Duphaston-Primed VS. GnRH Antagonist Ovarian Stimulation in PCOS: A Retrospective Review of Outcomes.

Original Article

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ABSTRACT

Introduction: To judge outcomes of fixed gonadotropin-releasing hormone antagonist (FGnRHan) protocol of OS versus fixed Duphaston-primed ovarian stimulation (D-POS) protocol regrades OS Response (OSR) in addition to pregnancy results in women diagnosed with PCOS who had submitted to ICSI&FET.

Patients and Methods: A retrograde evaluation of PCOS females who underwent ICSI&FET cycles between February 2018 and February 2024 at Al Yasmine IVF center-Benha-Kalubia government and Hospital of Benha University (HBU). The outcomes included the frequency of pregnancy-related items, such as live birth rates, clinical pregnancy rates, and ongoing pregnancy rates as well as the incidence of OSR items such as fertilization rates, premature LH surge, and other OSR results.

Results: The study encompassed 810 women, 390 undergoing D-POS, and 420 subjected to a GnRHan protocol. Baseline parameters exhibited similarity across both groups. Mature and fertilized oocytes demonstrated no significant disparity across both parties ($P > 0.5$). Instances of premature luteinization were infrequent in both parties, with no important statistical discrepancy ($P > 0.5$). Furthermore, there is no significant discrepancy (between the FD-POS and FGnRHan parties (48% [595/1240] vs.49% [564/1150], MD=1% [3% to 5%], P=0.62) regarding the clinical pregnancy average per frozen embryo transfer cycle (FTC). Parties' implantation and continuing pregnancy rates also remained statistically similar ($P > 0.05$). While the cost difference was considerably lower in D-POS than GnRHan group (5.5±2.3(4-8k) vs.8.1±3.3(6-11k), p =0.0001, k=1000LE)

Conclusion:FD-POS protocol emerges as a potent, convenient, easy to use, cost-effective, with similar clinical outcomes alternative to the GnRHan protocol in PCOS patients who underwent ICSI&FET.

Key Words: Duphaston, GnRH antagonist, ICSI&FET, PCOS ,PPOS.

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INTRODUCTION

PCOS is a complicated endocrine condition that influences around 5-20% of females in their reproductive years[1-5]. PCOS criteria includes hyperandrogenism, polycystic ovaries, and anovulation. These impact the general health of affected women and make PCOS a predominant cause of infertility among this demographic[1-5].

The challenge of infertility in PCOS patients has necessitated the evolution of various therapeutic strategies[1-5]. Ovarian stimulation (OS) response (OSR) stands out as a cornerstone in this therapeutic arsenal, aiming to induce the growth and maturation of multiple ovarian follicles, thereby increasing the chances of conception[1-5]. However, the journey of refining OS protocols has been marked by the need to balance efficacy with safety, especially given the risk of impacts such as Ovarian Hyperstimulation Syndrome (OHSS)[1-7].

In the dynamic landscape of reproductive medicine, two protocols have recently emerged as promising strategies for OS in PCOS females the fixed gonadotropin-releasing hormone antagonist (FGnRHan) protocol and the Fixed Duphaston-primed ovarian stimulation (FD-POS) protocol as a progestin-primed ovarian stimulation (PPOS)[1-3,6-11]. The FD-POS protocol incorporates Duphaston (dydrogesterone), a synthetic progestin, to prevent endogenous LH release during the follicular phase like the action of gonadotropin-releasing hormone (GnRH) antagonists in GnRHan protocol. This facilitates a controlled OSR, potentially reducing the risk of adverse outcomes[1-3,6-11], includes both OHSS and cycle cancellations. Both agents effectively prevent premature LH surges, ensuring a conducive environment for follicular growth and subsequent oocyte retrieval[1-3,6-11].

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The reports on PPOS protocols[12-32], when compared directly and indirectly to GnRHan protocols have shown promise in the realm in ICSI-FET procedures for PCOS patients. However, as with all medical interventions, it's imperative to continually assess and compare the efficacy, safety, costs, logistics and overall clinical outcomes associated with these protocols. Such evaluations not only guide clinicians in optimizing patient care but also provide valuable insights for future research and protocol refinement.

This retrospective review is poised to bridge this knowledge gap. By comparing the outcomes associated with the fixed GnRHan and fixed D-PPOS protocols in a cohort of PCOS women, we aim to offer a comprehensive perspective on the relative merits and potential limitations of each approach. Such insights are invaluable for clinicians, researchers, and patients alike, ensuring informed decision-making and the delivery of evidence-based care.

PATIENTS AND METHODS

This retrograde observational cohort analysis was accomplished at Al Yasmine IVF center-Benha-Kalubia government and Hospital of Benha University (HBU) between February 2018 and February 2024. The thesis involved a comprehensive investigation of PCOS females who submitted to freeze-all ICSI cycles, focusing on the comparison between a fixed 30 mg daily Duphaston-primed (D-PPOS) that started in menstrual cycle day 2 (MC2) and fixed GnRHan ovarian stimulation protocols that started in MC6.

The study population comprised 810 PCOS females, with 420 in the D-POS party and 390in the GnRHan party. We include women in this analysis if they were among 19 and 46 years old, their body weight ≥ 55 kg as well as diagnosed as PCOS depending on the modified Rotterdam parameters with two of the subsequent three, amenorrhea or oligomenorrhea, clinical/ biochemical hyperandrogenism, PCO morphology with the presence of more than 12 antral follicles of less than 9mm and/or ovarian volume more than 10mL on transvaginal ultrasonic photographing (TVS)[4,5], the control of LH surge during OS was either with fixed GnRH antagonist protocol group (FGnRHan party) or fixed Duphaston-primed group (FD-POS party) at a dose of 30 mg daily as 10 mg/8 hours, All OS cycles were a freeze-all strategy in addition to all frozen embryo transfer cycles (FTC) had been hormone replacement therapy (HRT).We omit candidates from this investigation, if they were with severe male factor, contraindications for the use of gonadotropins (Gn), uterine or ovarian abnormalities, grade 3, grade 4 endometriosis and other endocrinological abnormalities as hyperprolactinemia. Also, PCOS females who underwent a fresh embryo transfer even were underwent OS with FGnRHan protocols, underwent OS with protocols other than fixed DPOS or FGnRHan or utilized progestins other than Duphaston or at a dose other than 30 mg daily, underwent FTC with endometrial preparation other than HRT were also, excluded from this retrograde analysis. All included women in this analysis were provided a written informed agreement for the ICSI&FET management and for the research use of their anonymous data. The thesis protocol was authorized by Benha Faculty of Medicine institutional review board. (No: RC 4-12-2023).

According to our routine ICSI protocols, on the MC2 or MC3 all women subjected to basal hormonal assessments, including estradiol(E2), progesterone(P), AMH, LH, TSH, and FSH levels as well as basal TVS for antral follicle count (AFC) and ovarian volume. Also, the index of body mass (BMI in Kg/M^2), and age were estimated. OS began on the MC2 or MC3 with a different gonadotrophin (Gn) including HMG intramuscular (IM) as Epigonal (EPICO) or/and Merional (IBSA) or/and Menogon (Ferring) or other available products or/ and HMG biosimilars as recombinant FSH (r-FSH) as Gonapure 75-150 IU(MINAPHARM) or subcutaneous follitropin alpha injection (SI) of (Gonal-f), u-FSH as Fostimon (IBSA) and structured FSH&HCG as Meriofert (IBSA). The management protocol was concerned the patient's capability and the drug's obtainability at pharmacies. In the FGnRHan protocol group, a 0.25 mg of cetrorelix (Cetrotide) was injected daily subcutaneously from MC6 until the trigger day, where around 6 ampules were used for most candidates. Meanwhile, candidates in the FD-POS group received 30 mg of oral Dydrogesterone (DYD) as 10mg/8 hours (Duphaston) from MC2 or MC3 until the HCG Day. Ultimate oocyte maturation was triggered with HCG (5000-10000 IU/IM) utilizing available HCG as Epifasi 5000 IU (EPICO) or /and Choriomon 5000 IU (IBSA) as well as a single subcutaneous injection of 0.2 mg of the GnRH agonist, decapeptyl (Ferring) may be added, when at least three follicles of or more 18 mm in width were detected on TVS. Oocyte recovery was completed around 34-36 hours after, followed by intracytoplasmic sperm injection FOR ALL M2 oocytes. In our ART centers we utilized the cryotopic vitrification method to freeze all embryos in studied partes on the 3rd day following oocyte recovery. Frozen Embryo Transfer Cycles (FTC) were started as soon as possible, usually two months later, all women with available embryos had undergone at least one FTC, while some underwent twice, triple up to fifth FTC.

HRT endometrial preparation (EP) involved oral administration of 6 mg/day estradiol VALERATE (CycloPogyonva) starting from MC3 until the endometrial width in TVS reach 8 mm or more, after that P as pessary 400 or/and 100 prontogest ampules (MARCYRL,) or/and oral and vaginal capsules (Utrogestan 200) were administered.

On day 3 or 5 subsequent the starting of progesterone medication, Embryo transfer was conducted. In cases of pregnancy, estradiol and progesterone administration might continue up to the end of the initial trimester.

The study main outcomes measure involving, the frequency of biochemical pregnancy, which was assured if B-HCG were more than 5mIL/ml after 15 days after FET, the occurrence of Clinical pregnancy, which was assured via scan with either transvaginal or abdominal ultrasound 17 days later affirmative pregnancy check, viewing the occurrence of a gestational sac beside or not positive fetal cardiac activity, the frequency of Clinical pregnancy was calculated per FTC, the frequency of live birth rate per included women, which described as women provided of one or more living baby per included women who had undergone oocyte retrieval and the frequency of premature LH surge, which demarcated as a level of 10 IU/L or twofold over this level in cases where basal LH was >10 IU/L preceding to the day of trigger. Additional consequences included the other OSR parameters as total number of M2 oocytes recovered, fertilization rate, living embryos, endocrine summary in both treatment parties, length of OS, charge of utilized GnRH antagonist, the frequency of OHSS, the frequency of cycle cancelation percentage and overall Gn dose.

Statistical Analysis

Statistics were done utilizing SPSS version 21 for Windows (IBM® SPSS®, statistics21, USA), with descriptive summary calculates stated as mean (± 2 SD) (range) for continuous variables and number (percentages) for categorical variables. Statistical significance was determined at $P < 0.05$, utilizing Student's t-test for continuous consequences, using the chi-squared test for categorical consequences.

RESULTS

In this retrograde cohort thesis, we intended to compare the clinical consequences and ovarian responses between the FD-POS and FGnRHan protocols in females diagnosed with PCOS according to the modified Rotterdam parameters. This thesis was conducted at Al Yasmine IVF center-Benha-Kalubia government and BUH from February 2018 to January 2024.

In (Figure 1) we illustrate the flow chart of the thesis scheme, and the included couples as described in the Patients and methods section. We included 810 women, 420 undergoing the FD-POS protocol and 390 undergoing the FGnRHan protocol. all involved females were subjected to fertilization by ICSI and freeze all strategy.

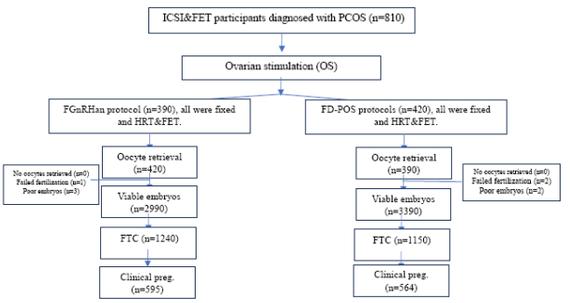

Fig. 1: Flow chart of FD-POS Protocol & FGnRHan Protocol in Females with PCOS who underwent ICSI&FET

In (Table 1) we present women demographic, baseline clinical and hormonal data. The females in the FD-POS party were analogous to the females in the FGnRHan party regarding age (y), BMI (kg/m^2), , primary infertility (%), secondary infertility (%), period of infertility (y), cause for ICSI usage as PCOS only/ PCOS+ endometriosis/ PCOS + male factor/ PCOS+ tubal issue/ PCOS+ another, Basal LH, FSH, AMH, E2, P, AFC, former ICSI trials and prior miscarriages, so the two party were parallel as regrades baseline criteria as we focus in this analysis on subcategory of infertile ladies with PCOS.

Table 1: Baseline characters and Hormonal report of females with PCOS who underwent ICSI-FET either with FD-POS Protocol or FGnRHan Protocol.

Characters	FD-POS Protocol (n=420)	FGnRHan Protocol (n=390)	Δ 95% CI	*P-value*
Age (y)	26.7 ± 4.2(18-43)	26.8 ± 5.4(22-39)	0.1 (0.56 to 0.76)	0.77
BMI (kg/m^2)	28.6 ± 5.3(24-37)	29.1 ± 5.7(22-37)	0.5 (0.26 to 1.26)	0.2
Fertilization type ICSI (%)	420(100%)	390(100%)	0% (0.97% to 0.9%)	
Primary infertility (%)	290(69%)	270(69%)	0% (6.37% to 6.34%)	1
secondary infertility (%)	130(31%)	120(31%)	0% (6.34% to 6.37%)	1
Duration of infertility (y)	3.9 ± 1.9(2-19)	4.1 ± 1.7(5-20)	0.2 (0.05 to 0.45)	0.12
Indication for ICSI:				
PCOS only	265(63.2%)	254(65.2%)	2% (4.6% to 8.6%)	0.55
PCOS + male factor	119(28.3%)	97(25%)	3.3% (2.8% to 9.3%)	0.3
PCOS+ endometriosis	15(3.5%)	9(2.4%)	1.1% (1.37% to 3.57%)	0.36
PCOS+ tubal factor	15(3.5%)	24(6%)	2.5% (0.46% to 5.63%)	0.09
PCOS+ other	6(1.5%)	6(1.4%)	0.1% (1.8% to 1.9%)	0.9
Basal FSH (IU/L)	4.9 ± 3.2(4-8)	5.1 ± 3.3(3-8)	0.2 (0.25 to 0.65)	0.38
Basal LH (IU/L)	8.9 ± 5.5(6-15)	9.1 ± 5.6(8-16)	0.2 (0.56 to 0.96)	0.61
Basal E2 (pg/mL)	56 ± 13(33-82)	57 ± 14(29-85)	1 (0.86 to 2.86)	0.3
Basal P (ng/mL)	0.72 ± 0.6(0.4-0.9)	0.69 ± 0.5(0.3-0.8)	0.03 (0.1 to 0.05)	0.44
AMH (ng/mL)	11.1 ± 5.3(6-16)	10.9 ± 5.4(6-17)	0.2 (0.94 to 0.54)	0.59
Basal AFC	23 ± 11(15-35)	24 ± 13(16-33)	1 (0.66 to 2.66)	0.24
Previous ICSI attempts	1.2 ± 0.8(0-3)	1.1 ± 0.8(0-4)	0.1 (0.21 to 0.01)	0.07
Previous abortions	0.6 ± 0.5(0-5)	0.7 ± 0.6(0-3)	0.1 (0.02 to 0.18)	0.01

Values presented as mean ± 2 standard deviation (range) or number (percent). $P<0.05$: Statistically significant

In (Table 2) we delineate the details of OS and summarize the OSR parameters in both parties. The total Gn dose and the period of stimulation were slightly shorter in the FGnRHan party, despite the changes were not statistically substantial ($P>0.05$). The EM width and the serum E2 on trigger day were significantly higher in FGnRHan party ($P=0.0001,0.02$ respectively), however these findings are of no clinical value as we concentrate in this analysis on freeze-all subgroup of PCOS. The P, LH values on HCG day, the sum of follicles >14mm, mature oocyte sum, whole oocyte harvested, 2PN Fertilization rate, no. of fertilized oocytes, no. of cleaved embryos, 2PN cleavage rate, viable embryo rate per oocyte recovered, no. of cryopreserved embryos, no. of good-quality embryos, top-quality embryos, sum of cycle cancelation, severe OHSS, moderate OHSS, premature luteinization remained comparable between the two groups, indicating similar ovarian responses to the stimulation protocols.

Table 2: Ovarian Stimulation characters, Hormonal report, and Outcomes of females with PCOS who underwent ICSI-FET either with FD-POS Protocol or FGnRHan Protocol.

characters	FD-POS Protocol (n=420)	FGnRHan Protocol (n=390)	Δ 95% CI	*P-value*
Total GN dose (IU)	2840 ± 395(2600-3900)	2790 ± 410(2400-3800)	50 (105.5 to 5.5)	0.07
Duration of stimulation (d)	10.2 ± 4.2(7-13)	9.9 ± 4.5(8-13)	0.3 (0.9 to 0.3)	0.3
EM. on trigger day (mm)	8.9 ± 2.4(6-11)	9.9 ± 2.7(8-12)	1 (0.65 to 1.35)	0.0001
E2 on trigger day (pg/mL)	5120 ± 590(4230-9500)	5250 ± 620(4180-9450)	130 (46.5 to 213.5)	0.002
LH on the trigger day IU/L	3.1±1.8(1.8-3.4)	2.9±1.5(1.7-9.1)	0.2 (0.43 to 0.03)	0.09
P levels on trigger day (ng/mL)	1.8 ± 1.3(0.8-3.6)	1.6 ± 1.5(0.6-3.8)	0.1 (0.29 to 0.09)	0.3
No. of >14 mm F. at trigger day	26±15(18-49)	28±16(19-46)	2 (0.14 to 4.14)	0.067
No. of oocytes retrieved	23±12(12-38)	24±14(13-40)	1 (0.8 to 2.8)	0.27
Oocyte retrieval rate (%)	57 ± 20 (37-92)	59 ± 22 (36 -91)	2 (0.89 to 4.89)	0.18
No. of MII oocytes	14 ± 8(9-32)	15 ± 10(0-35)	1 (0.24 to 2.24)	0.11
Mature oocyte rate (%)	69± 21(30-85)	72± 24(38-87)	3 (0.1 to 6.1)	0.06
No. of fertilized oocytes	10±8(7-29)	11±8(8-28)	1 (0.1 to 2.1)	0.08
2PN Fertilization rate (%)	67 ± 16(30-80)	66 ± 19(0-85)	1 (3.41 to 1.41)	0.42
No. of cleaved embryos	9±7(4-19)	10±8(0-19)	1 (0.03 to 2.03)	0.06
2PN cleavage rate, %	71± 27(42-90)	73± 23(0-90)	2 (1.47 to 5.47)	0.26
VE rate per oocyte retrieved (%)	34±15(10 -85)	35±14 (20 -85)	1 (1 to 3)	0.33
No. of cryopreserved embryos	8±7(4-14)	9±8(4-15)	1 (0.04 to 2.04)	0.06
No. of top-quality embryos	8±7(3-10)	9±8(3-12)	1 (0.04 to 2.04)	0.06
Good-quality embryos (%)	53 ± 24(20-80)	55 ± 28(20-95)	2 (1.6 to 5.6)	0.3
Premature luteinization %	5(1.2%)	6(1.5%)	0.3 (1.4% to 2.1%)	0.7
Total cycle cancelation	1(0.2%)	2(0.5%)	0.3 (0.8% to 1.6%)	0.5
Moderate OHSS	25(6%)	28(6.4%)	0.4 (2.9% to 3.8%)	0.8
Severe OHSS	4(1%)	5(1.3%)	0.3 (1.3% to 2.1%)	0.7

Values presented as mean ± 2 standard deviation (range) or number (percent). $P<0.05$: Statistically significant

In (Table 3) we present both positive clinical outcomes, adverse outcomes and estimated costs observed in both parties. The live birth percentage per participant who had undergone oocyte retrieval was marginally higher in the Duphaston-primed party, despite the deviation being not statistically substantial. The ancillary consequences, involving clinical pregnancy rate and implantation rate remained also comparable across both parties. In terms of costs, the actual significant difference was the cost of GnRH antagonist where in average women need around 6 ampules, and later in Egypt a lot of logistic problem were exist in its availability and prices, our retrospective analysis shown that the costs was meaningfully lower in D-POS party (5.5±2.3 vs. 8.1±3.3, MD=2.6 (2.2 to 2.9), *P*=0.0001), calculated per K(1000)LE.

Table 3: Clinical Results of females with PCOS who underwent ICSI-FET either with FD-POS Protocol or FGnRHan Protocol.

characters	FD-POS Protocol (n=420)	FGnRHan Protocol (n=390)	Δ 95% CI	*P-value*
No of FET cycle (n)	1240	1150		
No of thawed embryos (n)	3650	3290		
No viable embryos after thaw (n)	2990	2870		
No FET on the cleavage stage	1.9±0.7(1-4)	1.8±0.8(1-4)	0.1 (0.2 to 0.003)	0.06
No of FET on blastocyst stage	1.5 ±0.8(1-3)	1.4±0.9(1-3)	0.1 (0.21 to 0.01)	0.09
Hormone replacement therapy (n)	1240 (100%)	1150 (100%)	0% (0.33% to 0.3%)	
Endometrial thickness (mm)	10.3 ±3.9(8-13)	10.5 ±3.7(8-12)	0.2 (0.33 to 0.73)	0.45
Biochemical preg. rate/FETC, %(n)	58% (720/1240)	61% (713/1150)	3% (0.93% to 6.92%)	0.14
Clinical preg. rate/FETC, % (n)	48% (595/1240)	49% (564/1150)	1% (3% to 5%)	0.62
Implantation rate/FET, % (n)	46% (1376/2990)	44% (1263/2870)	2% (0.5% to 0.4%)	0.12
Miscarriage rate/FETC, % (n)	7.5% (93/1240)	6.5% (75/1150)	1% (1% to 3%)	0.34
Multiple preg. rate/Clin. Preg. (%)	22% (159/720)	20% (145/713)	2% (2.2% to 6.2%)	0.35
Ongoing preg. rate/FETC, % (n)	40% (502/1240)	42% (486/1150)	2% (1.94% to 5.94%)	0.32
Cumulative preg. rate per patient, %(n)	62% (261/420)	65% (254/390)	3% (4% to 10%)	0.4
Live birth rate per FETC, % (n)	39% (484/1240)	41% (472/1150)	2% (1.92% to 5.92%)	0.32
Live birth rate per patient, % (n)	34% (143/420)	36% (140/390)	2% (4.55% to 8.55%)	0.55
Costs of different item per patient (LE)	5.5±2.3(4-8k)	8.1±3.3(6-11k)	2.6 (2.2 to 2.9)	0.0001

Values presented as mean ± 2 standard deviation (range) or number (percent). *P*<0.05: Statistically significant

DISCUSSION

OS in PCOS females evolved over years, with a focus on optimizing protocols to enhance clinical outcomes while minimizing adverse effects such as OHSS. This retrospective review compares the outcomes of the D-PPOS and the GnRHan protocols in Freeze-all ICSI&FET cycles. Our results suggest that across the FD-POS and FGnRHan protocols are effective, and safe choices for OS in females with PCOS undergoing ICSI&FET cycles, as the consequences were comparable between the two parties (*P*>0.05), with no substantial alterations detected in main items as fertilization rate, live birth rate, clinical pregnancy rate and implantation rate despite that the FD-POS was more convenient as it orally used, easy to found the Duphaston and easy to store it as well as cost-effective than FGnRHan protocols (5.5±2.3(4-8k) vs.8.1±3.3(6-11k), MD=2.6 (2.2 to 2.9), *P*=0.0001, per K(1000) LE)

The similar efficacy of the two protocols is in line with previous four prospective RCTs[13,22,24,28], two prospective non-RCTs[23,29], nine retrospective evaluating different topics[14,16,17,18,19,20,30,31,32], and four reviews[8,9,10,11] studies that have reported comparable outcomes with the utilizing of PPOS and GnRHan protocols in general

and in subgroup of infertile females with PCOS who undertook ICSI&FET . The comparable safety profile across the two protocols, as indicated by the similar rates of OHSS and cycle cancellation, further supports their use in clinical practice. The up OHSS occurrence and the down cancellation percentage in our thesis in comparison to the results of aforementioned published studied could be due to our routine utilizing the HCG at least 5000 IU, if not at least10000 IU to grantee final oocytes maturation, as we didn't relying on GnRH agonist alone or with low HCG(1000-2000IU) doses like other trials, as in Egypt logistics regrades liable dugs transportation and preservation is thoughted to be defective as well as considering the self-sponsored infertility management in our nation .

Our study delineated that the PPOS protocol, utilizing Duphaston (DYD), a synthetic progestin, yielded comparable clinical outcomes to the GnRHan protocol, particularly in freeze-all cycles for PCOS women. This is in line with the ovarian stimulation response (OSR) outcomes and clinical results reported in Turkan's retrospective review in 2019 of 258 in D-PPOS and 267 in GnRHan groups[32], where the D-PPOS protocol emerged as a promising alternative to WHO recommended GnRHan protocol in higher responder PCOS infertile subgroup[1-7], especially considering its potential benefits in items of client suitability and charge-efficiency. Also, our thesis results were in line with FD-POS in PCOS, RCT from BUH where 76 PCOS women randomized equally to subgroup one utilized DYD from MC6 and the other was fixed GnRHan protocol as a control on MC6 with freeze all policy, they also reported similar outcomes in the two assessed domains, the OSR outcomes and the clinical pregnancy, safety outcomes with no weighty alterations between parties[22].

In the realm of clinical results, our thesis mirrored the findings of previous investigations, indicating similar pregnancy results between the antagonist protocols and DPOS, specifically in hyper-responsive patients. The utilization of mixtures of different Gn as HMG, uFSH, rFSH, as opposed to pure use of Gn, in our study did not impede follicular growth or deteriorate estradiol levels, suggesting the sufficiency of such mixture in the FD-POS protocol. The period of stimulation and sum of Gn doses were noted to be higher in the FD-POS party compared to the FGnRHan party, a tendency that has been noticed in prior investigations as well[29,32] This could be attached to the retrograde characteristics of our study, where the FD-POS group was primed for freeze-all cycles, possibly receiving a slightly up doses compared to the FGnRHan group. While estradiol levels were down in the FD-POS party than in the GnRHan party in contrary to reported in literatures. Also, similar results were reported in PPOS arms of studies comparing it with agonist protocols[12,25,26,27] and in a prospective study comparing different progestins in PPOS protocols, medroxyprogesterone acetate (MPA) with DYD[15]. Secondary to importance of this topic, a study protocol of a RCT between MPA and GnRHan published in 2021 in BMJ without reported published results till now[21]. Also, our thesis results are in parallel with two recently published retrospective studies from our country concentrating in OS in PCOS patients regarding OSR outcomes as well as pregnancy's related outcomes[33,34], the first compare DYD with conventional antagonist on 60 cases[33] while the second reported on 950 cases comparing all types of PPOS with Flexible GnRHAn Protocol[34].

While our thesis highlights the potential benefits of the FD-POS protocol, it is not devoid of limitations. The retrograde design harbors inherent biases, as selection, a lot of confounders and the assurance of freeze-all in the FD-POS group might have influenced the up Gn doses administered. However, our thesis also boasts strengths, including the successful utilization of Gn mixtures in the FD-POS protocol, the demonstration of the efficacy of DYD in suppressing LH in PCOS women, larger number of involved females in the thesis from a single center, and addressing OS in a significant portion subgroup of infertile hyper-responsive PCOS women.

CONCLUSION

Our study accentuates the potential of Duphaston as a cheap, convenient, heat stable alternative in avoiding premature LH surges through OS in PCOS women. The FD-POS protocol, characterized by elevated tolerability, consumer convenience, and downgrade costs, emerges as a promising avenue for simplifying ovarian stimulation cycles, thus fostering a extra patient-friendly protocol.

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ABBREVIATIONS

(ICSI&FET): Intra-Cytoplasmic Sperm Injection & Frozen Embryo transfer, (**FET):** Embryo transfer, (**PCOS):** Polycystic Ovary Syndrome, (**FGnRHan):** fixed GnRH antagonist, (**FD-POS):** Fixed Duphaston- Primed Ovarian Stimulation, (**HRT&FET):** Hormone replacement therapy- Frozen embryo transfer, (**FTC):** Frozen Embryo Transfer Cycle **(FD-POS):** Fixed Duphaston- Primed Ovarian Stimulation, (**FGnRHan):** fixed GnRH antagonist, (**Δ 95%CI):** Mean difference with 95% confidence interval, (**ICSI-FET)**: Intracytoplasmic sperm injection-Frozen Embryo transfer, (**AFC):** Antral follicle count, (**BMI):** body mass index, (**E2):** estradiol, (**FSH):** follicle stimulating hormone, (***P*):** progesterone,

(**LH):** luteinizing hormone, (**PCOS):** polycystic ovary syndrome, (**Basal):** day 2or3 of menstruations' **(FD-POS):** Fixed Duphaston- Primed Ovarian Stimulation, (**FGnRHan)**: fixed GnRH antagonist, (**Δ 95%CI):** Mean difference with 95% confidence interval, (**ICSI-FET)**: Intracytoplasmic sperm injection-Frozen Embryo transfer, (**GN):** gonadotropin, (**LH)**: luteinizing hormone, (**OHSS)**: ovarian hyperstimulation syndrome, (**E2):** estradiol, (***P*):** progesterone, **(F):** follicle, **(EM):** Endometrial thickness, **(ET):** embryo transfer, **(VE):** viable embryo **(FD-POS):** Fixed Duphaston- Primed Ovarian Stimulation, **(FGnRHan):** fixed GnRH antagonist, **(Δ 95%CI):** Mean difference with 95% confidence interval, (**ICSI-FET)**: Intracytoplasmic sperm injection-Frozen Embryo transfer, (**FET):** frozen-thawed embryo transfer, **(No):** number,**(FETC):** Frozen embryo transfer cycle, Clin. Preg.: clinical pregnancy, **(LE):** Egyptian pound. **(K):**1000

CONFLICT OF INTERESTS

There are no conflicts of interest

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