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Original article

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

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Abstract:

Background: Ovarian Stimulation Response (OSR) in polycystic ovarian syndrome (PCOS) ladies is controversial issues .**Aim:** to evaluate 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). **Patients and Methods:** A retrospective assessment of PCOS ladies undergoing ICSI-FET cycles at Riyadh fertility center, Agouza, Giza Governorate (RFC) and Benha University Hospital (BUH), over the last 5 years. The frequencies of clinical pregnancy, continued pregnancy, live births, fertilization, early LH surge, and other OSR results were the outcomes. **Results:** of 950 ladies included, 420 had FPPOS (study group) and 390 (control group) had the GnRHan protocol. Both groups' baseline metrics showed similarities. Oocytes that were mature and fertilized showed no discernible difference between the two groups ($P > 0.5$). Premature luteinization was rare in both groups, and there was no statistically significant difference ($P > 0.5$). Additionally, there was no discernible difference in the clinical pregnancy rate per frozen embryo transfer cycle (FETC) between the FGnRHan and FPPOS groups ($P > 0.5$). Also, continuing pregnancy rates, miscarriage rates, biochemical pregnancy rates, and implantation rates, showed statistically similarities across the groups ($P > 0.05$). Although there was a considerable decrease in cost calculated in local currency (5.8 ± 3.1 vs. 8.8 ± 4.1, $p = 0.001$) between the FPPOS and FGnRHan groups. **Conclusion:** in PCOS ladies who had ICSI-FET, the FPPOS protocol proves to be a powerful, practical, user-friendly, economical, and clinically equivalent alternative to the standard FGnRHan protocol.

Keywords: GnRH antagonist, PCOS, Progestins, PPOS, and ICSI-FET.

Introduction:

Polycystic ovarian syndrome (PCOS) is a prevalent metabolic malfunction and diverse endocrinal disorder that is well recognized as the primary cause of anovulatory infertility, impacting from 10% to 18% of women of reproductive age globally (1,2). PCOS is commonly identified by the presence of hyperandrogenism, elevated levels of luteinizing hormone (LH), and hyperinsulinemia, these lead to inhibited growth of ovarian follicles, anovulation, and infertility (3,4).

Ladies with PCOS who are receiving in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) treatment for infertility is on the rise. These patients are typically identified by their ability to produce a higher quantity of oocytes. However, oocytes obtained from PCOS ladies often exhibit suboptimal quality. This leads to decreased averages of fertilization, implantation, conception and an raised possibility of abortion and the development of ovarian hyperstimulation syndrome (OHSS) (5-7).

There is incremental evidence that suggests a potential connection among compromised oocyte maturation and progressive competence in females with PCOS and various abnormalities in endocrine, paracrine aspects, metabolic malfunction, and changes in the intrafollicular microenvironment through folliculogenesis and follicle development (8-10). Therefore, it is imperative to optimize clinical stimulation procedures to boost oocyte maturation and embryonic developing capability, ultimately improving pregnancy consequences in females with PCOS who are undergoing IVF/ICSI therapy.

Various ovarian stimulation (OS) regimens employed in PCOS ladies to avoid an early surge of LH through controlled OS (COS). These includes gonadotropin-releasing hormone (GnRH) agonist (GnRHa) or antagonist (GnRHan) protocols. GnRHan could competitively hinder the action of endogenous GnRH, resulting in a prompt and swift decrease in LH and FSH levels. Also, Unlike GnRHa, GnRHan don’t trigger an early, flare effect (11,12). When GnRHan is administered through subcutaneous injection during the late follicular stage, these antagonists effectively prevent the occurrence of an LH surge (13,14). RCTs that examined GnRHan versus GnRHa protocol in PCOS ladies, found comparable clinical pregnancy rates (CPR) between both groups, and GnRHan protocol are with lesser gonadotropin (Gn) needs, a briefer duration of stimulation, and a reduced occurrence of ovarian hyperstimulation syndrome (OHSS) (15). Latest studies found that the utilization of frozen-thawed embryos was associated with improved perinatal and pregnancy outcomes (16-18). Currently, the utilization of GnRHan regimens in conjunction with a freeze-all technique is being employed for women diagnosed with PCOS.

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 (19,20). Nevertheless, there is currently a lack of comparative data, especially including large number of patients, regarding the effectiveness and security of the PPOS and GnRHan protocols in enhancing oocyte quality among individuals with PCOS.

This retrospective analysis is well-positioned to close this knowledge gap. We seek to provide a thorough understanding of the relative benefits and possible drawbacks of both approaches by contrasting the results linked to the flexible GnRHan (FGnRHan) and fixed PPOS (FPPOS) procedures in a retrospective cohort of PCOS ladies.

Patients and Methods:

We examined all available medical records for this retrospective research at Riyadh fertility center, Agouza, Giza Governorate (RFC) and Benha University Hospital (BUH), Egypt, from January 2018 to October 2023. We selected records of ladies with PCOS who completed freeze-all ICSI -FET cycles, who underwent COS using either FGnRHan protocol or FPPOS protocol and COS cycles followed a freeze-all policy, and subsequent frozen embryo transfer cycles (FETC) were conducted using hormone replacement therapy (HRT). We extracted, organized, and anonymized the relevant data to our research. We get approval for our study from the institutional review board of Benha University of Medicine (NO:21/9/2023). The primary objective was to compare the outcomes of two different protocols: a fixed PPOS (FPPOS) and flexible GnRHan (FGnRHan) COS protocols (21).

We included 950 ladies in this retrospective analysis diagnosed with PCOS who had undergone completed freeze-all ICSI cycles, 520 ladies had undergone fixed PPOS with various progestins (FPPOS group, study group) and 430 ladies had undergone flexible GnRHan protocol (FGnRHan group, control group). We included ladies who meet the following criteria: their age falls between 20 and 45 years, their body weight exceeds 50 kg, a history of infertility more than one year, and they have been diagnosed with PCOS based on the modified Rotterdam criteria (22).

We omitted Ladies who had contraindications for the use of gonadotropins (Gn), severe male factor, grade 3 and grade 4 endometriosis, uterine or ovarian abnormalities as documented ovarian failure, clinically substantial systemic disease or other endocrinological abnormalities such as hyperprolactinemia from this study. Also, we omitted from this retrospective analysis, Ladies with PCOS who underwent a fET and those subjected to COS using GnRHan or PPOS protocols, other than fixed PPOS or flexible GnRHan protocols and those who underwent frozen embryo transfer cycles (FETC) with endometrial preparation (EP) methods other than hormone replacement therapy (HRT).

In accordance with our established ICSI-FET protocols, Ladies underwent assessment on either the MC2 or MC3 day, which involved clinical evaluations as age, BMI, transvaginal ultrasound (TVS) assessment as antral follicle count (AFC)and basal hormonal evaluations for

E2, P, LH, FSH, AMH, and TSH levels. The administration of Gn, as HMG intramuscularly as Merional (IBSA-Switzerland), Epigonal (EIPICO-Egypt), or Meriofert (IBSA - Switzerland), u-FSH as Fostimon (IBSA-Switzerland), and recombinant FSH (r-FSH) as follitropin alpha subcutaneous injection of Gonal-f (Merck, Germany) or Gonapure 75-150 IU (MINAPHARM-Egypt), was started on the MC2 or MC3. The treatment protocol was applied according to the patient's preference, the drug's availability at drugstores, clinical TVS and laboratory biochemical follow up, that usually take place every 2 to 3 days after 5 days of Gn injections. In the GnRHan group, Ladies received daily subcutaneous injections of 0.25 mg of cetrorelix (Cetrotide, Merck, Germany) or ganirelix (0.25mg, Orgalutran, Organon, The Netherlands) when the leading follicle research 12 mm , serum LH reach 10IU/L or serum E2 reach 600pg/mL (21) until the trigger day, most Ladies required approximately 5 to 6 ampules of GnRHan . In the PPOS group, Ladies were administered either 30 mg of oral Dydrogesterone (DYD) (Duphaston; Abbott Healthcare, New Zealand), progesterone (P) 600mg (Progest pharco, Egypt) or medroxyprogesterone acetate (MPA) 10 mg (provra-pfizer-Egypt) starting from MC2 or MC3 and continuing until the trigger day. The final maturation of oocytes was induced by administering human chorionic gonadotropin (HCG) 10000 IU via intramuscular injection, using either Choriomon 5000 IU (IBSA-Switzerland) or Epifasi 5000 IU (EIPICO-Egypt), or 5000 HCG plus 0.2 mg of the GnRH agonist triptorelin (decapeptyl Ferring, or triptofem (IBSA) was administered when at least three follicles measuring 18 mm or more in diameter were observed through TVS. The procedure of oocyte retrieval was conducted roughly 34-36 hours after HCG injection, afterwards followed by the process of ICSI for all M2 oocytes. In the ART laboratory, the cryotopic vitrification procedure was employed to preserve all embryos within the analyzed groups on the third day after oocyte retrieval. Frozen Embryo Transfer Cycles (FETC) were initiated promptly, typically occurring within two months following the initial procedure. All women who possessed viable embryos had experienced a minimum of one FETC, with some individuals undergoing two, three, or even four additional cycles.

The process of EP by HRT involved the oral intake of estradiol valerate in the form of white tablets (Cyclo Pogyonva/2mgE2/BAYER, Germany) at a daily dosage of 6 mg, commencing from the MC2 until the endometrial thickness reached 8 mm or more, as determined by TVS. Subsequently, progesterone was administered either as a pessary at a dosage of 400 mg or as ampules at a dosage of 100 mg (prontogest, MARCYRL, Egypt), or alternatively as oral capsules (progest 200, PHARCO, Egypt). The transfer of embryos was performed either on day 3 or day 5 after the commencement of progesterone administration. The administration of estradiol and progesterone may be continued until the conclusion of the first trimester in instances of pregnancy.

The primary outcomes of this research included the incidence of biochemical pregnancy, which was determined by a beta HCG level greater than 25mIU/ml after 15 days from frozen embryo transfer (FET). The incidence of clinical pregnancy

was assessed through ultrasound examination, either abdominal or transvaginal, 17 days after a positive pregnancy test. Clinical pregnancy was verified by the presence of a gestational sac with or without fetal cardiac activity. The incidence of clinical pregnancy was determined per FET cycle. The study also examined the incidence of live birth rate per incorporated women, which was defined as the proportion of women who gave birth one or more living babies among those who had undergone oocyte retrieval. Additionally, the study investigated the incidence of premature LH surge, which was defined as a level of 10 IU/L or twice the basal LH level if it was above 10 IU/L prior to the day of trigger. The secondary outcomes encompassed additional parameters related to ovarian stimulation and reproductive outcomes. These parameters included the total number of mature oocytes retrieved, fertilization rate, viable embryos, endocrine profile in both treatment groups, duration of ovarian stimulation, cost of the used GnRH antagonist, incidence of ovarian hyperstimulation syndrome (OHSS), incidence of cycle cancellation rate, and total gonadotropin (Gn) dose.

Statistical analysis:

The data underwent analysis using SPSS version 20.0 for Windows (IBM® SPSS®, statistics20, USA). Descriptive review measures were employed to express quantitative variables as mean two stander deviations (range) and qualitative variables as number (percent). Statistical significance was assessed at a significance level of $P < 0.05$. The two-sample student's t-test was employed to analyze quantitative outcomes, while the chi-squared test was used for qualitative outcomes. Logistic regression was conducted to examine the relationship between the dependent variable, ongoing pregnancy, and the independent variables, including the baseline characteristics of women managed, type of COS protocols, and costs.

Results:

Figure 1 depicts the flow chart of the study design and the patients involved, A total of 950 ladies with PCOS were included, with 420 of them undergoing the FPPOS treatment and 390 undergoing the FGnRHan protocol, with subsequently 1489 and 1746 FETC resulting in 635 and 764 clinical pregnancies, respectively.

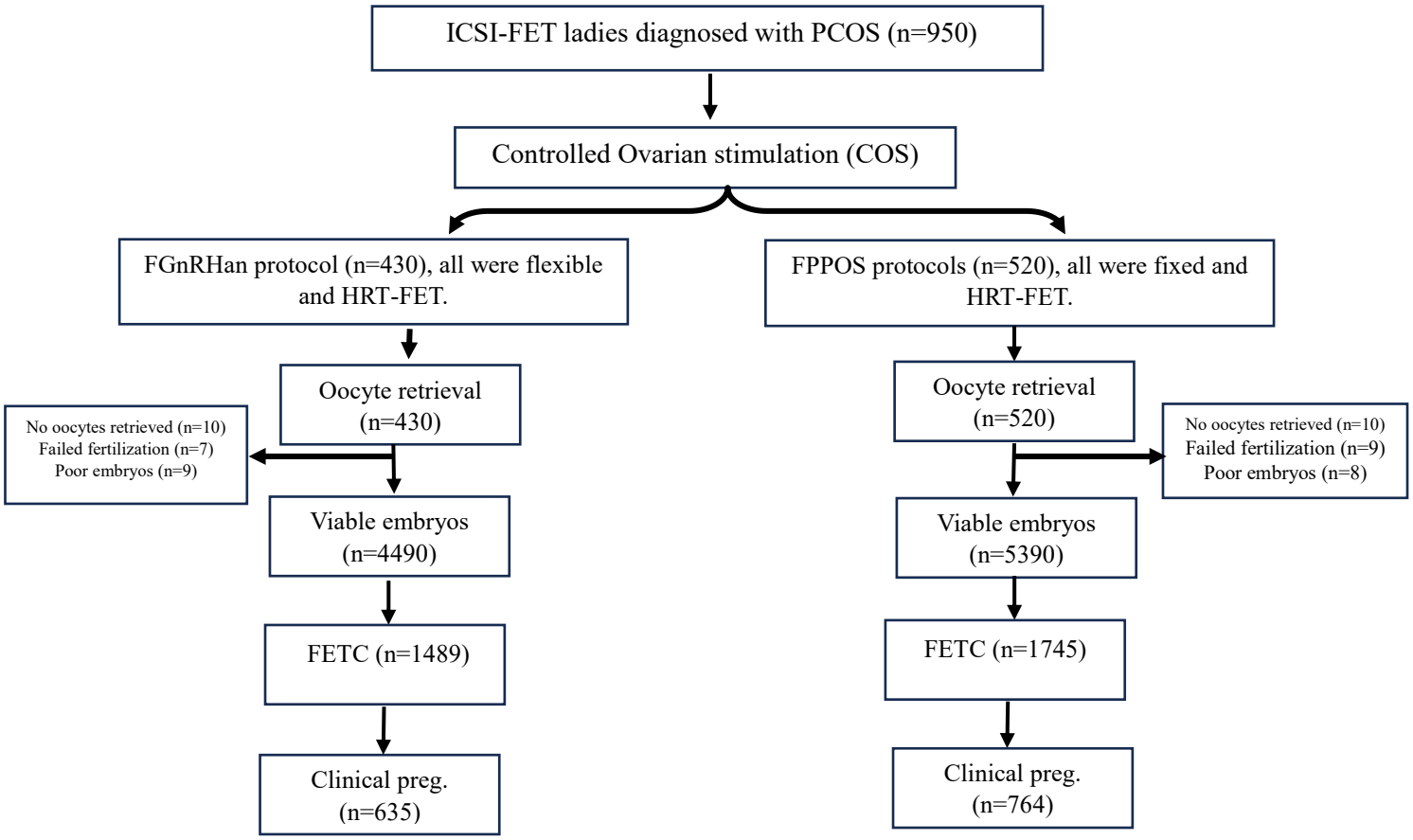
Table 1 displays demographic information, baseline clinical data, and hormonal data. Ladies in the FPPOS group exhibited similar characteristics to those in the FGnRHan group in terms of age, body mass index (BMI), fertilization type with a 100% ICSI and freeze-all approach), primary and secondary infertility rates, duration of infertility, indication f ICSI-FET (PCOS solely, PCOS with male factor, PCOS with endometriosis, PCOS with tubal factor, PCOS with other infertility causes), basal FSH, LH, E2, P, AMH, AFC, previous ICSI attempts, and previous abortions. Therefore, both groups were comparable in terms of baseline criteria. It is important to note that our analysis focuses specifically on a subgroup of infertile women with PCOS, and thus can be considered a partial propensity matched score analysis, with a particular emphasis on women suspected to exhibit an over-response.

Table 2 presents a comprehensive breakdown of the COS and provides a

summary of the ovarian stimulation response (OSR) parameters in both categories. The total dose of GnRH and the duration of stimulation were statistical significance lower in the FGnRHan control group (P<0.05). The endometrial thickness and the E2 levels on the day of trigger were found to be considerably greater in FGnRHan control group (P=0.0001). However, it is important to note that these findings may not hold clinical significance as our analysis focuses specifically on the freeze-all subset of ladies with PCOS. The LH and P levels on trigger day, the number of follicles larger than 14mm, total oocyte yield, mature oocyte count, number of fertilized oocytes, 2PN Fertilization rate, number of cleaved embryos, 2PN cleavage rate, viable embryo rate per oocyte retrieved, number of cryopreserved embryos, number of top-quality embryos, number of good-quality embryos, premature luteinization, total cycle cancellation, moderate OHSS, and severe OHSS were found to be similar between the two groups, suggesting comparable OSR to the COS protocols.

Table 3 displays a comprehensive overview of the positive clinical results, bad events, and anticipated expenditures seen in both groups. The group of participants who were primed with MC2 Progestins exhibited a slightly higher live birth rate per participant following oocyte retrieval. However, it is important to note that this difference did not reach statistical significance. The secondary outcomes, such as the rate of implantation and the rate of clinical pregnancy, exhibited no significant differences between the two groups. Regarding costs, a notable disparity was observed in the expense of the GnRHan. On average, women required approximately six ampules. In Egypt, there were numerous logistical challenges related to its availability and pricing. Our retrospective analysis revealed a significantly lower cost in the FPPOS group compared to the FGnRHan group (5.8±3.1(5-9k) vs. 8.8±4.1(7-12k), mean difference =3, 95% confidence interval = 2.54 to 3.45, p-value = 0.001), counted per 1000 LE (K).

Table 4 displays the logistic regression analysis conducted to examine the relationship between the dependent variable, ongoing pregnancy, and the independent variables, including the baseline characteristics of women managed and the type of COS protocols. The analysis focused on ladies with PCOS who had undergone ICSI-FET using either FGnRHan or FPPOS protocols. The results indicate that none of the independent variables, such as age, duration of infertility, number of prior attempts, basal FSH, LH, E2, P, costs, and type of COS protocols, had a significant negative effect on the pregnancy outcomes (P>0.05).



ICSI-FET: Intra-cytoplasmic sperm injection-Frozen embryo transfer, **FET:** Embryo transfer, **PCOS:** Polycystic Ovary Syndrome, **FPPOS:** Fixed Progesterone-Primed Ovarian Stimulation, **FGnRHan:** flexible GnRH antagonist, **HRT-FET:** Hormone replacement therapy- Frozen embryo transfer, **FETC:** Frozen embryo transfer cycle.

Fig. (1). Flow chart of FPPOS Protocol & FGnRHan Protocol in ladies with PCOS who underwent ICSI-FET

Table 1: Comparison of baseline attributes and Hormonal data of ladies with PCOS who underwent ICSI-FET either with FPPOS Protocol or FGnRHan Protocol.

attributes	FPPOS Protocol (n=520)	FGnRHan Protocol (n=430)	Δ 95% CI	P-value
Age (y)	25.9 ± 7.2(19-45)	26.2 ± 8.4(21-42)	0.1(0.69 – 1.29)	0.55
BMI (kg/m^2)	29.3 ± 7.8(26-39)	29.9 ± 8.6(20-39)	0.6 (0.44 to 1.64)	0.26
Fertilization type ICSI (%)	520(100%)	430(100%)	0% (0.89% to 0.73%)	
Primary infertility (%)	380(73.1%)	320(74.4%)	1.3% (4.35% to 6.86%)	0.65
secondary infertility (%)	140(27%)	110(25.6%)	1.4% (4.25% to 6.96%)	0.63
Duration of infertility (y)	4.5 ± 2.4(2-18)	4.8 ± 2.9(5-22)	0.3 (0.03 – 0.63)	0.08
Indication for ICSI:				
PCOS only	375(72%)	314(73%)	1% (4.73% to 6.65%)	0.73
PCOS + male factor	109(21%)	74(17.2%)	3.8% (1.26% to 8.74%)	0.14
PCOS+ endometriosis	18(3.5%)	11(2.5%)	1% (1.33% to 3.24%)	0.37
PCOS+ tubal factor	8(1.5%)	18(4.2%)	2.7% (0.59% to 5.15%)	0.01
PCOS+ other	10(1.9%)	13(3%)	1.1% (0.9% to 3.35%)	0.27
Basal FSH (IU/L)	5.1 ± 4.3(4-8)	5.4 ± 4.5(3-8)	0.3 (0.26 to 0.86)	0.29
Basal LH (IU/L)	9.9 ± 6.7(4-15)	9.7 ± 5.8(4-16)	0.2 (1 to 0.6)	0.63
Basal E2 (pg/mL)	57 ± 18(38-88)	58 ± 19(26-89)	1 (1.36 to 3.36)	0.41
Basal P (ng/mL)	0.71 ± 0.9(0.4-0.8)	0.73 ± 0.8(0.3-0.9)	0.02 (0.1 to 0.13)	0.72
AMH (ng/mL)	12.3 ± 5.9(6-17)	12.5 ± 5.7(6-18)	0.2 (0.54 to 0.94)	0.6
Basal AFC	24 ± 13(16-39)	22 ± 14(17-37)	2 (3.72 to 0.28)	0.02
Previous ICSI attempts	1.5 ± 0.8(0-6)	1.4 ± 0.9(0-6)	0.1 (0.21 to 0.01)	0.07
Previous abortions	**0.7 ± 0.5(0-5)**	**0.7 ± 0.6(0-3)**	**0 (0.07 to 0.07)**	**1**

FPPOS: Fixed Progesterone-Primed Ovarian Stimulation, **FGnRHan:** flexible GnRH antagonist, **Δ 95%CI:** Mean difference with 95% confidence interval, **ICSI-FET:** Intracytoplasmic sperm injection-Frozen Embryo transfer, BMI: body mass index, **AFC:** Antral follicle count, **E2:** estradiol, **FSH:** follicle stimulating hormone, **P:** progesterone, **LH:** luteinizing hormone, **PCOS:** polycystic ovary syndrome, **Basal:** day 2or3 of menstruations MC2 or MC3.Values presented as mean ± 2 standard deviation (range) or number (percent).P<0.05: Statistically significant

Table 2: Comparison of ovarian Stimulation attributes, Hormonal data, and Outcomes of ladies with PCOS who underwent ICSI-FET either with FPPOS Protocol or FGnRHan Protocol.

attributes	FPPOS Protocol (n=520)	FGnRHan Protocol (n=430)	Δ 95% CI	P-value
Total GN dose (IU)	2930 ± 390(2500-3990)	2820 ± 405(2300-3900)	110 (161 to 59)	0.0001
Duration of stimulation (d)	10.9 ± 5.5(7-13)	9.5 ± 4.9(8-13)	1.4 (2.07 to 0.73)	0.0001
EM. on trigger day (mm)	7.9 ± 5.4(6-10)	9.3 ± 4.7(8-13)	1.4 (0.75 to 2.05)	0.0001
E2 on trigger day (pg/mL)	5245 ± 540(4230-9760)	5425 ± 650(4450-9850)	180 (104 to 256)	0.0001
LH on the trigger day IU/L	2.6±1.8(1.8-10.4)	2.4±1.9(1.7-10.4)	0.2 (0.44 to 0.04)	0.1
P levels on trigger day (ng/mL)	2.8 ± 1.8(0.8-8.6)	2.6 ± 1.9(0.6-4.8)	0.2 (0.44 to 0.04)	0.1
No. of >14 mm F. at trigger day	25±14(18-48)	26±15(19-45)	1 (0.85 to 2.85)	0.3
No. of oocytes retrieved	24±12(0-39)	23±14(0-42)	1 (2.66 to 0.66)	0.24
Oocyte retrieval rate (%)	58 ± 22 (0-92)	56 ± 20 (0 -91)	2 (4.7 to 0.7)	0.15
No. of MII oocytes	13 ± 9(0-37)	14 ± 8(0-38)	1 (0.09 to 2.09)	0.07
Mature oocyte rate (%)	63± 24(0-86)	64± 25(0-80)	1 (2.13 to 4.13)	0.53
No. of fertilized oocytes	11±8(0-27)	12±9(0-26)	1 (0.04 -1.95)	0.07
2PN Fertilization rate (%)	65 ± 18(0-80)	67 ± 17(0-89)	2 (0.25 to 4.25)	0.08
No. of cleaved embryos	9±7(0-19)	10±8(0-20)	1 (0.04 -1.95)	0.04
2PN cleavage rate, %	73± 26(0-90)	75± 25(0-90)	2 (1.29 to 5.27)	0.23
VE rate per oocyte retrieved (%)	37±12(18 -83)	38±11(25 -87)	1 (0.48 to 2.48)	0.2
No. of cryopreserved embryos	8±5(4-16)	8±4(4-18)	0.0	1
No. of top-quality embryos	9±4(3-12)	9±5(3-11)	0.0	1
Good-quality embryos (%)	51 ± 26(20-84)	52 ± 25(20-95)	1 (2.27 to 4.27)	0.55
Premature luteinization %	9(1.7%)	9(2.1%)	0.4% (1.4% to 2.4%)	0.65
Total cycle cancelation	26(5%)	27(6.3%)	1.3% (1.65% to 4.43%)	0.4
Moderate OHSS	35(6.7%)	28(6.5%)	0.2% (3.1% to 3.4%)	0.9
Severe OHSS	5(1%)	8(1.9%)	0.9% (0.69% to 2.77%)	0.24

FPPOS: Fixed Progesterone-Primed Ovarian Stimulation, **FGnRHan:** flexible GnRH antagonist, **PCOS:** polycystic ovary syndrome, **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, Values presented as mean ± 2 standard deviation (range) or number (percent), P<0.05: Statistically significant

Table 3: Comparison of clinical Results of ladies with PCOS who underwent ICSI-FET either with FPPOS Protocol or FGnRHan Protocol.

Outcomes	FPPOS Protocol (n=520)	FGnRHan Protocol (n=430)	Δ 95% CI	P-value
No of FET cycle (n)	1745	1489		
No of thawed embryos (n)	5489	4784		
No viable embryos after thaw (n)	4769	3998		
No FET on the cleavage stage	1.9±0.9(1-4)	1.9±0.8(1-4)	0 (0.11 to 0.11)	1
No of FET on blastocyst stage	1.7 ±0.8(1-3)	1.6 ±0.9(1-3)	0.1 (0.21 to 0.01)	0.07
Hormone replacement therapy (n)	1745 (100%)	1489 (100%)	0% (0.26% to 0.22%)	
Endometrial thickness (mm)	9.7 ±3.9(8-13)	9.5 ±4.2(8-12)	0.2 (0.72 to 0.32)	0.45
Biochemical preg. rate/FETC, %(n)	63% (1094/1745)	64% (948/1489)	1% (2.33% to 4.32%)	0.56
Clinical preg. rate/FETC, % (n)	49% (855/1745)	47% (699/1489)	2% (1.45% to 5.45%)	0.26
Implantation rate/FET, % (n)	44% (2098/4769)	46% (1839/3998)	2% (0.1% to 4.1%)	0.06
Miscarriage rate/FETC, % (n)	9.5% (166/1745)	8.5% (127/1489)	1% (0.99% to 2.97%)	0.32
Multiple preg. rate/Clin. Preg. (%)	24% (/855)	22% (/699)	2% (2.23% to 6.16%)	0.35
Ongoing preg. rate/FETC, % (n)	40% (698/1745)	42% (625/1489)	2% (1.4% to 5.4%)	0.25
Cumulative preg. rate per patient, %(n)	62% (322/520)	65% (280/430)	3% (3.1% to 9.1%)	0.34
Live birth rate per FETC, % (n)	41% (/1745)	39% (/1489)	2% (1.4% to 5.4%)	0.25
Live birth rate per patient, % (n)	34% (177/520)	36% (155/430)	2% (4.1% to 8.1%)	0.52
Costs of different item per patient (LE)	5.8±3.1(5-9k)	8.8±4.1(7-12k)	3 (2.54 to 3.45)	0.0001

FPPOS: Fixed Progesterone-Primed Ovarian Stimulation, **FGnRHan:** flexible GnRH antagonist, **PCOS:** polycystic ovary syndrome, **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, Values presented as mean ± 2 standard deviation (range) or number (percent), P<0.05: Statistically significant

TABLE 4. Logistic Regression for Pregnancy outcomes in ladies with PCOS who underwent ICSI-FET either with FPPOS Protocol or FGnRHan Protocol.

Baseline Parameter	Odds ratio (OR)	P-value
Age (y)	0.78	0.31
BMI (kg/m^2)	0.82	0.09
Duration of infertility (y)	0.72	0.02
No. of prior attempts	1.75	0.76
FSH (IU/L)	1.54	0.34
LH (IU/L)	0.89	0.08
E2 (pg/mL)	0.87	0.34
P(ng/mL)	0.56	0.25
Type of COS protocol	0.59	0.34
Costs	1.78	0.25

FPPOS: Fixed Progesterone-Primed Ovarian Stimulation, **FGnRHan:** flexible GnRH antagonist, **PCOS:** polycystic ovary syndrome, **ICSI-FET:** Intracytoplasmic sperm injection-Frozen Embryo transfer, **P:** Progesterone, **COS:** controlled ovarian stimulation, **BMI:** body mass index, **FSH:** follicle stimulating hormone, **E2: estradiol, LH:** luteinizing hormone, **P:** progesterone, P<0.05: Statistically significant.

Discussion:

Controlled ovarian stimulation in ladies with PCOS has underwent significant improvements over the years, with a primary objective of refining procedures to improve clinical outcomes while mitigating the occurrence of adverse consequences, notably OHSS. This study compares the outcomes of FPPOS and FGnRHan, in the circumstances of Freeze-all ICSI-FET cycles. The findings of our study indicate that both FPPOS and FGnRHan protocols are viable options for COS in ladies with PCOS who are undergoing ICSI-FET. The outcomes of the two groups were comparable, as evidenced by a lack of significant differences (P>0.05) in live birth rate, fertilization rate, implantation rate, and clinical pregnancy rate. However, the FPPOS protocol demonstrated certain advantages over the FGnRHan protocol. Specifically, the FPPOS protocol was more appropriate due to its oral consumption, easy availability of the progestins, and ease of storage. Additionally, the FPPOS protocol was found to be more cost-effective compared to the FGnRHan protocol (P=0.0001), with a mean cost difference of 3000LE.

The comparable effectiveness of the two evaluated protocols in our study aligns with findings from previous studies, including the four prospective randomized controlled trials (23-26), two prospective non-randomized controlled trials (27, 28), nine retrospective studies covering various topics (29-38), and four reviews (39-42) . These studies have consistently reported similar outcomes when comparing the use of PPOS and GnRHan protocols, both overall and specifically among infertile women with polycystic ovary syndrome who underwent intracytoplasmic sperm injection-frozen embryo transfer. The identical rates of ovarian hyperstimulation syndrome (OHSS) and cycle cancellation observed in both protocols provide additional evidence to justify their utilization in clinical settings**.**

The higher incidence of OHSS and the lower rate of treatment cancellation observed in our analysis, compared to the results reported in the published studies, may be attributed to our routine practice of administering HCG at a minimum dose of 5000 IU, and sometimes at least 10000 IU, to ensure optimal maturation of oocytes. In contrast, other trials relied solely on GnRH agonist or used lower doses of HCG 1000-2000 IU. It is worth noting that in Egypt, issues related to the transportation and preservation of reliable drugs are defective, which may have influenced the outcomes. Additionally, the self-funded nature of infertility treatment in our country should be taken into consideration.

The clinical outcomes obtained from both FPPOS protocol and the FGnRHan protocol on freeze-all cycles conducted on ladies with PCOS were shown to be similar, this aligns with the Turkan's retrospective analysis of 258 ladies in the progestins group and 267 ladies in the GnRHan group (38) and with Egyptian RCT involved 76 PCOS ladies (24). The FPPOS group exhibited a greater duration of stimulation and total dose of Gn compared to the FGnRHan group, which aligns with findings from prior studies (29-38). Our research suggests that the FPPOS protocol may be a viable alternative to the WHO-recommended GnRHan protocol for

ladies with PCOS who are classified as hyper respondents in terms of COS (43-47). Within the domain of clinical outcomes, our study replicated the results of prior research, demonstrating comparable rates of pregnancy between the PPOS and antagonist protocols, particularly among individuals who exhibit hyper-responsiveness. Moreover, FPPOS protocol offers potential advantages in terms of user convenience and cost-effectiveness.

Although our study provides insights into the possible advantages of the FPPOS protocol, it is not without its drawbacks. The retrospective methodology of the study introduces inherent biases, such as selection bias and confounding variables. Additionally, the certainty of the freeze-all approach in the FPPOS group may have impacted the administration of greater Gn dosages. Nevertheless, our study possesses several notable strengths. Firstly, we successfully demonstrated the effectiveness of different progestins in suppressing LH in ladies with PCOS. Additionally, we effectively employed Gn mixtures in the FPPOS protocol. Furthermore, our study included a larger number of women from a single center, enhancing the robustness of our findings. Lastly, we specifically addressed COS, OSR, clinical and financial consequences in a significant subgroup of infertile PCOS ladies who exhibited hyper-responsiveness.

Conclusion:

The findings of our study highlight the potential of different progestins as an affordable, practical, and thermally stable option for preventing premature LH surges during Controlled ovarian stimulation in women with polycystic ovary syndrome. The Fixed Progesterone-Primed Ovarian Stimulation regimen, which exhibits attributes such as excellent tolerability, user convenience, and cost reduction, presents itself as a potentially advantageous method for streamlining ovarian stimulation cycles, thus promoting a more patient-centric approach.

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