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Original Article

Progestin-primed Ovarian Stimulation vs. GnRH Analogue as regard Pregnancy Loss and Neonatal Birthweights: A Retrospective Study

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Abstract

Background: Progestin primed ovarian stimulation (PPOS) has proved its effectiveness in COS in comparison with conventional protocols. Gonadotropin releasing hormone (GnRH) analogues have been shown to reduce pituitary activity and prevent LH surges, PPOS protocol has the same role with different mechanism in COS but data about its long term safety is still insufficient. **Objectives:** to compare the outcome of thawed embryos originating from Progestin Primed Ovarian Stimulation vs. that originating from GnRH analogue protocols especially as regard: Pregnancy outcome and neonatal birth weights. **Methods:** This retrospective study took place at IVF center, all case files during period from January to December 2022. Case files divided into 2 study groups A and B, Group A: thawed embryos originated from PPOS protocol and Group B: thawed embryos originated from conventional protocols using GnRH analogue group. **Result:** pregnancy loss rates were found to be 18.2% in the GnRH Analogue group and 20.4% in the PPOS group, with an odds ratio (OR) of 1.155 and a 95% confidence interval (CI) of 0.551-2.422. The p-value of 0.702 with no statistically significant disparity in pregnancy loss rates between the two groups. The percentages of low birthweight (2500 g) and high birthweight (4000 g) infants were comparable between the GnRH Analogue and PPOS groups with odds ratios close to 1. **Conclusion:** The pregnancy loss and the birthweights of neonates from PPOS were similar to those from GnRH analogue regimens. This provided us with the safety of PPOS. Furthermore, this evidence suggests that the external progestins administration during ovarian stimulation has no negative impact on the oocytes quality or on the subsequent embryos development in IVF cycles. Additional inquiries should prioritize the examination of the prolonged safety of offspring resulting from the PPOS technique.

Key words: Thawed Embryos, Progestin-primed Ovarian Stimulation, GnRH Analogue, Frozen Embryo, Transfer, Pregnancy Loss

Introduction

Approximately 10% of couples of reproductive age worldwide are affected by infertility, and in recent years, in vitro fertilization (IVF) has emerged as the most efficacious therapy for this condition[1]. IVF, first developed over four decades ago as a therapeutic measure for infertile couples with irreparable tubal factor, has recently expanded its use to include infertility caused by many reasons, as well as unexplained infertility[2].

OS procedures include the injection of external gonadotrophins to sustain FSH and LH levels beyond a crucial threshold necessary to encourage the concurrent development of numerous follicles during a single cycle[3]. However, the occurrence of multifollicular development leads to an elevated synthesis of sex steroids, which may cause an unplanned rise of luteinizing hormone (LH) and spontaneous ovulation before the harvest of oocytes [4, 5].

Utilizing GnRH analogues, both agonists and antagonists, has been used to inhibit early ovulation via pituitary suppression. In this scenario, the final maturation of the egg is usually induced by administering a concentrated dose of hCG, GnRH agonists, or a combination of both[6].

Gonadotropin-releasing hormone (GnRH) analogues, on the other hand, have several drawbacks including:

An increased likelihood of experiencing ovarian hyperstimulation syndrome (OHSS), symptoms related to low estrogen levels, as well as potential effects beyond the pituitary gland and the development of ovarian cysts [7, 8].

In contrast, GnRH antagonists are linked to a notably reduced quantity of oocytes collected[9, 10] as well as a greater rate of cycle cancellation[9, 11] . In addition to their distinct adverse effects, GnRH analogues might provide challenges for patients.

Subcutaneous administration is necessary, however the variations in available preparations and the associated high

prices sometimes make them inconvenient and unaffordable for patients. Hence, ART professionals were pre-occupied with the pursuit of an alternate COS procedure.

In 2015, we proposed a new method called progestin-primed ovarian stimulation (PPOS) for controlled ovarian stimulation (COS). This method involves using oral progestin to avoid an early LH surge. Alongside the freeze-all approach, a group of 150 women who had PPOS treatment achieved a clinical pregnancy rate of 47.8%, with an implantation rate of 31.9% recorded during that period. When comparing PPOS with traditional COS regimens, PPOS offer several benefits, including:

It may be administered orally, provides more control over LH levels, and carries a reduced risk of OHSS[10]. The study conducted by[8].

Progestins are more cost-effective than GnRH analogues and may be administered orally or by injection[10].

Could be selected as an operating system for the purpose of preserving fertility, managing projected hyper responders who are at risk of ovarian hyperstimulation syndrome (OHSS), and in any situation where the operating system and oocyte extraction do not necessarily lead to a fresh embryo transfer[12].

The unfavorable influence on the ability of the endometrium to receive an embryo is caused by the exposure to progestin during the follicular period. Therefore, PPOS might serve as a viable alternative procedure for preserving oocytes, doing preimplantation genetic testing (PGT), and performing in vitro fertilization (IVF) for women who are at risk of developing ovarian hyperstimulation syndrome (OHSS).[13, 14]

According to a randomized controlled study conducted by[8, 15], the occurrence of early LH surge was considerably reduced in the PPOS group (0%) compared to the GnRH antagonist protocol group (5.88%) for patients with

poor ovarian response (PORs). The rise in popularity of PPOS procedures may be attributed to their economic and therapeutic convenience. Nevertheless, there have been raised concerns over the result of pregnancy, the influence on babies, and the long- term safety[8, 10].

Aim of the work

We aimed in this study to compare the results of thawed embryos derived from Progestin- Primed Ovarian Stimulation to thawed embryos derived from GnRH analogue procedures, specifically in terms of pregnancy outcomes and neonatal birthweights.

Patients and Methods

The study was conducted in Private IVF center, all case files matched with our inclusion and exclusion criteria during the period of time starts from January 2022 till December 2022 was recruited in our study.

The case files were divided into 2 groups:
Group A: Case files in which thawed embryos originated from PPOS protocol were used.

Group B: Case files in which thawed embryos originated from conventional protocols using GnRH analogue group were used.

The outcome of both Groups was recorded.

The primary outcomes:

1) Incidence of pregnancy loss

2) Neonatal birth weight.

The secondary outcomes:

1)The pregnancy complications (especially Preterm labor).

2) live birth defects.

3) Newborn gender.

4) Gestational age at birth.

Ethical consideration

Ethical permission: was sought from a Local Ethics Committee (REC) in department of obstetrics and gynecology faculty of medicine Minia University with approval number (611/2023) obtained on Jan. 2023. The data that were obtained from participants were confidential. The study participants were not identified by name in any report or publication concerning this study. Patient consent was

waived due to the nature of the retrospective study.

Statistical analysis

Data was collected, coded then entered as a spread sheet using Microsoft Excel 2016 for Windows, of the Microsoft Office bundle; 2016 of Microsoft Corporation, United States. Data was analyzed using IBM Statistical Package for Social Sciences software (SPSS), (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp). The Kolmogorov-Smirnov test was used to verify the normality of distribution. Continuous data was expressed as mean ± standard deviation while categorical data as numbers and percentage. A statistical value <0.05 was considered as significant. The following tests were used: Chi-square test; used to study the association between two qualitative variables. Analysis of variance (ANOVA or F test): was used for continuous data to test for significant difference between more than two normally distributed groups. Kruskal-Wallis test: It is a non-parametric equivalent to ANOVA and used when ANOVA assumptions were violated to compare between more than two groups of skewed data. Post Hoc tests: Tukey honestly significant difference (Tukey-HSD) test was used as a post hoc test to adjust for multiple comparisons after significant ANOVA test to indicate which significant difference between pairs of groups whereas Bonferroni post hoc test was used after significant Kruskal- Wallis test.

Results

One treated with GnRH Analogue and the other with PPOS, showed no significant differences in maternal age (p=0.675), paternal age (p=0.195), or BMI (p=0.731). This indicates a balanced distribution of demographic variables between the groups, enhancing the comparability of our study groups.

Regarding infertility duration, the distribution among groups demonstrated that 68.2% of the GnRH Analogue group experienced a duration of 1-3 years, compared to 72.0% in the PPOS group

(p=0.570). Gravidity and the number of miscarriages exhibited similar patterns, with no significant variations between the groups (p=0.924 and p=0.518, respectively). Table (1)

Analysis of induced abortions, parity, and previous IVF attempts also revealed no significant discrepancies between the GnRH Analogue and PPOS groups (p=0.409, p=0.347, and p=0.776, respectively). The distribution of infertility indications, including tubal factors, male factors, unexplained causes, anovulatory conditions, endometriosis, and mixed causes, displayed no statistically significant differences between the groups (p=0.7677). Table (2)

Regarding Oocyte Yields, no significant differences were observed between the two groups across different yield categories (1-5, 6-15, and 16-35), with p-values ranging from 0.926 to 0.855. Table (3)

Endometrium Preparation methods, however, showed a significant difference (p=0.044*). Notably, the PPOS group had a higher percentage of patients undergoing natural cycle preparation (21.5%) compared to the GnRH Analogue group (35.2%). Endometrium Thickness demonstrated no significant disparities between groups (p=0.854), with the majority in both groups having an endometrial thickness 8 mm. Table (3)

Examining Embryo Stage, a significant difference (p=0.037*) was observed. The GnRH Analogue group had a higher percentage of patients with embryos in the cleavage stage (75.0%), while the PPOS group had a higher proportion with blastocysts (87.1%), showed a significant difference (p=0.037*). Embryos Transferred displayed no significant differences between groups (p=0.801), indicating a balanced distribution of the number of embryos transferred during ART cycles. Table (3)

Finally, the Basic FSH value exhibited no statistically significant difference between the GnRH Analogue and PPOS groups (p=0.385). Table (3)

The overall pregnancy loss rates were found to be 18.2% in the GnRH Analogue group and 20.4% in the PPOS group, with an odds ratio (OR) of 1.155 and a 95% confidence interval (CI) of 0.551-2.422. The p-value of 0.702 indicates no statistically significant disparity in pregnancy loss rates between the two treatment groups. Table (4)

In the assessment of pregnancy outcomes and neonatal variables within our study groups treated with GnRH Analogue (N=72) and PPOS (N=74), no significant differences were observed between the two groups across various parameters. The live birth rate was 79.2% in the GnRH Analogue group and 79.7% in the PPOS group, with an odds ratio of 0.966 (95% CI: 0.433-2.156) and a p-value of 0.933. Table (5)

Gestational weeks at delivery did not show significant variations between the groups (p=0.787), with majority of deliveries occurring after 37 weeks in both groups. Similarly, the mode of delivery (vaginal or cesarean section), the number of neonates (single or twins), and the sex of neonates demonstrated no statistically significant differences between the GnRH Analogue and PPOS groups. Table (5)

Birth weight, represented by mean ± SD and median (IQR), also exhibited no significant differences between the two groups (p=0.928). Table (5)

Furthermore, the percentages of low birthweight (2500 g) and high birthweight (4000 g) infants were comparable between the GnRH Analogue and PPOS groups, with odds ratios close to 1 and non-significant p-values. Table (5)

Neonatal events and congenital anomalies were infrequent in both groups, and no significant differences were observed in their occurrences (p=0.700 and p=0.551, respectively) congenital anomalies appeared in 2 neonates in GnRH analogue group (spina bifida, VSD separately) and 1 neonate in PPOS group (having hydrocephalus) . These findings suggest that the incidence of adverse neonatal outcomes did not significantly differ

between individuals treated with GnRH Analogue and PPOS. Table (5)

The process of managing and analyzing data was carried out using SPSS version 27.0. The statistical measures, including the means and standard deviations, of the quantitative variables for both males and females are provided. The data's normality was assessed using the Shapiro-Wilk test. The comparison between the two groups was conducted using the Mann-Whitney test for non-parametric variables and the Student's t-test for variables having a normal distribution. Variables that follow a normal distribution are represented by their mean and standard deviation (SD), whereas variables that do not follow a normal distribution are represented by their median and the values corresponding to the 25th and 75th percentiles. The chi-square test was used to analyze categorical variables. Significance was attributed to differences if the P-value was less than 0.05.

Table (1): Demographic data in the two studied groups

Variables	Group		p value
	GnRH Analogue (N=88)	PPOS (N=93)	
Maternal age (years)			0.675
Mean ±SD	30.07 ± 6.53	30.32 ± 5.81	
Median (IQR)	29.50 (24.00 - 34.50)	30.00 (26.00 - 34.00)	
Paternal age (years)			0.195
Mean ±SD	41.05 ± 9.48	39.23 ± 9.52	
Median (IQR)	42.00 (33.00 - 49.50)	39.00 (31.00 - 46.00)	
BMI (kg/m2)			0.731
Mean ±SD	24.88 ± 5.42	25.18 ± 5.63	
Median (IQR)	24.50 (21.00 - 30.00)	26.00 (20.00 - 30.00)	

BMI: body mass index

Table (2): Obstetric history in the two studied groups.

Variables		Group				p value
		GnRH Analogue (N=88)		PPOS (N=93)		
		N	%	N	%	
Infertility duration (years)	1–3	60	68.2%	67	72.0%	0.570
	>4	28	31.8%	26	28.0%	
Gravidity	0	45	51.1%	49	52.7%	0.924
	1	25	28.4%	24	25.8%	
	>2	18	20.5%	20	21.5%	
No. of miscarriages	0	72	81.8%	74	79.6%	0.518
	1	11	12.5%	16	17.2%	
	>2	5	5.7%	3	3.2%	
No. of induced abortions	0	62	70.5%	67	72.0%	0.409
	1 – 2	22	25.0%	18	19.4%	
	>3	4	4.5%	8	8.6%	
Parity	0	85	96.6%	87	93.5%	0.347
	>1	3	3.4%	6	6.5%	
Previous IVF attempts	0	69	78.4%	73	78.5%	0.776
	1 – 2	16	18.2%	15	16.1%	
	>3	3	3.4%	5	5.4%	
Infertility indications	Tubal	38	43.2%	35	37.6%	0.767
	Male factor	15	17.0%	14	15.1%	
	Unexplained	4	4.5%	9	9.7%	
	Anovulatory	3	3.4%	2	2.2%	
	Endometriosis	4	4.5%	5	5.4%	
	Mixed causes	24	27.3%	28	30.1%	

*, p: p value for comparing between the two studied groups. *: Statistically significant at p ≤ 0.05*

Table (3): Assessment of Oocyte Yields,Endometrium Preparation, Thickness, Embryo Stage, and Embryos Transferred in the two studied groups.

Variables		Group				p value
		GnRH Analogue (N=88)		PPOS (N=93)		
		N	%	N	%	
Oocyte yields	1 – 5	16	18.2%	19	20.4%	0.926
	6- 15	52	59.1%	53	57.0%	
	16 – 35	20	22.7%	21	22.6%	
Endometrium preparation	Natural cycle	31	35.2%	20	21.5%	**0.044***
	Mild stimulation	39	44.3%	58	62.4%	
	HRT	18	20.5%	15	16.1%	
Endometrium.thickness (mm)	<8 mm	6	6.8%	7	7.5%	0.854
	>8 mm	82	93.2%	86	92.5%	
Embryo stage	Cleavage	66	75.0%	81	87.1%	**0.037***
	Blastocyst	22	25.0%	12	12.9%	
Embryos transferred	1	13	14.8%	15	16.1%	0.801
	2	75	85.2%	78	83.9%	
Basic FSH value (mIU/mL)						0.385
Mean ±SD		4.70 ± 1.37		4.87 ± 1.33		
Median (IQR)		4.50 (3.50 - 6.00)		5.00 (4.00 - 6.00)		

IQR: Inter quartile range , SD: Standard deviation,
*p: p value for comparing between the two studied groups. *: Statistically significant at p ≤ 0.05*

Table (4): Pregnancy loss in the two studied groups.

Variables		Group				OR (95%CI)	p value
		GnRH Analogue(N=88)		PPOS (N=93)			
		N	%	N	%		
Pregnancy loss		16	18.2%	19	20.4%	1.155 (0.551-2.422)	0.702
	Biochemical pregnancy loss	2	2.3%	3	3.2%		
	Ectopic pregnancy	4	4.5%	2	2.2%		
	Early miscarriage (6–11 weeks)	6	6.8%	8	8.6%		
	Late miscarriage (12–24 weeks)	3	3.4%	5	5.4%		
	Stillbirth (≥24 weeks)	1	1.1%	1	1.1%		

*p: p value for comparing between the two studied groups. *: Statistically significant at p ≤ 0.05*

Table (5): Live birth, Gestational Weeks, Delivery Modes, Neonatal Multiplicity, Sex, Birth Weight, Low and High Birthweight, and Neonatal Events Including Congenital Anomalies in the two studied groups.

Variables		Group				OR (95%CI)	p value
		GnRH Analogue (N=72)		PPOS (N=74)			
		N	%	N	%		
Live birth		57	79.2%	59	79.7%	0.966(0.433-2.156)	0.933
Gestational weeks at delivery (weeks)	<32	0	0.0%	2	2.7%	1.115 (0.506-2.455)	0.787
	33-36	13	18.1%	8	10.8%		
	>37	59	81.9%	64	86.5%		
Mode of delivery	Vaginal	15	20.8%	17	23.0%		0.842
	C.S	57	79.2%	57	77.0%		
No. of neonates	Single	50	69.4%	57	77.0%		0.352
	Twins	22	30.6%	17	23.0%		
Sex of neonates	Male	39	54.2%	40	54.1%		0.989
	Female	33	45.8%	34	45.9%		
Birth weight (g) Mean ±SD Median (IQR)		3158.8 ± 604.2 3211.0 (2648.5 - 3678.5)		3147.1 ± 565.7 3135.5 (2712.0 - 3606.0)			0.928
Low birthweight (<2500 g)		9	12.5%	11	14.8%	0.969 (0.361-2.600)	0.951
High birthweight (>4000 g)		4	5.6%	4	5.4%	0.971 (0.234-4.041)	0.968
Neonatal events		5	6.9%	4	5.4%	0.766 (0.197 -2.974)	0.700
Congenital anomalies		2	2.8%	1	1.4%	0.479 (0.043 -5.407)	0.551

IQR: Inter quartile range , SD: Standard deviation,
*p: p value for comparing between the two studied groups. *: Statistically significant at p ≤ 0.05*

Discussion

According to our results, 68.2% of the GnRH Analogue group had experienced infertility for 1-3 years, whereas 72.0% of the PPOS group had a little higher rate. Both the gravidity patterns and the miscarriage frequencies were similar. We found no statistically significant difference in the duration of infertility, the frequency of pregnancy losses, or gravidity between the two groups.

In addition, our results are consistent with those of[16], who found an 80.8% live birth rate in the PPOS group and an 81.6% GnRH Analogue group. Crucially, with a p-value of 0.97 and an odds ratio (95% confidence interval) of 0.49 (0.88, 1.06), there was no statistically significant difference in live birth rates between the PPOS and GnRH analogue groups.

Because most births in both groups happened after 37 weeks of gestation, the present study did not find any statistically significant differences in the number of weeks until delivery between the groups (p=0.787).

We also found the same thing as[14], who found no statistically significant difference in the two groups gestational weeks at delivery. Most pregnancies in both groups ended at 37 weeks. Furthermore, they revealed that when comparing the GnRH Analogue and PPOS groups for baby gender and delivery technique, no statistically significant differences were found.

There was no statistically significant difference in birth weight between the two groups, according to the current analysis (p=0.928). Overall, the GnRH Analogue and PPOS groups had comparable rates of infants born with low birthweight (2500 g) and high birthweight (4000 g). While the p-values were not statistically significant, the odds ratios were rather near to 1.

Our findings do not differ significantly from those of[16] in that neither group had a significantly different birth weight. The rates of babies born with low birthweight (2500 g) and high birthweight (4000 g)

were equally distributed across the GnRH Analogue and PPOS groups**.**

Our study has its strength. Firstly, this trial is a relatively large small sample based on the population with a positive hCG test putting in consideration duration of only one year. Secondly, this trial is considered the 1st of its type in Upper Egypt giving us an overview about the answer of our research in comparison with national and international results. The total of pregnancy outcomes during the gestation provided us with a more complete picture about the topic. There're several weaknesses of the data set which cannot be neglected. Firstly, as any retrospective study unmeasured confounders is one of weakness of data set. Although maternal age, BMI, previous IVF attempts and oocyte yields were included and balanced in our study, it was not possible to estimate the effect of unmeasured confounders (such as education and socioeconomic status) on the ORs. Secondly, as pregnancy loss is conditional upon becoming pregnant, our analysis was restricted to women with serum hCG positive tests, so our generalization was only for the conceived population. Thirdly, possible adverse effects of progestins on the growing follicles or early-stage embryos may be exist and should be further explored before the stage of embryo transfer.

We found in this study that the pregnancy loss and the birthweights of neonates from PPOS were similar to those from GnRH analogue regimens. We hope that our research in pregnancy loss and neonatal birhweights particularly is a unique experience we are sharing with the international investigation about the safety and long term safety of PPOS protocols. Many researches were done comparing PPOS protocols and GnRH analogues as regard incidence of premature LH surge, number of oocytes obtained per cycle, oocyte quality, implantation rates and rate of OOHS, but more research is required of multicenter studies to examine the safety of PPOS protocol and the subsequent neonates.

From these results of this study -being a cheap oral available alternative- PPOS protocol can be used safely by ART specialists in IVF. Being a cheap protocol then, it minimize the cost of IVF required in COS. Being available in oral form so it can be used with those who have problems with parenteral protocols.

GnRH analogue recently have the problem of availability in Egypt unlike the available forms of progestins in the Egyptian market.

The unfavorable influence on the ability of the endometrium to receive a fresh embryo is caused by the exposure to progestin during the follicular period. Therefore, PPOS might serve as a viable alternative procedure for preserving oocytes, doing preimplantation genetic testing (PGT), and performing in vitro fertilization (IVF) for women who are at risk of developing ovarian hyperstimulation syndrome (OHSS).

Our recommendations are: Future research should employ meticulously prepared randomized controlled trials or extensive comparative observational studies. Ensure the inclusion of a representative sample of patients who share similar characteristics such as age, gender, and disease severity. Future studies should ensure a sufficiently high sample size to draw relevant results and account for confounding factors. In order to precisely evaluate long-term results, research should incorporate an extended duration of follow-up. We suggest that future research should incorporate multicenter studies to authenticate our findings.

Conclusions

The occurrence of pregnancy loss during the whole gestation period and the birthweights of neonates in FET cycles employing embryos from PPOS were similar to those from GnRH analogue regimens. This provided us with a comprehensive understanding of the safety of PPOS. Furthermore, this evidence suggests that the administration of external progestins during ovarian stimulation does not have a negative

impact on the quality of oocytes and the subsequent ability of embryos to develop successfully in IVF/ICSI cycles. Additional inquiries should prioritize the examination of the prolonged safety of offspring resulting from the PPOS technique.

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Author's contributions

AA: Planning, execution, analysis, interpretation & revision of this manuscript. MI: Collected the data and, responsible for interpretation of laboratory data of patients. MH: planning, execution, Final revision of manuscript. SR: planning, execution, analysis, interpretation & revision of this manuscript. All authors have read and approved the manuscript.

Conflict of interest

The authors declare that they have no known competing financial interests

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