ± SD.	2.28 ± 0.32	2.19 ± 0.47	0.461	

SD: Standard deviation, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$

Table 4. Comparison between studied cases according to E2, progesterone and AFC in day 3

	CET group (n = 30)	DYD group (n = 30)	Test of Sig.	p
E2 (pg/mL)				
Range.	9.6 – 79.3	5.3 – 74.9	t=	0.462
Mean ± SD.	44.31 ± 24.65	40.1 ± 19.07	0.740	
Progesterone (ng/mL)				
Range.	0.11 – 1.15	0.11 – 1.12	t=	0.806
Mean ± SD.	0.55 ± 0.31	0.57 ± 0.35	0.246	
AFC				
Range.	12 – 38	9 – 46	t=	0.538
Mean ± SD.	25.53 ± 8.67	27.13 ± 11.16	0.620	

SD: Standard deviation, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$.

Table 5: Comparison between studied cases according to Simulation data

	CET group (n = 30)	DYD group (n = 30)	Test of Sig.	p
Stimulation duration (days)				
Range.	8 – 11	9 – 12	t=	<0.001*
Mean ± SD.	9.57 ± 1.07	10.67 ± 1.12	3.877	
Gonadotropin dose per unit				
Range.	1100 – 2600 U	1150 – 2100 U	t=	0.016*
Mean ± SD.	1853.33 ± 448.36 U	1615 ± 273.59 U	2.485	

SD: Standard deviation, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$

Table 6: Comparison between studied cases according to trigger day data

	CET group (n = 30)	DYD group (n = 30)	Test of Sig.	p
Endometrial thickening on trigger day per mm				
Range.	8 – 13 mm	7 – 12 mm	t=	0.005*
Mean ± SD.	10.7 ± 1.91 mm	9.4 ± 1.48 mm	2.945	
E2level on trigger day				
Range.	1649.6 – 5234.2	1697.1 – 5956.1	t=	0.309
Mean ± SD.	3524.36 ± 964.27	3853.09 ± 1466.47	1.026	
NO. of 18mm follicles on trigger day				
Range.	9 – 24	9 – 23	t=	0.565
Mean ± SD.	16.23 ± 4.85	15.57 ± 4.02	0.579	
NO. oocyte retrieved				
Range.	8 – 23	8 – 23	t=	0.906
Mean ± SD.	15.2 ± 4.63	15.07 ± 4.09	0.118	
NO. mature oocyte				
Range.	7 – 17	7 – 17	t=	0.620
Mean ± SD.	11.33 ± 2.56	11.67 ± 2.62	0.498	
NO. fertilized oocyte				
Range.	4 – 13	4 – 15	t=	0.931
Mean ± SD.	8.77 ± 2.71	8.83 ± 3.2	0.087	
incidence of moderate or severe OHSS	3 10	1 3.3	1.071	0.301
incidence of premature lutelization%	1 2.5	0 0.0	1.017	0.313
LH on trigger day				
Range.	0.7 – 5.1	0.9 – 5.4	t=	0.191
Mean ± SD.	2.82 ± 1.32	3.29 ± 1.41	1.324	

SD: Standard deviation, $\chi 2$: Chi square test, t: student t-test, p: p value for comparing between studied groups, *: Statistically significant at $p \leq 0.05$

Discussion

This prospective comparative study was conducted at Benha University Hospital, involving 60 PCOS patients who met the inclusion criteria.

Regarding baseline data, our results were in line with **a study** reported that there were no significant differences in patients' age, BMI, AMH levels, previous IVF cycle, and type, cause and duration of infertility between the two groups (15).

Consistently, a study found that there was no significant difference between the PPOS group and the GnRH-antagonist group in terms of age, body mass index (BMI) and duration of infertility. The rate of primary infertility was slightly higher in the PPOS group (53.73%) than in the GnRH-antagonist group (51.11%). But the difference was not significant. There were no significant differences in the baseline hormones including basal FSH, basal LH and basal E2 between these two groups (16).

Along with our study, **a study** conducted a study reported that there were no significant differences in patients' age, dose and duration of gonadotropin (Gn) treatment, serum luteinizing hormone (LH) and E2 levels on the day of hCG injection, or the number of oocytes retrieved between the two groups (11).

Regarding range of gonadotropin doses administered, our results were in line with **a study** found that total amount of gonadotrophin and the duration of gonadotrophin usage were significantly higher in the DYD 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 DYD protocol (17).

Supporting our results, a study found that dydrogestrone group had a longer duration of HMG injections compared to the GnRH antagonist group, with a statistically significant difference (p-value = 0.013). However, they reported that the dydrogestrone group, on average, used more HMG vials compared to the GnRH antagonist group, with a statistically significant difference (p-value = 0.003) (15).

Comparably, a study reported that the PPOS group had a longer gonadotropin duration (10.40±1.78 vs. 9.11±1.55 days, P<0.001) and a higher dose of gonadotrophin (1971±576.67 vs. 1719.75±592.5 IU, P<0.001) than the GnRH-antagonist group (16).

In terms of Endometrial Thickening on Trigger Day, a study compared the efficacy of flexible protocols utilizing dydrogesterone with GnRH antagonist in suppressing premature LH surges during controlled ovarian hyperstimulation cycles. It was found that dydrogesterone could serve as an alternative to the antagonist regimen, particularly for

patients not planning immediate embryo transfer (8).

Regarding number of 18mm follicles on trigger day, our study was contrariwise to **a study** noted that the dydrogestrone group had a significantly higher estradiol level compared to the GnRH antagonist group (P-value < 0.001). The dydrogestrone group had a significantly higher LH level compared to the GnRH antagonist group (P-value < 0.001). Also, the dydrogestrone group had a significantly higher progesterone level compared to the GnRH antagonist group (P-value < 0.001) (15).

However, another study found that compared with the GnRH-antagonist group, the estradiol levels on the day of HCG administration were significantly decreased in the PPOS group (P<0.001). Due to estradiol levels, the number of oocytes retrieved was significantly less in the PPOS group than in the GnRH-antagonist group (P=0.049) (16).

Regarding the incidence of Moderate or Severe Ovarian Hyperstimulation Syndrome (OHSS), our study was parallel to research reported that dydrogesterone successfully replace GnRHant to block LH surge while an average of 6.8 days of GnRHant injections were needed in the corifollitropin alfa/GnRHant group. No patients suffered from OHSS. The other clinical outcomes including additional duration/dose of daily gonadotropin administration, number of oocytes retrieved, and fertilization rate were similar between the two groups (12).

However, a study reported no patients experienced mild-to-moderate OHSS in the PPOS group, but 6 patients in the GnRH-antagonist group developed moderate OHSS. The difference was significant (0 vs. 6.67%, P=0.038) (16).

A study was conducted for COH by two regimens: oral dydrogestrone + hMG (intervention group) and Utrogestan + hMG (control group) during IVF/ICSI. This study results found dydrogestrone is similar to Utrogetan in prevention of LH surge, embryonic characteristics, and pregnancy outcomes (18).

Additionally, studies reported the use of exogenous progestins in ovarian stimulation. They concluded reproductive outcomes from ovarian stimulation with progestins are similar to those from conventional ovarian stimulation, although they thought large trials are needed to confirm this. It seems progestins can suppress a premature LH-surge during follicular phase with lower cost, safe and easier administration (oral), and similar effectiveness and can be used as an alternative to GnRH analog. Despite the advantages of PPOS, it has some weaknesses such as a delayed embryo transfer and higher dose of gonadotropins used. They suggested further studies especially on neonatal outcomes are needed before this protocol can be introduced on a wider scale (19).

Conclusion

both protocols are effective in terms of achieving a similar number of mature oocytes, fertilization rates, and low incidences of OHSS. However, the Dydrogestrone protocol demonstrated a shorter duration of ovarian stimulation and a lower total gonadotropin dose compared to the Antagonist Protocol.

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