ORIGINAL ARTICLE: ASSISTED REPRODUCTION

Progesterone level at oocyte retrieval predicts in vitro fertilization success in a short-antagonist protocol: a prospective cohort study

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Objective: To evaluate the distribution of P levels on the day of oocyte retrieval as it relates to pregnancy outcome in an antagonist protocol, which may be at higher risk for elevated P levels.
Design: Prospective cohort study.
Setting: Academic IVF center.
Patient(s): One hundred eighty-six women undergoing controlled ovarian hyperstimulation with an antagonist protocol.
Intervention(s): None.
Main Outcome Measure(s): Implantation, pregnancy, and spontaneous abortion rates were collected.
Result(s): Implantation rate (positive hCG 14 days after ET) and pregnancy rate were significantly higher when the P level was <12 ng/mL on the day of oocyte retrieval. Miscarriage rates were higher when the P level was ≥ 12 ng/mL, although this did not reach statistical significance.
Conclusion(s): Elevated P on the day of oocyte retrieval is associated with significantly lower implantation and ongoing pregnancy rates. This is the first study to date to both uncover the distribution of P on the day of oocyte retrieval in an antagonist cycle and determine the impact an elevation may have on pregnancy outcome. (Fertil Steril® 2013;■:■–■. ©2013 by American Society for Reproductive Medicine.)
Key Words: Progesterone level, oocyte retrieval, antagonist cycle

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Endometrial receptivity is tightly linked to the hormonal milieu present at the time of ET in an IVF cycle. During controlled ovarian hyperstimulation (COH), excessive follicular development and supraphysiologic serum concentrations of E_2 can lead to a premature rise of P in the late follicular phase (1–3), resulting in asynchrony associated with implantation failure (4). Additional hypotheses that have been considered to explain this phenomenon include the elevation of follicular LH levels secondary to incomplete desensitization to GnRH agonists (GnRHa), serum accumulation of hCG from hMG, increased LH receptor sensitivity of the granulosa cells, poor ovarian response with increased LH sensitivity, and the disruption of signaling in the ovarian granulosa cells (5–11). Although the mechanism remains unclear, most investigators favor a cumulative deleterious effect on the endometrium (12–14).

Several studies have evaluated the impact of elevated P at the time of hCG trigger in GnRHa down-regulated cycles, with conflicting results; while several have supported the notion that elevated P negatively impacts pregnancy rates, other investigators have been unable to substantiate this finding (1, 3, 5, 6, 12, 16,18–29). Notably, far fewer studies have investigated the negative impact of premature P elevation in antagonist cycles, and none have evaluated the impact of elevated P at a time more proximal to ET (1, 9, 19,33–35).

The day of oocyte retrieval is a provocative time point, particularly in

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antagonist cycles, as the agent used to prevent the LH surge is stopped 36 hours before oocyte retrieval. However, the average half-life of GnRHant, when given in multiple doses, is approximately 20 hours, which ultimately leads to a rapid recovery from pituitary suppression (15). Because of this, an endogenous LH surge may also occur, which, along with that mimicked by the hCG trigger, may raise P levels beyond what occurs with hCG trigger alone, at a time more proximal to the retrieval, and the result may have a deleterious effect on the endometrial lining. Despite this challenging possibility, no studies that have sought to determine [1] the normal distribution of P levels at 36 hours after hCG trigger or [2] threshold P levels at this time point beyond which pregnancy is unlikely.

We hypothesized that elevations in P levels at the time of oocyte aspiration would lead to decreased pregnancy rates. Thus, we designed a prospective cohort study to describe both the distribution of P on the day of retrieval in women who conceive vs. those who do not and the relationship between an elevated P and pregnancy outcome in an antagonist protocol.

MATERIALS AND METHODS

Study Population and Design

This study was approved by the Institutional Review Board of the University of Pittsburgh Medical Center. All women in this study were treated by IVF or IVF with intracytoplasmic sperm injection (ICSI) at the assisted reproductive technology unit at Magee Women's Hospital, Pittsburgh, Pennsylvania. Consecutive women starting IVF/ICSI-ET cycles were enrolled in a prospective descriptive study between February 2010 and May 2012. Participants undergoing COH with a recombinant FSH analog (rFSH) with or without LH or hMG were recruited. The E_2, LH, P levels were obtained at four time points: [1] start of the stimulation cycle, [2] day of GnRHant start, [3] day of hCG trigger, and [4] day of oocyte retrieval. Only patients who completed the IVF/ICSI-ET cycle and had blood work in our laboratory were included. Women who had a blood test either in another laboratory or on an alternative day than those outlined above were excluded. As the distribution of P on the day of retrieval has never previously been described, this was a hypothesis-driven exploratory analysis.

A GnRHant superovulation protocol was used, as described elsewhere, and oral contraceptives were not used for pretreatment (2, 16). Briefly, women began with gonadotropin injections (Gonal-F, EMD Serono, or Follistim, Merck, and/or Luveris, EMD Serono, and/or Menopur, Ferring) on menstrual cycle day 3 or 4 and added the GnRHant Ganirelix (Merck) or Cetrorelix (Cetrotide, Serono) when at least one leading follicle reached 14 mm in size. GnRHant was not started later than day 6 of stimulation. Close monitoring of ovarian response occurred throughout, and when at least two follicles were $\geq$18 mm in size, 10,000 IU of hCG (Ferring) was administered to simulate the LH surge of a natural cycle. The GnRHant was then continued up to and including the day of hCG trigger. Thirty-six hours later, women underwent transvaginal ultrasound–guided oocyte recovery under IV sedation. Oocytes were fertilized in vitro by conventional IVF or ICSI, and ET occurred 3 days afterwards. All embryos transferred were 6 cells or greater and were of A or B quality. All women had luteal phase support with P given as a daily injection or as a vaginal suppository starting on the evening of oocyte retrieval, after serum P levels for the study were drawn. Serum βhCG levels were obtained 14 days after oocyte retrieval. All patients with a βhCG $>$10 IU/L were followed with further blood tests and/or with serial transvaginal ultrasound until 8 weeks of gestation, at which time they were referred for obstetric care. Supplementary P was continued until 10 weeks of gestation, and the choice of supplementation was based on patient preference (IM P in oil [50 mg daily] or vaginal P supplementation with endometrin [100 mg per vagina twice daily]). Implantation was defined as having a positive βhCG 14 days after ET. Ongoing pregnancies were defined as those that were followed until 8 weeks of gestation but final pregnancy outcome had not yet been determined.

Hormone Assays

Blood samples were drawn at four designated time points between 0630 and 1000 hours, in standard SST gel tubes (Becton Dickinson). Samples were allowed to clot before centrifugation at 3,000 *g* for 10 minutes to separate the serum. Samples were transferred to the laboratory within 1 hour of collection and analyzed on the same day for E_2, LH, and P with sequential competitive immunoassay (Beckman Coulter Access 2) All laboratory results were given to the investigators as they became available, and the encountered within-assay variability was $<$10%.

Statistical Analysis

Data were analyzed on Statview software (JMP) or STATA software (StataCorp. 2009. *Stata Statistical Software: Release 11*).

To determine the relationship between serum P and cycle outcome, we first performed a Student's *t*-test at four critical time points during an in vitro stimulation cycle: at baseline, at antagonist start, at hCG trigger, and at the time of retrieval. We then used the Kolmogorov-Smirnov test to determine whether there was a normal distribution of *P* values in our study population.

To assess the influence of other variables that may contribute to pregnancy rates, a multivariate analysis was performed using the following variables: age; total gonadotropin dose; total number of oocytes retrieved; and E_2, LH, and P values at baseline, on the day of antagonist start, on the day of hCG trigger, and on the day of oocyte retrieval. To describe the relationship between P on the day of oocyte retrieval and pregnancy rates, a linear regression was performed. P levels were divided into eight discrete ranges: 0–1.9, 2–3.9, 4–5.9, 6–7.9, 8–9.9, 10–11.9, 12–13.9, and 14–15.9 ng/mL. The levels used to determine the eight groups were chosen to provide equal intervals around the values obtained. The upper limit of 16 was chosen because 95% of patients who conceived had P levels of $<$16 ng/mL, and no patients with a P level of $>$18.1 ng/mL conceived. Pregnancy rates for each interval were then calculated, and the linear regression was derived. From this, we determined a P level

on the day of retrieval beyond which pregnancy appeared unlikely.

Using this critical P threshold, we dichotomized the cohort and compared both cycle and pregnancy outcomes. We used *t*-tests to compare the mean of continuous variables, along with a variance comparison test to determine the use of a *t*-test with equal or unequal variance. Chi-square tests and Fisher's exact tests were implemented on categorical variables.

Finally, to assess whether or not the predictive value of P was dependent on the type of gonadotropin stimulation used (recombinant FSH alone or along with hMG), we repeated the above analyses in these subgroups.

RESULTS

Patient Characteristics

Among the 217 women recruited to the study, 186 completed an IVF/ICSI-ET cycle during the study period and were included in the final analysis. Twenty-four patients did not meet the final inclusion criteria because they either did not have their blood test performed on the appropriate date(s) or had missing data (n = 23), their IVF cycle was converted to an IUI (n = 3), or they did not undergo immediate ET (n = 5). Forty-eight of the 186 patients took hMG or LH in addition to rFSH for gonadotropin stimulation.

Baseline characteristics of study participants are shown in Table 1. Sixty-two patients (33%) had a viable intrauterine pregnancy that was either ongoing (94%) or successfully delivered (6%) by the conclusion of the study. The overall rate of early pregnancy failure (biochemical or miscarriage) was 2%. There were no ectopic pregnancies, and 115 patients (62%) failed to conceive.

The P levels at baseline (P=.99), antagonist start (P=.08), and hCG trigger (P=.38) were not associated with pregnancy outcome. Notably, however, P on the day of oocyte retrieval was significantly correlated with pregnancy outcome (P=.007).

On multivariate analysis, each individual time point model used the following variables: age; total number of oocytes retrieved; total FSH dose; and the P, LH, and E_2 levels for that specific time point. P levels at baseline (P=1.00), antagonist start (P=.16), and hCG trigger (P=.26) were not correlated with pregnancy outcome. However, again, P on the day of oocyte retrieval remained statistically significantly correlated with pregnancy outcome (P=.002) (Supplementary Table 1).

Next, as P levels on the day of oocyte retrieval during a GnRHant cycle have never previously been described, we wanted to further explore their distribution at this unique time point and to additionally investigate whether these levels were significantly different in those women who have conceived vs. in those who have not. The mean (± SD) level of serum P on the day of oocyte retrieval in all of our patients was 9.35 ± 0.41 ng/mL (range, 0.1–41.0 ng/mL). The mean P level on the day of retrieval in patients who went on to have a clinical pregnancy was statistically significantly lower than the level in those who did not conceive (7.8 ± 4.45 vs. 10.2 ± 6.08; P=.007). Of those patients who conceived, 5% had a P level of ≤0.7 ng/mL, and 75% of patients had a P level of <10.6 ng/mL (Table 2). Notably, no one conceived with a P level of >18.1 ng/mL.

To describe the relationship between P on the day of oocyte retrieval and pregnancy rate, P levels were then divided into eight discrete ranges. As 95% of patients had serum P of <16.1 ng/mL and no patients conceived if they had a P of >18ng/mL, observations with a P of >16.1 ng/mL (n = 19) on the day of retrieval were excluded to maintain equal intervals and identify a point beyond which pregnancy was more unlikely. Ongoing pregnancy rate was calculated for each P level, and an exponential regression was derived (Fig. 1). P levels on day of oocyte retrieval were inversely associated with pregnancy rates: as P levels increased, pregnancy rates decreased. Additionally, there appeared to be a steeper decline in pregnancy rates once the P values were >12 ng/mL, suggesting that this may be a clinically important level beyond which pregnancy is less likely. Notably, patients with P >18 were high responders. Their diagnoses before IVF were male factor (45%), unexplained infertility (36%), polycystic ovarian syndrome (10%), and tubal factor (9%). This was a younger group (average age, 32.5 ± 4.45), who had otherwise good prognostic ovarian reserve testing before cycle start (day 3 FSH, 7.5 ± 3.1; day 3 antral follicle count, 24.9 ± 7.5), a greater than average number of oocytes retrieved (number

TABLE 1

Clinical characteristics of participants.

	Mean ± SD or percentage of total population
Age	34.1 ± 4.2
Nulliparity	60
Infertility diagnosis	
Male factor	36.3
Unexplained	32.9
Decreased ovarian reserve	8.4
Anovulation	8.4
Uterine/tubal	7.7
Endometriosis	4.7
Recurrent Pregnancy Loss	1.6
Basal FSH (mIU/mL)	8.4 ± 6.34
Antral follicle count	19.78 ± 7.9
No. of embryos transferred	2.0 ± 0.8
Total rFSH (mIU)	3,081.8 ± 1,923.6

Nayak. Premature P_4 rise in antagonist cycles. Fertil Steril 2013.

TABLE 2

Distribution of P values (ng/mL) on the day of retrieval in the total study population, as well as in those women who conceived and in those who did not.

%	All study participants	Those who conceived	Those who did not conceive
5	1.1	0.7	1.9
25	5.7	5.5	6
50	8.5	7.6	9.2
75	12.2	10.8	12.5
95	18.5	16.1	20.6

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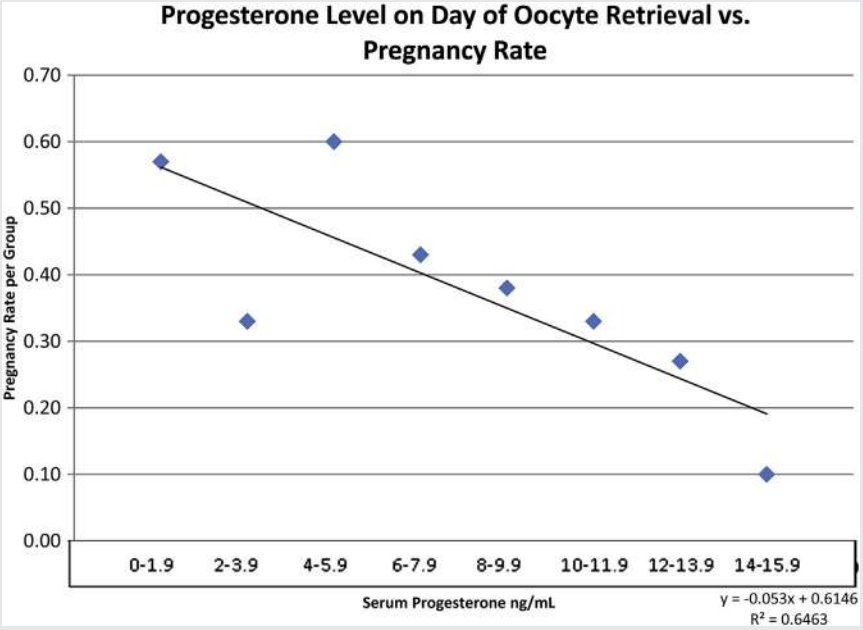
FIGURE 1



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of oocytes, 22.18 ± 8.6), and good-quality embryos transferred (all 6 cells or greater, A or B quality).

Clinical pregnancy rates and implantation rates were both significantly higher in patients with a P <12 ng/mL at oocyte retrieval compared with patients who had a P ≥12 ng/mL at that time (38.6% vs. 20%; *P*=.02; 43.9% vs. 31.6%, *P*=.01). Miscarriage rates stratified by P level were not significantly different (12% vs. 16.7%, *P*=.64; Table 3). Finally, there was a moderate to strong correlation between P on the day of retrieval and the number of oocytes retrieved (r = 0.51; *P*<.001); patients with an elevated P on the day of retrieval had a significantly higher number of oocytes retrieved (18.33 ± 1.13 vs. 11.3 ± 0.51; *P*<.001; Table 3). Oocyte maturation rate and fertilization rate were not different when stratified by P level at oocyte retrieval.

Finally, we performed independent subgroup analyses of those patients stimulated with either rFSH (n = 138) alone or in combination with LH (n = 48). In those patients for whom both rFSH and LH were used during superovulation, there was no association between prematurely elevated P and pregnancy outcome at any time point assessed (baseline *P*=.65, antagonist start *P*=.38, hCG trigger *P*=.58, oocyte retrieval *P*=.98). We attributed this finding to the relatively small sample size of this subgroup. However, in the rFSH-only group, P at the time of oocyte retrieval was the only point that was significantly associated with pregnancy outcome (baseline *P*=.99, antagonist start *P*=.13, hCG trigger 0.38, oocyte retrieval *P*=.002), and this association persisted after controlling for age, total number of oocytes retrieved, total FSH dose, and LH and E_2 at the time of retrieval (*P*=.005).

Notably, the type of P supplementation was not associated with pregnancy outcome (*P*=.69). Additionally, type of P supplementation was not significantly different in those with P ≤12 ng/mL (*P*=.87) or >12 (*P*=.19) on the day of oocyte retrieval. As such, the type of luteal support was not a significant contributing factor to these results.

DISCUSSION

Premature leutinization refers to a rise in serum P on or before the day of hCG administration, and its incidence varies among different down-regulatory protocols in COH; the frequency has been reported as being as high as 35% (5%–35%) in GnRHa cycles and as high as 38% (9%–38%) in GnRHant cycles (9,17–20). Evidence for the impact of this phenomenon on both implantation rates and pregnancy outcomes in GnRHa cycles has previously been extensively examined and reviewed, however, only one study to date has evaluated the effect of an elevated P on the day of oocyte retrieval in GnRHa cycles (1, 3, 5, 6, 19,21–33). On the contrary, the study of elevated P, either at the time of hCG trigger or during other critical time points during antagonist cycles, has been less studied (1, 9, 19,34–36). Additionally, there have been no studies that have specifically addressed the potential impact of elevated P on the day of oocyte retrieval in GnRHant cycles.

A previous study by Niu and colleagues looked at P levels on the day of oocyte retrieval in GnRHa IVF cycles (21). This group found that P levels correlated with the number of oocytes retrieved and embryos obtained but did not predict

TABLE 3

Characteristics of participants stratified by P level on day of oocyte retrieval (mean ± SD).

	P < 12 ng/mL, n = 135	P ≥ 12 ng/mL, n = 51	*P*
Age	34.35 ± 0.38	33.53 ± 0.56	.24[a]
Nulliparity (%)	74/55.22	30/58.82	.66[b]
Basal FSH (mIU/mL)	8.33 ± 0.19	8.92 ± 1.49	.70[c]
Antral follicle count[d]	18.81 ± 0.69	22.49 ± 0.97	.004[a]
No. of embryos transferred	2.05 ± 0.06	1.98 ± 0.12	.57[a]
Oocytes retrieved[d]	11.27 ± 0.51	18.33 ± 1.13	.001[c]
Baseline E_2 (pg/mL)	45.92 ± 1.51	44.43 ± 3.29	.68[c]
Baseline P (ng/mL)	0.85 ± 0.05	1.16 ± 0.23	.19[c]
Percent mature oocytes (95% confidence interval)	0.78 ± 0.02	0.75 ± 0.03	.28[a]
Fertilization rate (95% confidence interval)	0.36 ± 0.01	0.33 ± 0.02	.20[a]
Implantation rate (%)[d]	58/43.94	12/31.58	.01[b]
Pregnancy rate (%)[d]	51/38.64	10/20.00	.02[b]
Miscarriage rate (%)	7/12.07	2/16.67	.64[e]

[a] *t*-test with equal variance.
[b] χ^2-test.
[c] *t*-test with unequal variance.
[d] Significant at $P < .05$.
[e] Fisher's exact test.

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pregnancy outcome. We similarly showed a positive association between P on the day of oocyte retrieval and the number of oocytes retrieved, although we did so in GnRHant cycles. Additionally, we found that patients with elevated P on the day of oocyte retrieval had lower pregnancy rates.

In agreement with prior studies that assessed P levels on the day of hCG trigger and on the day before oocyte aspiration in both GnRHa and GnRHant cycles, we found that pregnancy rates decrease when P levels exceed a threshold level (1, 19,29–35). When examining P levels at the time of hCG trigger, previous studies have suggested discriminatory levels from 1.2 to 4.0 ng/mL as a critical threshold in predicting successful pregnancy (1, 37). We chose to interrogate P at a time more proximal to oocyte retrieval in antagonist cycles. Given the short half-life of GnRHant, and the culture of stopping antagonists up to 36 hours before retrieval, it is biologically plausible to see an endogenous LH surge, which would lead to elevations in P levels on the day of oocyte aspiration, which together would have a cumulative negative impact on the endometrium. Several strategies have been suggested to allow for endometrial recovery before transfer, such as extended embryo culture. There have been two studies that sought to determine whether prolonged embryo culture and blastocyst transfer would mitigate the adverse effect of elevated P that is seen on the day of hCG administration (34, 38). Papanikolaou et al. showed a significant negative effect on pregnancy outcome when a P threshold of 1.5 ng/mL was encountered on the day of hCG trigger and cleavage-stage embryos were subsequently transferred (34). Importantly, no negative effect was seen when using the same P threshold and subsequent blastocyst transfer, suggesting that the deleterious effect is at the level of the endometrium. Recently, Corti et al. explored this question using the same P threshold on the day of trigger, however, they did not find that extended embryo culture lessened the negative endometrial effect on pregnancy outcome; this may be partially explained by the overall younger and potentially better prognosis patient population in the former study (38). Because of these conflicting findings, further larger studies are required in the future to determine whether extended culture or embryo freezing is the preferred route for managing patients with elevated P.

Importantly, the distribution of P at this critical time point has never been described, but the advantage of identifying a threshold beyond which pregnancy outcomes may be affected can aid in the practitioner's ability to counsel the patient. Using a time more proximal to oocyte retrieval, we discovered that a P level of ≥ 12 ng/mL may be predictive of significantly poorer pregnancy and implantation rates. These results raise several important clinical considerations. First, the negative effect of an elevated P at the time of oocyte retrieval appears to be limited to the endometrium, as no effect on oocyte maturation or fertilization rate was detected; this has been corroborated by previous studies in donor-recipient IVF cycles as well as in frozen embryo cycles (6, 9, 31,39–41). Therefore, a simple solution may be cryopreserving embryos when P levels exceed this threshold. The advantages of a frozen ET over a fresh ET have been described in the literature, particularly as pregnancy success rates approach equivalence in many IVF labs. Thus, the P level on the day of oocyte retrieval may help to stratify which patients may benefit from embryo cryopreservation in lieu of a fresh ET. Second, we hypothesize that there may be a benefit in continuing the GnRHant beyond the day of oocyte retrieval to not only prevent the elevation in P but to also prevent the potential cumulative negative effect that the premature rise may have on the endometrium after hCG trigger. As the cumulative negative effect on the endometrium may be abated in this fashion, we further hypothesize that this would lead to an improvement in pregnancy rates, however, this has not yet been studied, and any potential adverse effects of the antagonist on the embryo would need to be considered.

It should be mentioned that we found considerable overlap in P levels between women who did and did not conceive, and as such, this value should only be used to guide

counseling and not as an absolute value beyond which a fresh transfer would be denied. P levels of >3 ng/mL have been used as a marker for successful trigger when measured the following day. It is critical to identify not only a threshold but also a range of P levels after trigger and more proximal to ET, as the former will capture successful trigger levels and the latter help to identify those patients for which pregnancy is unlikely. As an elevated P does not appear to affect the number of mature oocytes retrieved or fertilization rates, further larger studies that randomize patients to undergo a frozen transfer or extended culture will help to elucidate the utility of the use of elevated P at the time of oocyte retrieval in a clinical setting.

In conclusion, this study is novel for two reasons: [1] it is the first study to evaluate P levels at the time of oocyte retrieval in an antagonist protocol and [2] elevated P levels on the day of retrieval significantly reduce both implantation rates and pregnancy rates. In addition, P levels at earlier time points within a stimulation cycle do not always correlate with P levels at the time of oocyte retrieval, and as such, this may be a useful addition to a patient's evaluation. In patients contemplating ET in favor of subsequent frozen ET, P at oocyte retrieval may be one more piece of information that would impact their decision.

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SUPPLEMENTARY TABLE 1

Multivariate analysis of P at different time points and pregnancy.

Hormone level	Mean ± SD (95% confidence interval)	*P*
P at baseline	0.93 ± 0.07 (0.79, 1.07)	1.00[a]
P on day of antagonist start	0.98 ± 0.07 (0.83, 1.13)	.16[a]
P on day of hCG trigger	1.71 ± 0.15 (1.42, 1.99)	.26[a]
P on day of oocyte retrieval[b]	9.35 ± 0.41 (8.53, 10.16)	.002[a]

[a] *t*-test with unequal variance.
[b] Significant at $P < .05$.

Nayak. Premature P_4 rise in antagonist cycles. Fertil Steril 2013.