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Research Article

# Progesterone Primed Protocol Versus Antagonist Protocol in Polycystic Ovarian Syndrome in Freeze-All Cycles

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## Abstract:

**Background:** Women with polycystic ovary syndrome (PCOS) undergoing in vitro fertilization protocols are typically characterized by an increased number of oocytes retrieved. The oocytes are often of poor quality, leading to lower pregnancy rates, and higher miscarriage rates. Progestin-primed ovarian stimulation regimen was established for assisted reproduction. However, its feasibility and outcomes in PCOS patients need further evaluation. This work aims to evaluate the progesterone-primed protocol versus antagonist protocol in polycystic ovarian syndrome in a freeze-all cycle.

**Methods:** A randomized controlled trial was conducted on women with polycystic ovarian syndrome to evaluate the progesterone primed protocol versus antagonist protocol in polycystic ovarian syndrome in freeze-all cycles, at the Department of Obstetrics and Gynaecology (outpatient infertility clinic), Menoufia University Hospital, during the period time of the study.

**Results:** Chemical pregnancy rate was found in 122 (69.7%) of group A and in 145 (82.9%) of group B. Moreover, a clinical pregnancy rate was found in 112 (64.0%) of group A and 145 (82.9%) of group B. As well as early miscarriage was found in 20 (11.4%) of group A and in 50 (28.6%) of group B.

**Conclusion:** The progesterone protocol is comparable with the GnRH-ant protocol regarding oocyte/embryo yields and the probability of clinical pregnancy in PCOS patients, but the two regimens were distinct in the regulation of pituitary LH secretion. Also, Pituitary downregulation with progesterone as PPOS results in more oocytes retrieved and blastocysts to a GnRH antagonist protocol.

**Keywords:** antagonist protocol; polycystic ovarian syndrome; In vitro fertilization; progesterone primed

## Introduction

Polycystic ovarian syndrome (PCOS) is a common endocrine condition. Approximately 6.3–21.4% of women of reproductive age are afflicted by this condition [1]. In vitro fertilization (IVF) is a significant treatment for women with polycystic ovary syndrome (PCOS) [2]. Despite the increased quantity of oocytes in PCOS patients, low fertility rates, subpar oocyte quality, and elevated abortion rates remain significant concerns. Consequently, novel protocols are required to enhance therapeutic outcomes [3]. Currently, we are witnessing the use of 'freeze-all' procedures that preserve all oocytes or embryos, allowing for unrestricted ovarian stimulation, including the potential negative impacts of hormones on endometrial receptivity [4].

In recent years, gonadotropin-releasing hormone (GnRH) antagonist procedures have been increasingly utilized across diverse patient populations, including those with poor, normal, or elevated ovarian responses [5; 6]. The GnRH antagonist competitively binds to the GnRH receptor in the pituitary gland but fails to induce the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [7]. GnRH antagonist treatments are categorized into two categories based on the timing of initiation. (i) fixed protocol, in which the GnRH antagonist commences at a predetermined period, often between days 5 and 6 of ovarian stimulation, and (ii) flexible protocol, in which the antagonist is provided daily after the leading follicles attain a diameter of 14 mm [8].

Recent research has concentrated on substituting GnRH analogs with progestins for the regulation of the LH surge, owing to the negative characteristics associated with GnRH analogs [9]. Progestin was considered a potential alternative for inhibiting premature LH surge during controlled ovarian stimulation [10]. Endogenous progesterone may impede the elevation of LH in the absence of a spontaneous LH surge during controlled ovarian stimulation in the luteal phase, according to certain studies [11]. Progesterone diminishes the pulsatility of GnRH from the hypothalamus, hence decreasing the release of LH linked to elevated estradiol levels [12].

In 2015, Dr. Yanping Kuang from China proposed the use of protest-primed ovarian stimulation (PPOS), an innovative ovarian stimulation protocol that combines progestin with exogenous gonadotrophins and regulates ovulation with a GnRH agonist, employing 'freeze-all' techniques. Rather than an elevation of progesterone as observed in conventional ovarian stimulation methods [13]. Progestin is employed as a substitute for the GnRH analogue in this innovative PPOS protocol to eliminate early LH during the follicular phase [14; 15]. Furthermore, progestin is administered orally and is readily accessible [16]. This innovative ovarian stimulation regimen has demonstrated effective prevention of a premature LH surge in cycles preceding embryo cryopreservation and does not impact on oocyte quality. The choice of appropriate progestin is crucial for the efficacy of the PPOS procedure [17]. This study is to assess the efficacy of the progesterone-primed treatment compared to the antagonist regimen in polycystic ovarian syndrome during freeze-all cycles.

## Patients and Methods

### *Study design and patient grouping*

A randomized controlled trial involved 350 women diagnosed with polycystic ovarian syndrome at the Department of Obstetrics and Gynecology (outpatient infertility clinic), Menoufia University Hospital, conducted from January 2023 to July 2025. A total of 350 women were categorized into two groups: Group A comprised 175 women undergoing the progesterone-primed treatment, whereas Group B consisted of 175 women undergoing the antagonist protocol. Women with PCOS were diagnosed according to the Rotterdam criteria (2003), which encompass polycystic ovaries, oligo-anovulation, and biochemical or clinical indicators of hyperandrogenism [18].

### *Ethical consideration*

All procedures were conducted in compliance with the ethical norms established by the institutional committee. All procedures were conducted in accordance with the 1964 Declaration of Helsinki and its subsequent amendments, or equivalent ethical standards, as well as the ethical mandates of the institutional and/or national research committee. The study obtained clearance from the Ethical Committee of the Faculty of Medicine, Menoufia University (IRB approval number: 5/2-2330OBSGN3-1). The objectives and procedures of the study were elucidated to the participants, and written informed consent was acquired from all individuals following an explanation of the study's nature and scope.

### *Patients' criteria*

This study recruited women aged 18 to 40 years with polycystic ovarian syndrome. We excluded women having a history of intrauterine abnormalities (submucosal fibroma, uterine polyp, and intrauterine adhesions), severe endometriosis, systemic illnesses, and those whose husbands had azoospermia.

### *The study protocol*

All individuals were administered with 150 subcutaneous doses of Cinnal-f starting on the second day of the cycle. Women in the progesterone-primed (PPOS) group received a 20 mg oral dose of Dydrogesterone starting on the second day of the cycle and continuing until the triggering day. Vaginal sonography was performed on all patients starting from the sixth day of their menstrual cycle. In the antagonist group, when the dominant follicles attained a size of 12–13 mm, 0.25 mg of Cetrotide was administered subcutaneously daily until the day of triggering. Serum LH, E2, and P were assessed when dominating follicles attained a size of 17 mm. The final triggering was executed via subcutaneous injection of Decapeptyl 0.2 mg and intramuscular injection of human chorionic gonadotropin (HCG) 1000 IU in both groups.

### *Oocyte Retrieval, Embryo Culture and Frozen-thawed Embryo Transfer*

Oocyte retrieval was performed 36 hours later under anesthesia and ultrasound supervision. Oocyte insemination and embryo culture were conducted using established protocols. The assessment of embryo quality encompassed the quantity and regularity of blastomeres as well as the extent of fragmentation. Embryo morphology was evaluated by The Istanbul Consensus Workshop (2011). OHSS was delineated by an established classification approach [19]. All high-quality embryos (grades A and B) were cryopreserved via vitrification on the third day post-oocyte retrieval. The embryos of inferior quality were subjected to prolonged cultivation until reaching the blastocyst stage. At this stage, only blastocysts with superior morphology (grade exceeding 322) were cryopreserved. Embryos that were frozen and subsequently thawed, exhibiting over 50% intact blastomeres, were deemed to have successfully survived the freezing process. Only viable embryos were transplanted. All embryos were cryopreserved at the cleavage stage, and the frozen embryo transfer was conducted two months later. The preparation of the endometrium for frozen-thawed embryo transfer (FET) cycles was conducted as previously outlined [20]. Patients administered progesterone supplementation until the tenth week of gestation.

### *Outcomes of the study*

The outcomes of the study in frozen cycles included early miscarriage, chemical pregnancy rate, and clinical pregnancy rate.

### *Statistical analysis*

All data were aggregated and analyzed utilizing SPSS version 25 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as means (± standard deviation (SD), whereas categorical variables are represented through relative frequency distributions and percentages. Categorical data were examined via the Chi-square test (Fisher or Monte Carlo), whereas descriptive variables were assessed by the Mann-Whitney U test, Student's T-test, regression analysis, and Spearman correlation. Statistical significance was determined at $p < 0.05$.

## Results

Figure 1 illustrates a flowchart of the research population. Among the 369 women diagnosed with polycystic ovarian syndrome at Menoufia University Hospital. Nineteen patients were eliminated from the study: eight women rejected consent, and eleven women did not satisfy the inclusion criteria. Three hundred fifty women expressed willingness to participate and were allocated into two groups: Group A (progesterone), consisting of 175 participants, and Group B (antagonist), also comprising 175 participants (Figure 1).

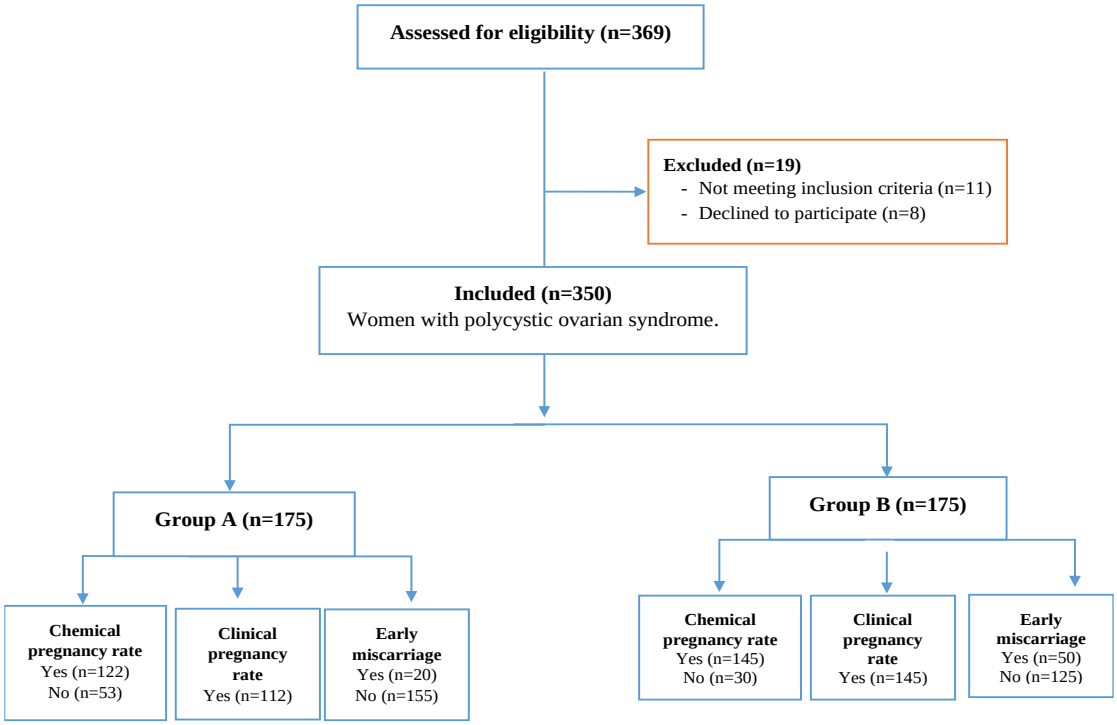



**Figure 1:** Flowchart of women with polycystic ovarian syndrome.

There was no significant difference among the studied groups regarding age (P=0.052). While BMI and duration of infertility were significantly higher among group A (29.80± 2.92, 3.93±1.32) than group B (27.74± 3.72, 3.48±1.52) respectively (P<0.001). Also, there was significant difference among the studied groups regarding type and cause of infertility (P<0.001), 1ry type infertility was found in 97 (55.4%) of group A and in 154 (88.0%) of group B, while 2ry type infertility was found in 78 (44.6%) of group A and in 21 (12.0%) of group B. PCOS alone was found in 69 (39.4%) of group A and in 129 (73.7%) of group B, while PCOS combined was found in 106 (60.6%) of group A and in 46 (26.3%) of group B, (Table 1).

| Variable | Group A (n= 175) | | Group B (n=175) | | *t* | *P value* |
|---|---|---|---|---|---|---|
| | N | % | N | % | | |
| **Age (years)**<br>Mean ± SD.<br>Median (range) | 30.53±2.94<br>31.00 (23.00-36.00) | | 30.09±2.13<br>30.00 (25.00-35.00) | | 1.948 | 0.052 |
| **BMI (Kg/m$^2$)**<br>Mean ± SD.<br>Median (range) | 29.80± 2.92<br>30.00 (22.00-34.00) | | 27.74± 3.72<br>28.00 (20.00-35.00) | | 5.712 | **<0.001*** |
| **Duration of infertility (years)**<br>Mean ± SD.<br>Median (range) | 3.93±1.32<br>4.00 (2.00-7.00) | | 3.48±1.52<br>3.00 (2.00-8.00) | | U=11559.000 | **<0.001*** |
| **Type of infertility**<br>1ry<br>2ry | 97<br>78 | 55.4<br>44.6 | 154<br>21 | 88.0<br>12.0 | $X^2$ =45.762 | **<0.001*** |
| **Cause of infertility**<br>PCOS alone<br>PCOS combined | 69<br>106 | 39.4<br>60.6 | 129<br>46 | 73.7<br>26.3 | $X^2$ =41.866 | **<0.001*** |

**Table 1:** Basic characteristics of the participants in two groups.

Progesterone (Group A), Antagonist (Group B), (Polycystic ovary syndrome (PCOS), Body mass index (BMI), Independent t test (t), Mann Whitney u test (U), Chi square test (X2), *Significant.

Additionally, number of oocytes, number of fertilized oocytes 1 and number of blastocysts were significantly higher among group A (20.01± 3.18, 15.39± 2.96, 12.99± 8.78) than group B (16.89±2.69, 12.46±2.73, 12.46±2.73) respectively (P<0.001). While number of fertilized oocytes 2 and final endometrium thickness before start of progesterone were significantly lower among group A (1.57± 0.50, 10.19±0.91) than group B (1.98±0.15, 10.72±0.92) respectively (P<0.001). In our study, A notable disparity existed among the examined groups for chemical pregnancy rate, clinical pregnancy rate, and early miscarriage (P<0.001). The chemical pregnancy rate was observed in 122 (69.7%) of group A and in 145 (82.9%) of group B. Furthermore, the clinical pregnancy rate was observed in 112 (64.0%) of

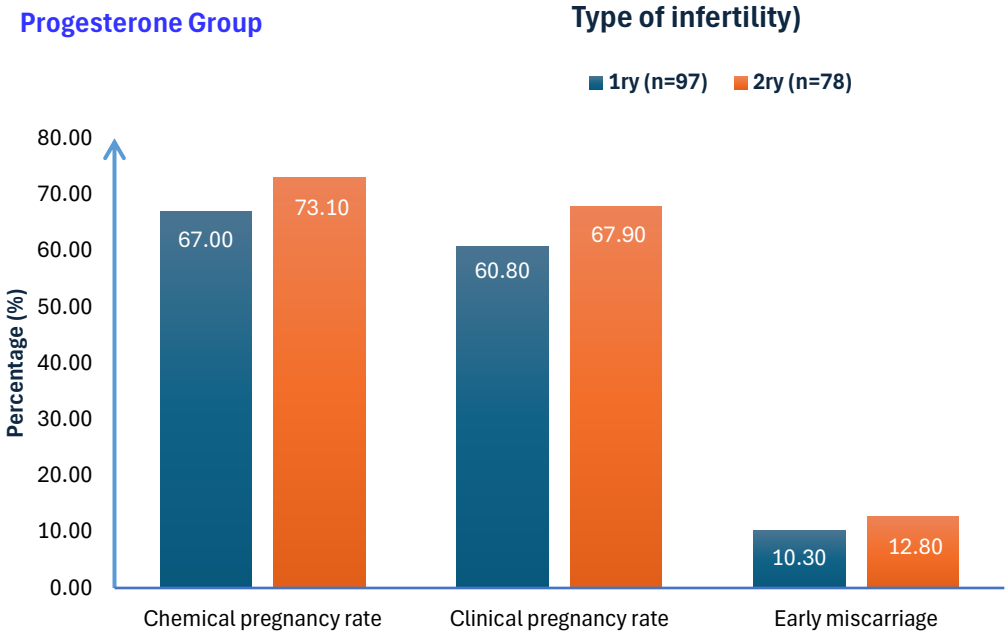
group A and in 145 (82.9%) of group B. Early miscarriage occurred in 20 (11.4%) of group A and in 50 (28.6%) of group B, (Table 2).

| Variable | Group A (n= 175) | Group B (n=175) | *U* | *P value* |
|---|---|---|---|---|
| **Number of oocytes**<br>Mean ± SD.<br>Median (range) | <br>20.01± 3.18<br>20.00 (10.00-28.00) | <br>16.89±2.69<br>17.00 (12.00-24.00) | 6912.000 | **<0.001*** |
| **Number of fertilized oocyte1**<br>Mean ± SD.<br>Median (range) | <br>15.39± 2.96<br>16.00 (8.00-24.00) | <br>12.46±2.73<br>12.00 (8.00-19.00) | 7287.000 | **<0.001*** |
| **Number of fertilized oocyte2**<br>Mean ± SD.<br>Median (range) | <br>1.57± 0.50<br>2.00 (1.00-2.00) | <br>1.98±0.15<br>2.00 (1.00-2.00) | 9100.000 | **<0.001*** |
| **Number of blastocysts**<br>Mean ± SD.<br>Median (range) | <br>12.99± 8.78<br>12.00 (5.00-89.00) | <br>12.46±2.738.00 (4.00-13.00) | 2986.500 | **<0.001*** |
| **Final endometrium thickness before start of progesterone**<br>Mean ± SD.<br>Median (range) | <br>10.19±0.91<br>10.00 (0.00-12.00) | <br>10.72±0.92<br>10.50 (9.50-12.00) | 11315.000 | **<0.001*** |
| **Outcomes in frozen cycles** | | | $X^2$ | *P value* |
| Chemical pregnancy rate | 122 (69.7%) | 145 (82.9%) | 8.355 | **<0.001*** |
| Clinical pregnancy rate | 112 (64%) | 145 (82.9%) | 15.947 | **<0.001*** |
| Early miscarriage | 20 (11.4%) | 50 (28.6%) | 16.071 | **<0.001*** |

**Table 2:** Fertilized oocytes, blastocytes and endometrium thickness before start of progesterone and Outcomes in frozen cycles.

Progesterone (Group A), Antagonist (Group B), Mann Whitney u test (U), Chi square test (X2), *Significant.

Among group A and B, there was no significant relation among types of infertility regarding chemical pregnancy rate, clinical pregnancy rate and early miscarriage (P>0.05), (Figure 2). Among group A and B, there was no significant relation among causes of infertility regarding chemical pregnancy rate, clinical pregnancy rate and early miscarriage (P>0.05), (Figure 3).



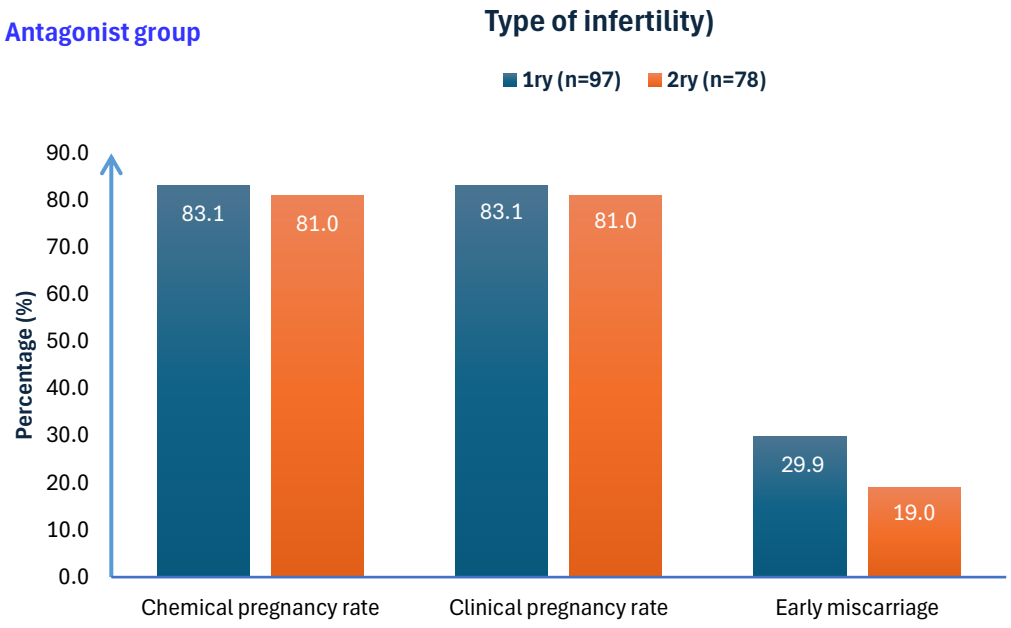
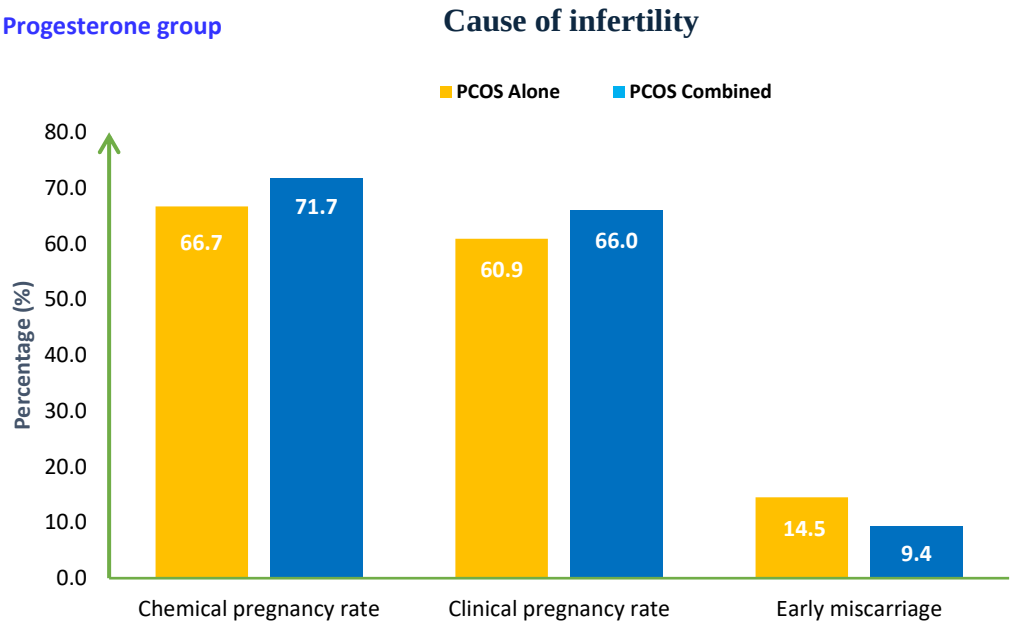



**Figure 2:** Outcomes in frozen cycles in relation to type of infertility among the studied groups.



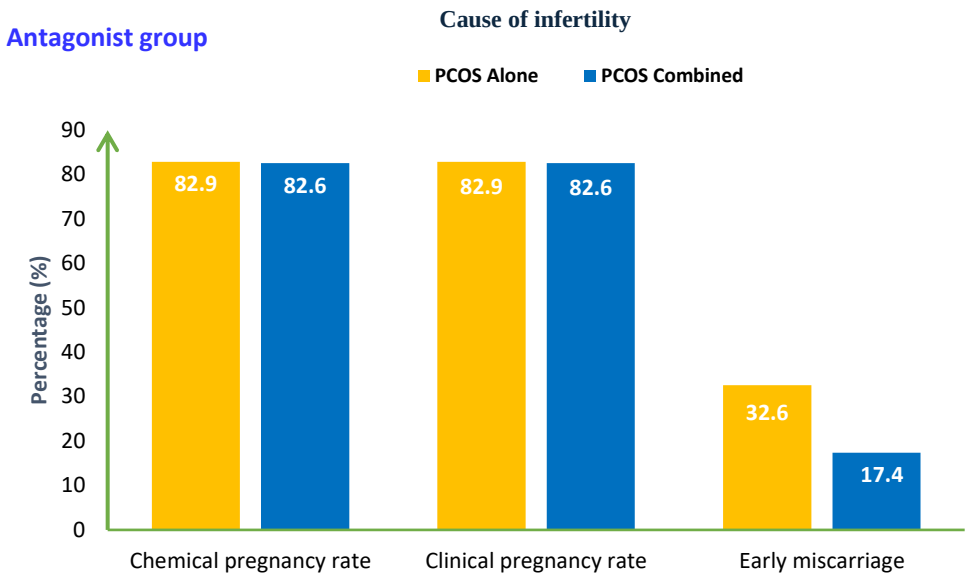



**Figure 3:** Outcomes in frozen cycles in relation to cause of infertility among the studied groups.

Regression analysis indicated that BMI, duration of infertility and final endometrium thickness before start of progesterone were the most factors affected chemical pregnancy rate (P<0.05). While other parameters didn't show any significant affection on chemical pregnancy rate (P>0.05). Regression analysis indicated that BMI, duration of infertility, number of blastocysts and final endometrium thickness before start of progesterone were the most factors affected clinical pregnancy rate (P<0.05). While other parameters didn't show any significant affection on clinical pregnancy rate (P>0.05). Regression analysis indicated that cause of infertility and number of blastocysts were the most factors affected by early miscarriage rate (P<0.05). While other parameters didn't show any significant affection on early miscarriage rate (P>0.05), (Table 3).

| Chemical pregnancy rate | B | Std. Error | Wald | Sig. | Exp(B) | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Age (years) | -0.038 | 0.056 | 0.461 | 0.497 | 0.963 | 0.86 | 1.07 |
| BMI (Kg/m$^2$) | -0.099 | 0.044 | 5.181 | **0.023*** | 0.906 | 0.83 | 0.99 |
| Duration of infertility (years) | 0.212 | 0.110 | 3.727 | **0.048*** | 1.236 | 1.00 | 1.53 |
| Type of infertility | 0.092 | 0.300 | 0.095 | 0.759 | 1.097 | 0.61 | 1.98 |
| Cause of infertility | -0.053 | 0.275 | 0.037 | 0.847 | 0.948 | 0.55 | 1.63 |
| Number of oocytes | 0.027 | 0.049 | 0.304 | 0.581 | 1.028 | 0.93 | 1.13 |
| Number of fertilized oocyte1 | -0.097 | 0.051 | 3.707 | 0.054 | 0.907 | 0.82 | 1.00 |
| Number of blastocysts | 0.004 | 0.022 | 0.028 | 0.866 | 1.004 | 0.96 | 1.05 |
| Number of fertilized oocyte2 | -0.031 | 0.335 | 0.009 | 0.925 | 0.969 | 0.50 | 1.87 |
| Final endometrium thickness before start of progesterone | 0.352 | 0.160 | 4.850 | **0.028*** | 1.421 | 1.04 | 1.94 |
| **Clinical pregnancy rate** | | | | | | | |
| Age (years) | -0.092 | 0.056 | 2.726 | 0.099 | 0.912 | 0.82 | 1.02 |
| BMI (Kg/m$^2$) | -0.087 | 0.043 | 4.133 | **0.042*** | 0.917 | 0.84 | 1.00 |
| Duration of infertility (years) | 0.281 | 0.110 | 6.503 | **0.011*** | 1.325 | 1.07 | 1.65 |
| Type of infertility | 0.071 | 0.296 | 0.057 | 0.811 | 1.073 | 0.60 | 1.92 |
| Cause of infertility | 0.057 | 0.273 | 0.043 | 0.836 | 1.058 | 0.62 | 1.81 |
| Number of oocytes | 0.081 | 0.052 | 2.492 | 0.114 | 1.085 | 0.98 | 1.20 |
| Number of fertilized oocyte1 | -0.078 | 0.053 | 2.230 | 0.135 | 0.925 | 0.83 | 1.03 |
| Number of blastocysts | -0.106 | 0.052 | 4.094 | **0.043*** | 0.900 | 0.81 | 1.00 |
| Number of fertilized oocyte2 | 0.037 | 0.331 | 0.013 | 0.911 | 1.038 | 0.54 | 1.99 |
| Final endometrium thickness before start of progesterone | 0.313 | 0.155 | 4.098 | **0.043*** | 1.368 | 1.01 | 1.85 |
| **Early miscarriage** | | | | | | | |
| Age (years) | -0.012 | 0.065 | 0.036 | 0.850 | 0.988 | 0.87 | 1.12 |
| BMI (Kg/m$^2$) | -0.007 | 0.044 | 0.028 | 0.868 | 0.993 | 0.91 | 1.08 |
| Duration of infertility (years) | 0.249 | 0.106 | 5.533 | 0.019 | 1.283 | 1.04 | 1.58 |
| Type of infertility | -0.045 | 0.363 | 0.016 | 0.900 | 0.956 | 0.47 | 1.95 |
| Cause of infertility | -0.974 | 0.353 | 7.603 | **0.006*** | 0.378 | 0.19 | 0.75 |
| Number of oocytes | 0.061 | 0.057 | 1.129 | 0.288 | 1.063 | 0.95 | 1.19 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Number of fertilized oocyte1 | -0.022 | 0.055 | 0.152 | 0.696 | 0.979 | 0.88 | 1.09 |
| Number of blastocysts | -0.142 | 0.069 | 4.250 | **0.039*** | 0.868 | 0.76 | 0.99 |
| Number of fertilized oocyte2 | 0.186 | 0.448 | 0.173 | 0.678 | 1.205 | 0.50 | 2.90 |
| Final endometrium thickness before start of progesterone | 0.189 | 0.179 | 1.115 | 0.291 | 1.208 | 0.85 | 1.72 |

**Table 3:** Regression analysis for the parameters affecting pregnancy rate (chemical, clinical) and Early miscarriage.

Body mass index (BMI), Confidence Interval (CI), *Significant.

In group A, no significant correlation was observed between chemical pregnancy rate, clinical pregnancy, and early miscarriage with age, BMI, duration of infertility, type of infertility, cause of infertility, number of oocytes, number of fertilized oocytes 1, number of blastocysts, number of fertilized oocytes 2, and final endometrial thickness before the initiation of progesterone in the examined cases (P>0.05). In group B, no significant correlation was observed between age, duration of infertility, type of infertility, cause of infertility, number of oocytes, number of fertilized oocytes, number of blastocysts, and final endometrial thickness before the initiation of progesterone, with the chemical and clinical pregnancy rates (P>0.05). A substantial positive link existed between the chemical pregnancy rate, BMI, and the number of fertilized oocytes (P<0.05). In group B, no significant correlation was observed between the early miscarriage rate and age, BMI, type of infertility, cause of infertility, number of oocytes, number of fertilized oocytes 1, number of fertilized oocytes 2, and final endometrial thickness before the initiation of progesterone in the examined cases (P>0.05). A substantial negative connection existed between the rate of early miscarriage and the length of infertility (P<0.001). Additionally, a strong positive connection was seen between the early miscarriage rate and the quantity of blastocysts (P=0.001), (Table 4).

| Correlation test | | Among group A | | | Among group B | | |
|---|---|---|---|---|---|---|---|
| | | Chemical pregnancy rate | Clinical pregnancy rate | Early miscarriage | Chemical pregnancy rate | Clinical pregnancy rate | Early miscarriage |
| Age (years) | $r^s$ | 0.005 | 0.075 | 0.136 | -0.031 | -0.031 | -0.117 |
| | *P value* | 0.943 | 0.322 | 0.072 | 0.684 | 0.684 | 0.122 |
| BMI ($Kg/m^2$) | $r^s$ | -0.118 | -0.132 | -0.020 | 0.270 | 0.270 | -0.046 |
| | *P value* | 0.121 | 0.082 | 0.796 | <0.001* | <0.001* | 0.547 |
| Duration of infertility/ years | $r^s$ | -0.103 | -0.115 | 0.114 | -0.041 | -0.041 | -0.317 |
| | *P value* | 0.174 | 0.129 | 0.132 | 0.590 | 0.590 | <0.001* |
| Type of infertility | $r^s$ | -0.066 | -0.074 | -0.039 | 0.019 | 0.019 | 0.078 |
| | *P value* | 0.388 | 0.332 | 0.606 | 0.806 | 0.806 | 0.306 |
| Cause of infertility | $r^s$ | -0.054 | -0.053 | 0.078 | 0.004 | 0.004 | 0.148 |
| | *P value* | 0.482 | 0.489 | 0.307 | 0.959 | 0.959 | 0.051 |
| Number of oocytes | $r^s$ | -0.106 | -0.140 | -0.141 | 0.067 | 0.067 | 0.023 |
| | *P value* | 0.163 | 0.065 | 0.063 | 0.381 | 0.381 | 0.770 |
| Number of fertilized oocytes 1 | $r^s$ | -0.073 | -0.084 | -0.015 | 0.198 | 0.198 | 0.022 |
| | *P value* | 0.335 | 0.270 | 0.845 | 0.009* | 0.009* | 0.777 |
| Number of blastocysts | $r^s$ | -0.050 | 0.008 | -0.068 | 0.102 | 0.102 | 0.255 |
| | *P value* | 0.515 | 0.914 | 0.374 | 0.179 | 0.179 | 0.001* |
| Number of fertilized oocytes 2 | $r^s$ | 0.118 | 0.120 | 0.016 | -0.336 | -0.336 | -0.097 |
| | *P value* | 0.118 | 0.113 | 0.838 | <0.001* | <0.001* | 0.203 |
| Final endometrium thickness before start of progesterone | $r^s$ | -0.103 | -0.058 | -0.064 | -0.103 | -0.103 | -0.052 |
| | *P value* | 0.175 | 0.444 | 0.402 | 0.176 | 0.176 | 0.497 |

**Table 4:** Correlation coefficient between pregnancy and early miscarriage rates with the studied variables among the studied groups.

Progesterone (Group A), Antagonist (Group B), Body mass index (BMI), *Significant.

## Discussion

Polycystic ovarian syndrome (PCOS) is a prominent condition and a frequent contributor to infertility, affecting over 80% of women with anovulatory infertility [21, 22]. Individuals with PCOS exhibit an elevated risk for ovarian hyperstimulation syndrome (OHSS), necessitating meticulous risk control techniques. Patients must be appreciated of the possible adverse effects of ovulation induction medications, the risks associated with IVF on the fetus, and the likelihood of multiple gestations [23-25]. The protocol of the Progestin-primed ovarian stimulation (PPOS) is an innovative ovarian stimulation regimen utilizing a freeze-all method, employing progestin as a substitute for a GnRH analog to inhibit premature LH surges during the follicular phase [13, 26]. Since 2016, it has been extensively utilized in patients undergoing IVF, demonstrating favorable IVF outcomes [27, 28]. Nevertheless, no studies compared the efficacy of the PPOS protocol and the GnRH-antagonist regimen in patients with PCOS in Egypt. This study intends to compare the progesterone-primed regimen with the antagonist protocol in polycystic ovarian syndrome during freeze-all cycles.

In our investigation, the quantity of fertilized oocytes and blastocysts was markedly greater in group A compared to group B. The quantity of fertilized oocytes and the ultimate endometrial thickness before the initiation of progesterone were considerably lower in group A compared to group B. According to our research, Xiao et al. [29] showed that the number of oocytes retrieved in the PPOS protocol group markedly diminished in comparison to the GnRH antagonist protocol group. The PPOS regimen was linked to a reduced likelihood of mild-to-moderate ovarian hyperstimulation syndrome (OHSS). Despite the GnRH antagonist treatment yielding a greater number of oocytes, the viable embryo rate per retrieved oocyte was comparable to that of the PPOS technique. The PPOS regimen was linked to a reduced likelihood of mild-to-moderate ovarian hyperstimulation syndrome (OHSS). While the GnRH antagonist technique yielded a greater number of oocytes, the viable embryo rate per retrieved oocyte was comparable to that of the

PPOS protocol. The GnRH antagonist treatment group had a considerably larger quantity of cryopreserved embryos. The cryopreserved embryos in the PPOS protocol cohort were sufficient for 2 to 3 transfers (1 to 3 embryos per transfer). The cumulative pregnancy rate per patient was comparable in two further trials conducted by Fatemi et al. [30] and Bosch et al. [31]. Our findings align with Kuang et al. [27], who compared the PPOS procedure with the GnRH agonist short protocol, demonstrating that the rates of oocyte retrieval, mature oocytes, fertilization, and cleaved embryos were comparable between the two groups. The FET results demonstrated that embryos derived from the PPOS procedure exhibited comparable developmental potential to those from the GnRH agonist short protocol.

Our study revealed a notable increase in the number of retrieved oocytes in the dual stimulation group compared to the double follicular stimulation group (8 versus 6 oocytes). Glujovsky et al. [32] examined two randomized controlled trials, and one pilot study investigated dual stimulation in poor ovarian responders compared to a single wave of the usual antagonist strategy. The dual stimulation nearly increased the number of ripe oocytes. We observed a trend indicating an increase in mature oocytes retrieved from the dual stimulation protocol, although this difference was statistically insignificant (6 versus 4.5 oocytes). Additionally, there was a significantly higher number of retrieved oocytes following dual stimulation compared to conventional stimulation. It is imperative to emphasize that we have juxtaposed the dual stimulation technique with two waves of antagonist follicular stimulation. Their conclusion indicates that luteal stimulation in poor responders may be more efficacious than follicular stimulation, as will be discussed further. Iwami et al. [33] discovered no significant differences in stimulation duration, mature oocyte count, fertilization rate, or embryo quantity, aligning with our findings. Cui et al. [34] identified a statistically significant increase in the number of embryos in the progestin-primed treatment. Concerning pregnancy outcomes, both trials revealed no disparity in continued pregnancy or live birth rates.

Our work contradicts the findings of Cui et al. [34], who compared progestin-primed stimulation with the antagonist procedure. No significant variations were seen in the total days of stimulation, the total dosage of gonadotropins, or the number of mature oocytes between the two procedures. determined that progestin-primed dual stimulation is a legitimate alternative for patients with diminished ovarian reserve. Likewise, Begueria et al. [35] indicated that there were no differences in the quantity of mature oocytes, duration of stimulation, fertilization rate, or embryo quality between the two treatments. The number of oocytes, the count of fertilized oocytes, and the number of blastocysts were considerably more in the progesterone group compared to the antagonist group. The quantity of fertilized oocytes and the ultimate endometrial thickness before the initiation of progesterone were considerably lower in group A compared to group B. Zhu et al. [36] reported that the quantities of retrieved oocytes, MII oocytes, fertilized oocytes, cleaved embryos, and viable embryos in the progesterone protocol exceeded those in the GnRH-ant regimen, however, no statistical significance was seen. Furthermore, the rates of oocyte retrieval and fertilization were markedly elevated in the progesterone treatment. No instances of moderate or severe OHSS were observed in our investigation. In addition to the "freeze-all" technique, alternative preventative methods, such as vaginal birth, administration of the dopamine agonist cabergoline, and the utilization of GnRH agonist in place of human chorionic gonadotropin for triggering, contribute to the prevention of OHSS. The results validated that the progesterone protocol may serve as a viable alternative regimen for PCOS patients undergoing IVF/ICSI therapies with embryo cryopreservation. Eftekhar et al. (2) discovered that the maturity rate of oocytes in the PPOS group was significantly inferior to that in the antagonist group. Furthermore, the fertilization rate decreased in the PPOS group. No notable variations were observed in the quantity of harvested oocytes or the rate of ongoing pregnancies. Nevertheless, a substantial dosage of HMG was administered in the PPOS group. Considering the specific risk of OHSS, two instances were documented in the short protocol group compared to none in the PPOS group. Furthermore, Jawed et al. [37] found that the oocyte maturity rate is a predictor of the fertilization rate; hence, a diminished oocyte maturity rate may correlate with a reduced oocyte fertilization rate.

Our investigation demonstrated a considerable disparity among the examined groups for chemical pregnancy rate, clinical pregnancy rate, and early miscarriage. According to our study, Eftekhar et al. (2) showed that the clinical pregnancy rate for FET in PPOS was lower, at 14.6% compared to 29.9%. The implantation rate was reduced in the PPOS group. There was a notable disparity among the examined groups for the rates of chemical pregnancy, clinical pregnancy, and early miscarriage. The chemical pregnancy rate was observed in 122 individuals from the progesterone group and in 145 individuals from the antagonist group. Furthermore, the clinical pregnancy rate was observed in 112 (64.0%) of group A and 145 (82.9%) of group B. Early miscarriage occurred in 20 (11.4%) of group A and 50 of group B. Furthermore, it was determined that there was no significant correlation between the causes of infertility and the rates of chemical pregnancy, clinical pregnancy, and early miscarriage among the progesterone and antagonist groups. Fatemi et al. (30) discovered that while the number of cryopreserved embryos was much greater in the GnRH antagonist treatment group, the cryopreserved embryos in the PPOS protocol group were sufficient for 2–3 transfers (1–3 embryos per transfer). The aggregate pregnancy rate per patient was comparable. In contrast, Kuang et al. (13) performed a primary randomized trial on PPOS. Medroxyprogesterone acetate was incorporated into gonadotropin-induced stimulation during the follicular phase, and this treatment was compared with the conventional short regimen. They established that pregnancy, implantation, and loss rates were not significantly different across the groups. These findings align with the conclusions of Iwami et al. [33], which indicated that the frequencies of continuing and clinical pregnancies were comparable in both groups. This may result from the limited sample size of our patients and varying situations.

## Conclusion

In conclusion, the progesterone protocol is comparable with the GnRH-ant protocol regarding oocyte/embryo yields and the probability of clinical pregnancy in PCOS patients, but the two regimens were distinct in the regulation of pituitary LH secretion. Also, Pituitary downregulation with progesterone as PPOS results in more oocytes retrieved and blastocysts to a GnRH antagonist protocol.

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