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Embryo Ploidy and Ovarian Response in Gonadotropin-Releasing Hormone Antagonist Versus Progestin-Primed Ovarian Stimulation Protocols with Recombinant Luteinizing Hormone: A Within-Patient Study

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ABSTRACT

OBJECTIVE: To compare embryo ploidy rates and ovarian response outcomes between gonadotropin-releasing hormone (GnRH) antagonist and progestin-primed ovarian stimulation (PPOS) cycles with recombinant luteinizing hormone (rLH) administered from stimulation onset.

STUDY DESIGN: This retrospective within-patient cohort study included 41 women undergoing in vitro fertilization (IVF) with preimplantation genetic testing for aneuploidy (PGT-A) at a single center. Each patient completed both GnRH antagonist and PPOS cycles with rLH supplementation initiated on stimulation day 1. Cycles using GnRH agonists, urinary LH, random-start approaches, or with major gonadotropin dose discrepancies were excluded. The primary outcome was euploidy rate per biopsied blastocyst. Secondary outcomes included gonadotropin consumption, numbers of retrieved and mature oocytes, fertilization, blastulation, and euploidy per metaphase II (MII) oocyte. Paired t-tests or Wilcoxon signed-rank tests were used as appropriate. Statistical significance was set at $p < 0.05$.

RESULTS: In total, 175 blastocysts were biopsied (86 antagonists; 89 PPOS). Euploidy rates per biopsied embryo were comparable (32.36% vs 33.72%). No significant differences were observed in oocyte yield, MII oocytes, fertilization, or blastulation rates. Gonadotropin consumption was significantly higher in antagonist cycles ($p = 0.013$), while hormonal profiles at trigger were comparable.

CONCLUSION: When rLH supplementation is standardized, PPOS and antagonist protocols yield comparable embryo ploidy and similar ovarian response in IVF-PGT-A cycles. PPOS remains an effective alternative, particularly in freeze-all strategies. Larger prospective studies are needed to clarify the benefit of rLH across stimulation protocols.

Keywords: Embryo euploidy; Luteinizing hormone; Ovulation stimulation; Preimplantation diagnosis; Progestin-primed ovarian stimulation

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Introduction

Controlled ovarian stimulation (COS) is a cornerstone of assisted reproductive technology (ART), aiming to increase both the number and quality of oocytes retrieved for in vitro fertilization (IVF). GnRH antagonist protocols are widely adopted due to their favorable safety profile, shorter stimulation period, and effectiveness in preventing premature luteinizing hormone (LH) surges (1).

More recently, progestin-primed ovarian stimulation

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(PPOS) has been introduced as an alternative approach, using oral progesterone from the beginning of stimulation to prevent premature LH surges. This protocol has been shown to yield similar numbers of oocytes and embryos compared to antagonist protocols and is especially attractive in freeze-all cycles (1,2).

Several publications have reported that supplementing ovulation stimulation protocols with recombinant LH (rLH) may improve ovarian response and embryo quality (3-5). Embryo ploidy status is a crucial marker of embryo quality, strongly associated with implantation potential and live birth following preimplantation genetic testing for aneuploidy (PGT-A) (6-8). Ploidy is influenced by female age, male age, ovarian reserve, body mass index (BMI), gonadotropin dosing, and lifestyle factors such as smoking, sleep, stress, and exposure to environmental toxins (9-12). Many of these factors are uncontrollable and can disrupt meiotic spindle integrity, contributing to aneuploidy. Although rLH supplementation is proposed to enhance follicular development and oocyte competence, particularly in women with advanced maternal age or diminished ovarian reserve, its potential influence on embryo ploidy remains insufficiently clarified.

Given these considerations, this study aims to investigate embryo ploidy and ovarian response outcomes in PPOS and antagonist cycles supplemented with rLH in women undergoing ovarian stimulation for PGT-A. The use of LH supplementation has become an increasingly common tendency in contemporary clinical practice, particularly in patients with suboptimal response profiles. This retrospective within-patient study design was chosen to minimize biological variability and to provide a more reliable assessment of the differences attributable to stimulation protocols.

Material and Method

Study Design and Participants: This retrospective cohort study was conducted at a single tertiary IVF center between January 2018 and January 2024. The Bahceci Health Group Ethics Committee approved the study protocol, and all data were retrieved from the center's electronic medical record system (Approval date: 20.01.2025; application number: 161) and collected in accordance with the Declaration of Helsinki. Written informed consent for IVF treatment, PGT-A procedures, and the use of anonymized clinical data for research purposes was obtained from all participants.

The study population consisted of women aged 18-47 years undergoing IVF with PGT-A due to advanced maternal age, recurrent pregnancy loss, or recurrent implantation failure. During the study period, we screened 19,237 IVF cycles. Of these, 5,689 cycles included PGT-A and were assessed for eligibility. Patients were considered eligible for the within-patient analysis if they had undergone both a GnRH antagonist cycle and a PPOS cycle, with rLH supplementation initiated from stimulation day 1 in both cycles, and with an interval of at least 1 month but less than 24 months between the two treatments.

Cycles using GnRH agonists, random-start stimulation, or PGT for monogenic disorders (PGT-M) or structural rearrangements (PGT-SR), severe male factor, as well as those employing urinary LH, or those with missing embryological or genetic data were excluded. A starting FSH dose difference of 75 IU or more, a different FSH/LH ratio, or LH initiation other than day 1 were also accepted as exclusion criteria. After applying these criteria, 41 women were eligible. Of these, 20 participants underwent the antagonist protocol, and 21 underwent the PPOS protocol as the first treatment cycle.

Treatment Protocol: Stimulation was initiated in the early follicular phase using recombinant FSH (Gonal-F®, Merck Serono, Switzerland, or Puregon®, Organon, Germany) supplemented with recombinant LH (Luveris®, Merck Serono, Switzerland) or a combination of recombinant FSH and recombinant LH (Pergoveris®, Merck Serono, Switzerland). In all cycles, rLH was added since day 1. The choice of the preparation and starting dose was based on age, ovarian reserve parameters, and physician judgment. In the PPOS cycles, patients received either dydrogesterone (Duphaston®, Abbott, Turkey) 10 mg twice daily or medroxyprogesterone acetate (Tarlusal®, Deva, Turkey) 5 mg twice daily orally initiated on day 1. In antagonist cycles, cetrorelix acetate was administered either as Cetrotide® (Merck Serono) or Oxotide® (VEM, Turkey) once a follicle reached 12 mm. Antagonists were administered daily until the trigger day.

Final oocyte maturation was triggered using choriogonadotropin alfa (Ovitrelle®, Merck Serono, Italy) 250 mcg and/or triptorelin acetate (Gonapeptyl®, Ferring, Germany) 0.2 mg when the leading follicle reached ≥17 mm. Transvaginal oocyte retrieval was performed 35-36 hours after trigger administration.

Oocyte Insemination, Embryo Culture, and Biopsy: Following standard denudation procedures, ICSI was performed (13). Embryos were cultured to the blastocyst stage and assessed by the Gardner and Schoolcraft morphological grading system (14).

Assisted hatching was performed on day 3 using a laser to create a~20 μm opening in the zona pellucida. Trophectoderm biopsy was performed on day 5-6 using the pulling method in mHTF medium (Irvine Scientific, USA) with supplements. Between 5 and 8 trophectoderm cells were collected per embryo and transferred into PCR tubes.

Vitrification and PGT-A: Blastocysts were vitrified within two hours after biopsy using commercial kits (Irvine Scientific, Denmark) with the Cryotech open carrier system. PGT-A was performed using whole-genome amplification followed by next-generation sequencing (NGS) with the Ion ReproSeq PGS Kit and Ion S5 platform. Data were analyzed

with Ion Reporter software (hg19 reference). Embryos were classified as euploid if no chromosomal abnormality or low-level mosaicism (<50%; <30% for chromosomes 13, 18, and 21) was detected; otherwise, they were classified as aneuploid.

Statistical analysis

The primary outcome was euploidy rate per biopsied blastocyst, defined as the proportion of euploid embryos among biopsied blastocysts. Secondary outcomes included total gonadotropin consumption, estradiol and progesterone levels on trigger day, number of oocytes retrieved, euploidy rates per metaphase II (MII) oocyte, MII oocytes, 2PN embryos, maturation, fertilization, and blastulation rates, and mean number of euploid and aneuploid embryos.

Statistical analysis was performed using SPSS 27. Continuous variables were expressed as mean ± SD or median (min–max); categorical variables were reported as frequency (n, %). We used the Shapiro-Wilk test and box plots to assess normality. Paired t-tests were applied to normally distributed continuous variables, and Wilcoxon signed-rank tests to non-normally distributed variables. The marginal homogeneity test compared categorical distributions. Statistical significance was set at $p<0.05$.

Results

We initially screened 19,237 IVF cycles performed between January 2018 and January 2024. Among these, 5,689 PGT-A cycles were identified and further evaluated. After applying the inclusion and exclusion criteria for the within-patient paired comparison, 41 women who had undergone both a GnRH antagonist cycle and a PPOS cycle with rLH supplementation from stimulation day 1 (Supplementary Figure 1) were included in the study. The mean age of the participants was 38.37±5.67 years. In total, 175 blastocysts were biopsied, 86 in the antagonist group and 89 in the PPOS group. The mean age of the male partners was 41.61±6.86 years. Mean infertility duration was 5.76±3.75 months. The mean BMI was 24.18±4.1 kg/m². Most couples (80.5%) had primary infertility, while 12.2% of male partners had a diagnosed mild condition (Table I).

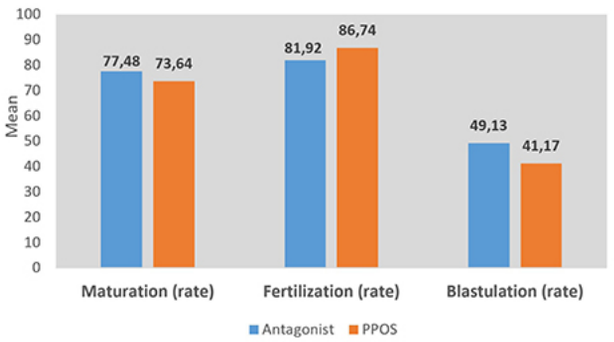

Figure 1: *Comparison of maturation, fertilization and blastulation rates in antagonist and PPOS cycles*

Table I: *Demographic characteristics of population (n=41)*

Female age (years)	Mean±SD	38.37±5.67
Male age (years)	Mean±SD	41.61±6.86
Infertility duration (month)	Mean±SD	5.76±3.75
BMI (kg/m²)	Mean±SD	24.18±4.1
Infertility type n (%)	Primary	33 (80.5)
	Secondary	8 (19.5)
Male Factor n (%)	Absent	36 (87.8)
	Present	5 (12.2)

SD: Standard deviation

Estradiol and progesterone levels on trigger day did not differ significantly between groups. However, gonadotropin consumption was significantly higher in antagonist cycles compared to PPOS cycles (2619.21±707.42 IU vs. 2325.30 ± 505.93 IU; p=0.013). The number of oocytes retrieved, MII oocytes, and 2PN embryos were similar between groups (9.66±5.48 vs 9.27±6.69, difference between means (DBM) -0.39±4.38, 95% CI -1.77, 0.99), p=0.412; 6.95±3.97 vs 6.78±4.88, DBM –0.17±3.54, 95% CI –1.29, 0.95) p=0.463; 5.88±3.27 vs 5.29±3.86, DBM –0.59±2.99, 95% CI -1.53, 0.36 p=0.188) (Table II).

Fertilization, maturation, and blastulation rates also showed no significant differences (Figure 1). The mean patient-specific euploidy rate per biopsied embryo was 32.36% in the antagonist group versus 33.72% in the PPOS group (DBM 1.36±50.01, 95% CI -14.42, 17.15; p=1.000).

Table II: *Comparison of ovarian stimulation cycle outcomes*

	Antagonist[a]	**PPOS[a]**	**Difference**	**95% CI[b]**	**p**
Oestradiol on trigger day (pg/mL)	1835.59 (1148.11)	1523.80 (805.82)	-311.79 (1093.09)	-656.81, 33.23	0.163[c]
Progesteron on trigger day (ng/mL)	0.69 (0.38)	1.03 (2.77)	0.34 (2.75)	-0.52, 1.21	0.422[c]
Progesteron on trigger day (ng/mL)	2619.21 (707.42)	2325.30 (505.93)	-293.90 (727.31)	-523.47, -64.34	**0.013**[d*]
Number of COCs†	9.66 (5.48)	9.27 (6.69)	-0.39 (4.38)	-1.77, 0.99	0.412[c]
Number of MII‡	6.95 (3.97)	6.78 (4.88)	-0.17 (3.54)	-1.29, 0.95	0.463[c]
Number of 2PN§	5.88 (3.27)	5.29 (3.86)	-0.59 (2.99)	-1.53, 0.36	0.188[c]

*a: Mean (SD), b: Confidence interval, c: Wilcoxon signed rank test, d: Paired samples-t test, *p<0,05, SD: Standard deviation, †: Cumulus oophorus complex; ‡;Metaphase II; §:Pronucleus*

Similarly, the mean patient-specific euploidy rate per MII did not differ significantly between antagonist and PPOS cycles (9.95% vs 11.39%, DBM 1.44±22.90, 95% CI -5.79, 8.67;

p=0.909) (Table III). The mean numbers of biopsied blastocysts and euploid embryos were comparable. The trigger-type distribution (hCG, agonist, or dual) did not differ significantly, with dual triggering being the most common across both protocols.

Discussion

This study demonstrated that embryo ploidy rates did not differ significantly between GnRH antagonist and PPOS cycles when rLH supplementation was routinely applied. Despite higher gonadotropin requirements in the antagonist group, both protocols resulted in comparable oocyte yield, fertilization, blastulation, and euploid embryo rates. These findings support the clinical equivalence of the two stimulation strategies in the context of PGT-A cycles, provided with LH activity.

These results align with previous retrospective reports showing no significant differences in ploidy outcomes between PPOS and antagonist protocols (15-17), and with the prospective age-matched case–control study by La Marca et al (18). Pai et al. reported lower euploidy rates per injected oocyte in women ≥38 years undergoing PPOS compared with antagonist cycles, while outcomes were similar in younger women (16). A recent randomized controlled trial including women aged 38-45 years found no significant differences in euploidy per patient between the two protocols (19). However, LH activity was not standardized among those studies. In our cohort, with a mean age of 38.37 years, ploidy outcomes were likewise comparable, consistent with these findings.

Heterogeneity of LH-Activity Across Studies: Interpretation of the published literature is complicated by variability in LH activity across stimulation regimens. Many studies did not specify the distribution of rFSH, hMG, rLH, or combinations in the groups where PPOS versus antagonist cycles were compared (16,19). In the absence of exogenous LH activity, some studies reported similar results (18,20). The inconsistent LH exposure limits direct comparison and may explain the variability observed across studies.

The deeper pituitary suppression observed with PPOS could theoretically reduce the availability of endogenous LH (21), making exogenous LH supplementation particularly relevant. Mechanistic studies support this concept, showing stronger suppression of endogenous LH under PPOS regimens compared with antagonist cycles (22,23). Under such conditions, adding rLH may help maintain appropriate androgen substrate levels and support granulosa cell function, but further causal investigation is warranted.

In our cohort, uniform rLH use may have mitigated protocol-related differences, although causality cannot be inferred. Although several reviews suggest LH supplementation may benefit older women or those with reduced ovarian reserve (3,24), it remains unclear whether specific stimulation protocols derive differential advantage from rLH.

Gonadotropin Consumption and Hormonal Profiles: In retrospective studies evaluating PPOS protocols incorporating medroxyprogesterone acetate (MPA), gonadotropin consumption did not differ significantly between PPOS and antagonist cycles (25,26). More recent evidence from a randomized controlled trial using dydrogesterone for PPOS reported slightly lower gonadotropin requirements compared with antagonist protocols (19). Another randomized trial directly comparing dydrogesterone versus MPA within PPOS regimens demonstrated higher gonadotropin consumption in the MPA group (27).

In our study, total gonadotropin consumption was significantly lower in PPOS cycles than in antagonist cycles. Although MPA was used in 61% of PPOS cycles, this did not translate into higher overall gonadotropin requirements in the PPOS group. Individualized starting doses and differences in stimulation dynamics may have contributed to the observed difference; however, the retrospective design precludes determination of the underlying mechanism.

Hormonal profiles at trigger were comparable between protocols in our study, in contrast to earlier studies using mi-

Table III: *Comparison of embryo outcomes between Antagonist and PPOS groups*

	Antagonist[a] n=86	**PPOS[a] n=89**	**Difference**	**95% CI[b]**	**p**
Biopsied blastocysts	2.10 (1.32)	2.17 (1.48)	0.07 (1.59)	-0.43, 0.57	0.814[c]
Euploid embryos	0.71 (0.93)	0.66 (0.79)	-0.05 (1.09)	-0.39, 0.30	0.879[c]
Aneuploid embryos	1.39 (1.14)	1.51 (1.36)	0.12 (1.27)	-0.28, 0.52	0.389[c]
Euploidy rate/per biopsied embryo	32.36 (38.27)	33.72 (40.73)	1.36 (50.01)	-14.42, 17.15	1.000[c]
Euploidy rate per MII†	9.95 (12.51)	11.39 (18.59)	1.44 (22.90)	-5.79, 8.67	0.909[c]

Euploidy rates were calculated separately for each cycle and are presented as the mean (SD) of patient-specific rates.
a: Mean (SD), b: Confidence Interval, c: Wilcoxon Signed Rank Test, SD: standard deviation, †: Metaphase-2

cronized progesterone, which reported higher estradiol and progesterone levels in PPOS cycles (20). The weaker suppressive potency of micronized progesterone compared with GnRH antagonists may partially explain these discrepancies (28).

Strengths of the Study: To our knowledge, this is the first study to compare euploidy outcomes between antagonist and PPOS protocols, specifically with standardized rLH supplementation. A major strength of this study is its within-patient design, which significantly reduces interindividual confounding. Factors such as environmental exposures known to affect meiotic spindle integrity and ploidy are inherently controlled (29,30). This design provides a more accurate comparison of stimulation protocols than traditional between-patient studies. Furthermore, the balanced distribution of women whose first cycle was PPOS or antagonist minimizes sequencing bias. Although determining the required sample size to detect small ploidy differences in within-patient studies is complex, these designs substantially increase statistical power.

Limitations: This study is limited by its retrospective design and variability in the interval between cycles, which may introduce unmeasured bias despite requiring a minimum one-month washout period. Although the within-patient design minimizes interindividual variability, causal inference regarding the effect of rLH supplementation cannot be established. Additionally, while rLH exposure was standardized, other subtle clinical decision-making factors may have influenced stimulation dynamics. An important limitation is that euploidy rate per biopsied blastocyst is conditional on embryos reaching the blastocyst stage and fulfilling biopsy criteria. Although fertilization and blastulation outcomes were evaluated separately in the present study, the primary endpoint does not inherently capture potential protocol-related differences occurring before biopsy eligibility. Therefore, comparable euploidy rates among biopsied blastocysts should be interpreted together with broader embryological outcomes, including fertilization, blastulation, and the number of biopsy-eligible blastocysts.

Furthermore, because inclusion required patients to undergo at least two stimulation cycles, the study population may represent a relatively poorer-prognosis subgroup. Patients who achieved an adequate number of euploid embryos after their first cycle may have been less likely to undergo a second stimulation cycle and, consequently, to be included in this within-patient analysis. Finally, the relatively small sample size limits statistical power, particularly for detecting modest between-protocol differences, and may restrict the generalizability of the findings.

In conclusion, these findings suggest that PPOS and antagonist protocols, with rLH supplementation, yield equivalent embryo ploidy and comparable ovarian response outcomes in women undergoing stimulation for PGT-A. PPOS remains a patient-friendly and efficient alternative, particularly in freeze-all cycles. Larger randomized controlled trials with standardized LH activity are needed to determine whether rLH supplementation confers differential benefits across specific patient subgroups or stimulation strategies.

Declarations

Ethics approval and consent to participate: Written informed consent for IVF treatment, PGT-A procedures, and the use of anonymized clinical data for research purposes was obtained from all participants. The Bahceci Health Group Ethics Committee approved the study (approval date: 20 January 2025; application no. 161). All procedures were performed in accordance with the Declaration of Helsinki.

Availability of data and materials: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare they have no competing interests.

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