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Research Article

Blastocysts Derived from Oocytes Retrieved in Cycles with Elevated Late-Follicular Progesterone Per Follicle Show Reduced Reproductive Potential; An Analysis Based on Progesterone Levels Per Individual Follicle

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Abstract

Introduction: Late-follicular progesterone elevation has been implicated in impaired reproductive outcomes, but its impact on embryo competence in freeze-all strategies remains unclear.

Aims: To investigate whether progesterone normalized by follicle number on the trigger day (progesterone-per-follicle, P/fol) is associated with clinical pregnancy after frozen–thawed embryo transfer (FET).

Methods: We performed a retrospective cohort study at a single high-volume reproductive center including ovarian stimulation cycles between January 2020 and December 2024 that generated at least one vitrified blastocyst and were managed with a freeze-all policy. Stimulation protocols included natural, minimal, mild, GnRH antagonist, and modified progestin-primed regimens. P/fol was calculated as serum progesterone (ng/mL) divided by the number of follicles ≥15 mm on the trigger day. Subsequent single or double blastocyst FETs were performed in natural/ovulatory or hormone-replacement cycles. The primary outcome was clinical pregnancy, defined as an intrauterine gestational sac. Multivariable logistic regression assessed the association between log-transformed P/fol and clinical pregnancy, adjusting for female and male age, anti-Müllerian hormone, body mass index, gravidity, and trigger-day follicle count.

Results: A total of 6,908 FET cycles were analyzed; 1,408 resulted in clinical pregnancy. Mean trigger-day progesterone and P/fol were 0.55 ng/mL and 0.19 ng/mL, respectively, and the mean number of vitrified blastocysts per cycle was 1.5 ± 1.6. Higher P/fol was independently associated with reduced odds of clinical pregnancy (adjusted odds ratio 0.61; 95% confidence interval 0.46–0.79; p<0.001).

Conclusions: Elevated late-follicular P/fol is associated with decreased reproductive potential of resultant blastocysts, even when using a freeze-all strategy with transfer into a newly prepared endometrium. Monitoring P/fol may help identify suboptimal cycles and guide optimization of ovarian stimulation and trigger timing.

Keywords: Blastocyst; Frozen Embryo Transfer; In Vitro Fertilization; Ovarian Stimulation; Progesterone

Introduction

Since the report by Poter et al. in 1984 [1] describing the gonadotropin-releasing hormone agonist (GnRH-a) long protocol, ovarian stimulation has become a standard practice in assisted reproductive technology (ART). In the 1990s, multiple studies reported that elevated serum progesterone (P) during the long protocol was associated with reduced pregnancy rates. [2-4] at that time-when fresh embryo transfer predominated-this decline was attributed to an asynchrony between progesterone-induced endometrial decidualization and the developmental pace of the embryo. [5]

In 2018, Racca and colleagues showed that elevated late-follicular P was associated with a reduced cumulative pregnancy rate; higher P was also linked to lower embryo utilization on day 3 and day 5. [6] Similarly, Huanf et al. reported that trigger-day P ≥2.5 ng/mL was associated with a lower proportion of good-quality day-3 embryos. [7] Although that study did not assess pregnancy outcomes, fewer good-quality embryos likely translate into poorer clinical results. Most prior work stratified outcomes by trigger-day serum P alone. Physiological sources of P include the corpus luteum, adrenal cortex, placenta, and the follicle itself. Because circulating P is often ascribed to the corpus luteum, elevated P during stimulation has traditionally been labeled "premature luteinization." However, before ovulation granulosa and theca cells have not fully luteinized. An alternative explanation is that the large amount of intrafollicular P diffuses ("seeps") into the circulation along its steep concentration gradient. Reports indicate that follicular-fluid P can be ≥1,000-fold higher than serum, [8] supporting this hypothesis. To normalize circulating P for follicle burden, we defined progesterone-per-follicle (P/fol) as trigger-day serum P divided by the number of follicles ≥15 mm and examined its association with clinical pregnancy after freeze-all and subsequent frozen-thawed embryo transfer (FET).

Materials And Methods

Study population and cycle selection

We retrospectively screened 26,279 oocyte pick-up (OPU) cycles (1 January 2020–31 December 2024). To ensure precise ascertainment of oocyte maturity, only ICSI cycles were considered; cycles planned for conventional insemination were excluded. We further excluded cycles requiring surgical sperm retrieval (MESA [microsurgical epididymal sperm aspiration] or TESE [testicular sperm extraction]), cycles using artificial oocyte activation, and fresh-transfer cycles. Among the remaining records, cycles yielding no blastocysts were excluded. The primary analysis set comprised 8,507 cycles; a physiological analytic subset (see below) included 6,908 cycles (Figure 1).

Analytic subset

To minimize confounding from excessive follicular response or peri-ovulatory hormonal surge, we restricted to cycles that, on the trigger day (two days before OPU), met all of the following: <10 follicles ≥15 mm, LH <12 IU/L, and E2 ≤3,000 pg/mL (Figure 1).

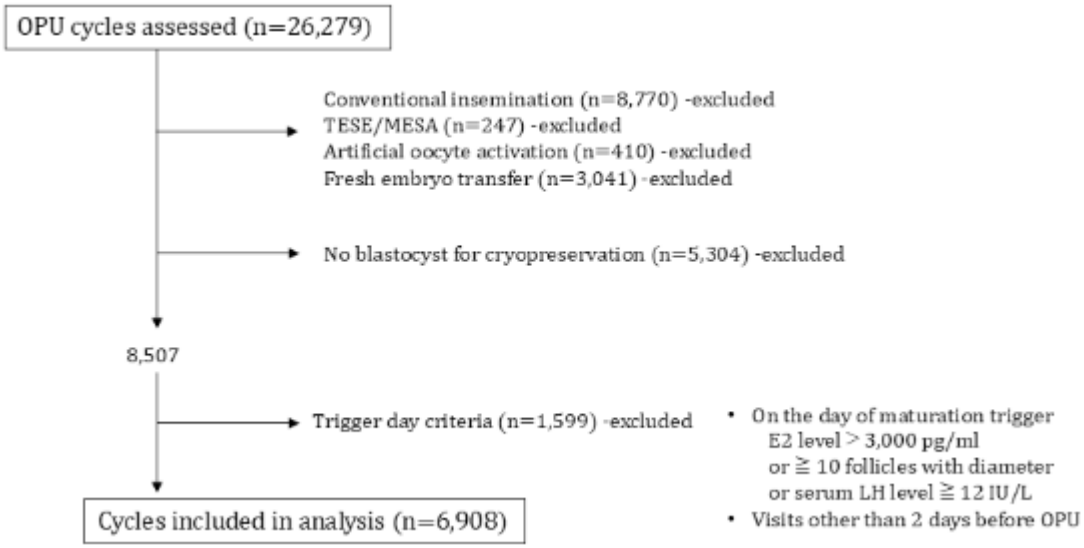

Figure 1: Flowchart of cycle selection for analysis. Among 26,279 OPU cycles, we excluded cycles for the following reasons: fresh embryo transfer (n=3,041); conventional insemination rather than ICSI (n=8,770); use of testicular/epididymal sperm (n=247); artificial oocyte activation (n=410); no blastocysts available for cryopreservation (n=5,304); not meeting trigger-day biochemical/follicular criteria (E2 > 3,000 pg/ml, or ≧ 10 follicles measuring ≧ 15mm in diameter, or serum LH level ≧ 12 IU/L) and clinic visits on days other than 2 days before OPU (n=1,599). A total of 6,908 cycles were included in the final analysis.
Abbreviations: OPU; oocyte pick-up, TESE; testicular sperm extraction, MESA; microsurgical epididymal sperm aspiration, E2; estradiol.

Ovarian Stimulation

Baseline assessment occurred on menstrual cycle day (MC) 2–3 (estradiol [E2], follicle-stimulating hormone [FSH], and luteinizing hormone [LH]; transvaginal ultrasound). Stimulation protocols included natural; minimal (clomiphene citrate [CC] or letrozole [LTZ] alone); mild (CC or LTZ plus recombinant FSH); GnRH antagonist; and modified progestin-primed ovarian stimulation (PPOS). Less common GnRH-agonist long/short protocols were grouped as "other."

- Natural: no medication except for the maturation trigger [9].
- Minimal: CC 50–100 mg/day or LTZ 2.5–5.0 mg/day from MC3 to the day before trigger.
- Mild: CC 100 mg/day or LTZ 5 mg/day for 7 days (MC3–MC9) plus recombinant-FSH with dose adjustments based on MC3 FSH [10].
- PPOS: as in mild, plus oral medroxyprogesterone acetate 10 mg twice daily from MC6 until trigger [11].
- GnRH antagonist: CC 100 mg/day or LTZ 5 mg/day for 7 days with daily rFSH 150–300 IU from MC3; ganirelix acetate 0.25 mg/day added based on monitoring and continued until trigger. Final oocyte maturation was induced when ≥2 follicles reached ≥20 mm using one of: recombinant hCG 250 μg, intranasal GnRH agonist 300 μg twice 30 min apart, or a dual trigger. OPU occurred 35–36 h later [12].

Hormone assays

Baseline E2, FSH, and LH levels (MC3) were measured using commercially available chemiluminescent enzyme immunoassay (CLEIA) kits (AIA-Pack CL®, TOSOH Corporation, Tokyo, Japan). On MC10, serum E2, LH, and P were measured using the same analytical platform. Anti-Müllerian hormone (AMH) was measured using a commercially available immunoassay kit (VIDAS® AMH Assay, bioMérieux Japan, Tokyo, Japan).

Oocyte retrieval and embryo culture

OPU was performed transvaginally under ultrasound guidance using 20- or 21-gauge needles; aspiration was by manual syringe or pump. Anesthesia (intravenous, local, or none with NSAID analgesia) was per patient preference. Cumulus–oocyte complexes were denuded immediately and nuclear maturation assessed. Semen was obtained as fresh or previously cryopreserved ejaculate. To minimize heterogeneity, the present analysis was restricted to ICSI cases, and Piezo-ICSI was used. [13] Embryos were cultured individually to the blastocyst stage under mixed-gas conditions (5% O_2, 6% CO_2, 89% N_2) in a time-lapse incubator. [14] Vitrification occurred on day 5 or 6. [15] Blastocysts were graded by Gardner and Schoolcraft; those ≥4BB were considered good-quality [16] and were eligible for cryopreservation.

Frozen-thawed embryo transfer and outcomes

Blastocysts were thawed by standard protocol. Endometrium was prepared using either ovulatory cycles (natural or LTZ-induced) or hormone-replacement cycles. [17] One or two blastocysts were transferred. Serum hCG was measured 9–10 days after transfer; clinical pregnancy was defined by an intrauterine gestational sac on ultrasound 16–17 days after transfer.

Statistical analysis

Multivariable logistic regression tested the association between log-transformed P/fol and clinical pregnancy, adjusting for female age, male age, gravidity, AMH, BMI, and follicle count (≥15 mm). Two-sided $p<0.05$ was considered significant.

Results

The distribution of ovarian stimulation protocols among 6,908 cycles was shown in Figure 2. Among 6,908 cycles in the analytic subset, protocol distribution was: natural 4%, minimal 16%, mild 39%, GnRH antagonist 4%, modified PPOS 31%, and other 6% (Figure 2).

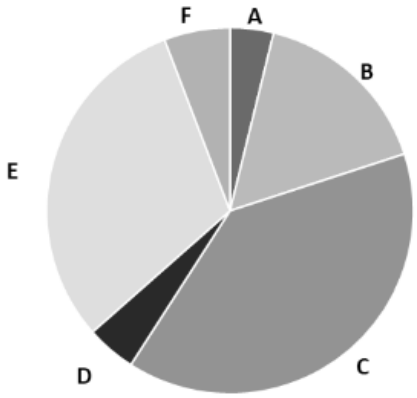

Figure 2: This pie chart shows the percentage of patients using each ovarian stimulation. A. Natural cycle: 4%, B. Minimal stimulation: 16%, C. Mild stimulation: 39%, D. Antagonist protocol: 4%, E. Modified PPOS protocol: 31%, F. Other methods, including the long and short protocols: 6%.
PPOS: progestin-primed ovarian stimulation.

Cycle characteristics are summarized in Table 1. Mean (±SD) female age was 39.2 ± 4.5 years and the male partner age was 41.1 ± 7.5 years. Mean body mass index (BMI) was 21.2 ± 2.9 kg/m^2, gravidity 1.5 ± 1.4, and AMH 1.9 ± 2.1 ng/ml. Overall ART outcomes are summarized in Table 2. On the trigger day, the mean number of follicles ≥15 mm was 3.6 ± 2.2. The mean number of oocytes retrieved was 4.4 ± 3.7, of which 3.4 ± 3.7 were mature (MII). Fresh ejaculated sperm was used in 87.3% of cycles. Mean serum P was 0.55 ng/mL (range 0.05–50.00), and mean P/fol was 0.19 ng/mL (range 0.01–26.96). The mean number of vitrified blastocysts per cycle was 1.5 ± 1.6. Across 6,908 transfers, 1,408 clinical pregnancies were observed.

Table 1: Baseline demographics and clinical characteristics of the study cohort.

	Values
Number of cycles (cycles), n	6,908
Maternal age, years#	39.2 ± 4.5
Paternal age, years#	41.1 ± 7.5
BMI, kg/m^2 #	21.2 ± 2.9
AMH, ng/ml#	1.9 ± 2.1
Number of previous pregnancies, times#	1.5 ±1.4

#; mean ± Standard deviation

Table 2: ART outcomes of the cycles under consideration.

	Values
Number of follicles (≥15mm) on the trigger day. n#	3.6 ± 2.2
Number of retrieved oocytes, n#	4.4 ± 3.7
Number of metaphase II oocytes, n#	3.4 ± 3.7
Number of cycles using fresh sperm, n (%)	5,940 (87.3)
Number of cycles using frozen sperm, n (%)	864 (12.7)
Progesterone level on the trigger day, ng/ml [median range]	0.55 [0.05-50.00]
Progesterone level per follicle* (P/fol), ng/ml [median range]	0.19 [0.01-26.96]
Fertilization rate, %#	83.1 ± 27.3
Number of developed blastocysts, n#	1.6 ± 2.0
Number of vitrified blastocysts, n#	1.5 ± 1.6
Number of thawed blastocyst transfer cycle	6,098
Number of thawed BT*** in ovulatory cycle, n (%)	N/A
Number of thawed BT in hormone replacement cycle, n (%)	N/A
Number of clinical pregnancies, n	1,408

#; mean ± Standard deviation

**MII; metaphase II

***follicles; follicles (≥15mm) on the day of maturation trigger

****BT; blastocyst transfer

On the trigger day, the distribution of P/fol was highly right-skewed (Figure 3A). After log transformation, the variable approximated a normal distribution (Figure 3B), fulfilling assumptions for linear regression; we therefore proceeded with correlation and regression analyses. Log-P/fol showed a strong positive correlation with the number of oocytes retrieved ($r = 0.416$; 95% CI, 0.397–0.436; $p < 1\times10^{-280}$; Figure 3C), whereas the association with the oocyte retrieval rate was only weakly positive (Figure 3D). In contrast, higher Log-P/fol was inversely associated with the number of mature (MII) oocytes, the fertilization rate, the number of blastocysts, and the number of good-quality blastocysts (Figure 4A–4D).

In multivariable analysis, higher P/fol remained an independent negative predictor of clinical pregnancy (adjusted OR 0.61; 95% CI 0.46–0.79; $p<0.001$), alongside female age, AMH, gravidity, and follicle count (Table 3).

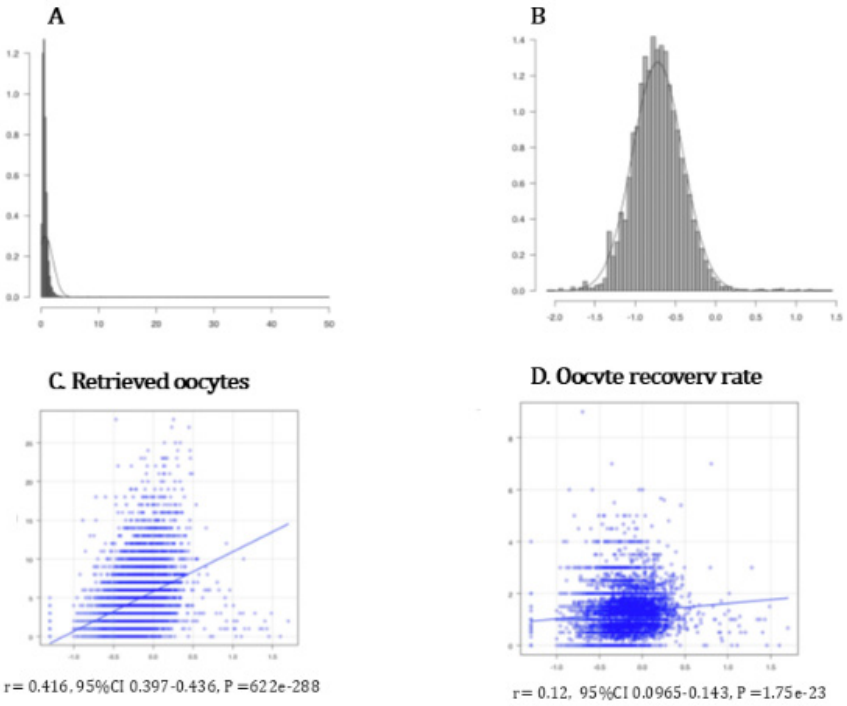

Figure 3: [A] A histogram of the progesterone-per-follicle for follicles ≥15 mm (P/fol) variable, overlaid with a fitted distribution curve. The x-axis represents the P/fol, while the y-axis indicates the number of cases (X 1,000). [B] A histogram of the log-transformed P4/fol variable, overlaid with a fitted normal distribution curve. The x-axis represents the log-transformed P4/fol, and the y-axis represents the number of cases (x 100). [C] Correlation chart between log-P/fol and the number of retrieved oocytes. The x-axis represents log-P/fol, and y-axis represents the number of retrieved oocytes. [D] Correlation chart between log-P/fol and oocyte recovery rate. The x-axis represents log-P4/fol and y-axis represents the oocyte recovery rate

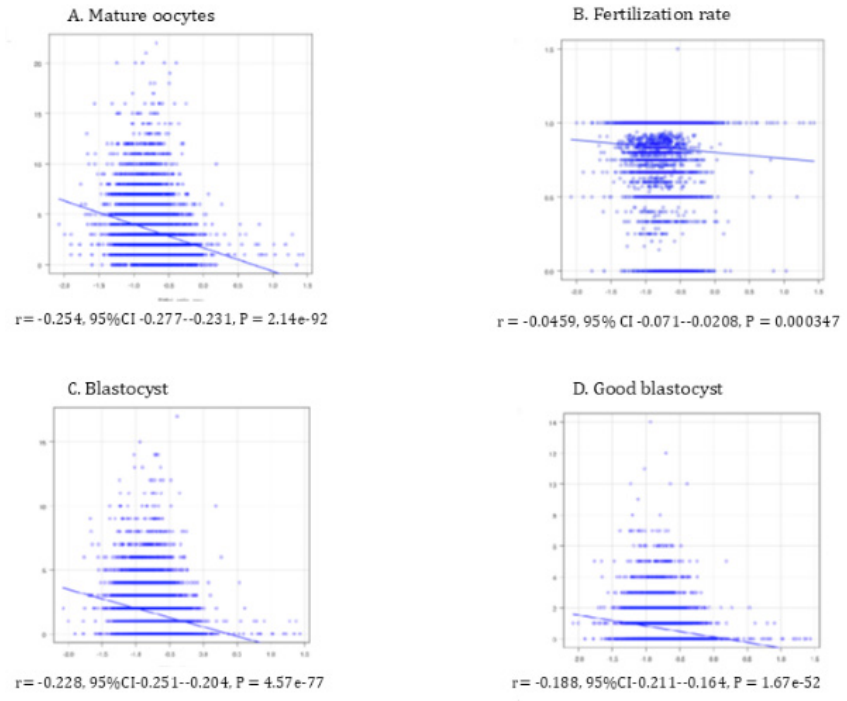

Figure 4: [A] Correlation chart between P4/fol_log and number of mature oocytes. The x-axis represents the P4/fol_log value, and y-axis represents the number of mature oocytes. [B] Correlation chart between P4/fol_log and fertilization rate. The x-axis represents the P4/fol_log value, and y-axis represents fertilization rate. [C] Correlation chart between P4/fol_log and number of blastocysts. The x-axis represents the P4/fol_log value, and y-axis represents the number of blastocysts. [D] Correlation chart between P4/fol_log and number of bood blastocysts. The x-axis represents the P4/fol_log value, and y-axis represents the number of good blastocysts.

Table 3: Independent predictors of clinical pregnancy: multivariable logistic regression (adjusted odds ratios, 95% CI).

Variable	Adjusted Odds Ratio (95% CI)	P value
Female age	0.85 (0.83-0.86)	P<0.001
Male age	1.10 (0.99-1.01)	0.98
Body Mass Index (BMI)	1.10 (1.00-1.01)	0.58
AMH level	1.04 (1.01-1.07)	P<0.001
Gravida	1.47 (1.4-1.54)	P<0.001
Follicle Count (≥15mm on the trigger day)	1.12 (1.07-1.16)	P<0.001
Progesterone per follicle_log (≥15mm)	0.61 (0.46-0.79)	P<0.001

Discussion

In prior reports, elevated circulating P during ovarian stimulation-particularly in the late follicular phase/around trigger-has been likely to adverse reproductive outcomes, even when embryos vitrified at the blastocyst stage and transferred later. The prevailing view is that late-follicular P elevation compromises embryo competence, thereby reducing live birth rates. [6] Consistent with this, higher trigger-day P (e.g., ≥2.5 ng/mL) correlates with a lower proportion of good-quality embryos[7], and morphological signs of granulosa-cell luteinization are associated with diminished blastocyst formation and fewer high-quality blastocysts. [18] These data support an oocyte/embryo-centric effect rather than a purely endometrial milieu.

In our cohort using freeze-all with subsequent FET, higher trigger-day progesterone-per-follicle (P/fol) independently predicted lower implantation (clinical pregnancy) rates (adjusted OR 0.61; 95% CI 0.46–0.79; p<0.001; Table 3). Because this association persists despite transfer in a newly prepared endometrium, endometrial asynchrony alone2 is insufficient; the harm likely occurs at the oocyte/embryo level.

We propose two, non–mutually exclusive hypotheses to explain this association. First, direct P toxicity within a high-P follicular microenvironment may impair oocyte competence. In line with this, trigger-day P ≥2.5 ng/mL is linked to fewer good-quality embryos,[7] and lower P exposure in culture upregulates competence-related transcripts such as OCT4/MATER, promoting cleavage. [19] Second, serum P rise may be a surrogate for compromised follicle physiology-i.e., follicles that poorly retain P ("seepage"), reflecting suboptimal granulosa–theca and cumulus-oocyte complex function. Given reports that late-follicular progesterone elevation does not affect embryo euploidy rates, [20] it is plausible that the adverse outcomes reflect intrinsic follicular dysfunction-i.e., follicles that cannot effectively retain progesterone within the antrum-rather than an effect on aneuploidy. We therefore examine the mechanisms by which circulating P-i.e., P that "seeps" from developing follicles into the bloodstream which we term "seeping P"-arises during stimulation and why this phenomenon may adversely influence ART outcomes.

We propose the following mechanism for the observed "seeping P." Within the two-cell, two-gonadotropin paradigm, inadequate LH signaling limits CYP17A1 activity, curtailing conversion of pregnenolone/progesterone to androstenedione, thereby allowing intrafollicular P to accumulate and seep into the circulation.[21,22] Oocyte-secreted factors (OSFs), including growth differentiation factor 9 (GDF9) and bone morphogenetic protein 15 (BMP15) restrain premature granulosa/cumulus luteinization and reduce P production across species, indirectly supporting a role in limiting serum P elevation.[23-25] Lower follicular-fluid GDF9 with age and associations of higher BMP15 with better ART outcomes suggest that reduced OSF activity characterizes poorer-quality follicles; this provides a plausible basis for our finding that high S-P/fol relates to lower clinical pregnancy rates. Notably, late-follicular P does not appear to alter embryo euploidy, [20] further implicating intrinsic follicular dysfunction rather than aneuploidy effects.

Conclusions

Beyond preventing premature ovulation (LH-centric vigilance), ovarian stimulation should proactively monitor P and P/fol to preempt late-follicular P rise. Earlier triggering, individualized dosing, and protocols that blunt progesterone escape may protect embryo quality. These data motivate prospective trials to test whether P-conscious stimulation improves implantation and live-birth rates.

Conflict Of Interest Statement

The authors have no relevant conflicts of interest to declare.

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Ethics Statement

Institutional Review Board of Sugiyama Clinic (18-001).

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