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Research Article

Profound Pituitary Suppression Following Oral Contraceptive Pretreatment in Gonadotropin-releasing Hormone Antagonist Cycles Does Not Impact Outcome: A Retrospective Cohort Study

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Abstract

Background: This retrospective study evaluated the effect of profound pituitary suppression with oral contraceptive pill (OCP) pretreatment in gonadotropin-releasing hormone (GnRH) antagonist cycles stimulated with recombinant follicle stimulating hormone plus highly purified human menopausal gonadotropin.

Methods: The analysis included women aged 20-46 years (N=318) who utilized OCP pretreatment in a private academic *in vitro* fertilization center between January 2008 and January 2010. Patients were retrospectively divided based on endogenous luteinizing hormone (LH) level (≤1.5 [n=75] vs. >1.5 [n=243] mIU/mL) on stimulation day 1.

Results: In the LH ≤1.5 and >1.5 mIU/mL groups, respectively, the mean number of stimulation days was 10.9 and 9.5 days (P<0.0001); mean total gonadotropin use was 4,328 and 3,543 IU (P<0.0001). Oocyte retrieval was greater in the LH ≤1.5 versus >1.5 mIU/mL group (17.7 *vs.* 14.9 oocytes; P=0.02). Pregnancy outcomes were similar between groups. Longer OCP duration correlated with lower day 1 LH levels (r=–0.161, P=0.007). Greater LH suppression correlated with increased total gonadotropin dose (r=–0.227, P<0.001) and days of stimulation (r=–0.445, P<0.001).

Conclusion: Women with profound LH suppression following OCP pretreatment demonstrated comparable prognosis compared with women without profound LH suppression, despite requiring longer stimulations and a higher total gonadotropin dose.

Keywords: Oral contraceptive pill; Gonadotropin-releasing hormone; Antagonist; Pituitary suppression; Luteinizing hormone; *in vitro* fertilization

Abbreviations: FSH: Follicle-stimulating Hormone; GnRH: Gonadotropin-releasing Hormone; hCG: Human Chorionic Gonadotropin; hMG: Human Menopausal Gonadotropin; IVF: *in vitro* Fertilization; NS: Non-significant; OCP: Oral Contraceptive Pill; OHSS: Ovarian Hyperstimulation Syndrome; LH: Luteinizing Hormone; rFSH: Recombinant Follicle-stimulating Hormone; SD: Standard deviation

Introduction

Oral contraceptive pills (OCPs) are widely used as adjunct treatment prior to ovarian stimulation during *in vitro* fertilization (IVF) cycles [1]. By controlling the patient's menstrual cycle, OCP pretreatment helps to downregulate the patient's hypothalamic pituitary axis, improve follicular synchrony, permit scheduling of the ovarian stimulation and oocyte retrieval [1-3].

Both GnRH agonist and antagonist protocols are commonly used for IVF cycles. Compared with gonadotropin-releasing hormone (GnRH) agonist protocols, GnRH antagonist protocols provide the advantages of a shorter stimulation period and the use of lower gonadotropin exposure, which decreases the risk of ovarian hyperstimulation syndrome (OHSS) due to the ability to use a GnRH agonist trigger [4,5]. In part, due to these reasons, the use of GnRH antagonist cycles is increasing. However, while GnRH agonist protocols have flexibility with regard to the starting day of stimulation, stimulation in GnRH antagonist protocols (in the absence of OCP pretreatment) is dependent on the patient's menstrual cycle and must therefore be started on cycle day 2 or 3 [4,6,7]. This dependency on the patient's menstrual cycle has practical and economic implications for both the patient and clinic. With the use of OCP pretreatment, however, stimulation can be started within 5 days of contraceptive withdrawal, allowing patients and physicians to schedule IVF treatments [4,6,7]. Cycle scheduling allows fertility clinics to better distribute the number of oocyte retrievals in a week, resulting in a more balanced workload, improved efficiency, and potentially a decrease in the occurrence of errors. These advantages can be particularly important within the embryology laboratory [1,8]. Scheduling is also more convenient for the patient, as it provides flexibility in timing the start of stimulation [1,8].

In addition to providing more flexibility in GnRH antagonist protocols, OCP pretreatment results in a more homogeneous follicular cohort, which may improve synchronization of follicular growth during stimulation and increase oocyte yield [2,3]. In poor responders, OCP pretreatment appears to increase the number of oocytes for retrieval and may improve pregnancy rates [9,10]. OCP pretreatment is thought to suppress endogenous follicle-stimulating hormone (FSH) to normal levels and resensitize follicles to exogenous FSH [10,11]. Interestingly, a retrospective study of women with polycystic ovary syndrome (vs. normal controls) undergoing IVF treatment also found that the use of successive OCP (≥3 months) improved serum hormone levels,

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antral follicle counts, and implantation and pregnancy rates [12]. The use of OCP pretreatment has also been associated with a reduction in endometrial thickness compared with no pretreatment, possibly due to the sustained suppression of luteinizing hormone (LH) and estradiol at the start of stimulation [13,14]. Although several studies have suggested a positive association between pregnancy rate and greater endometrial thickness on the day of ovulation trigger, up to a maximum of 12 to 14 mm [15], a reduced endometrial thickness at the start of the cycle may be beneficial in some patients to avoid overly thick endometrium following ovarian stimulation with human menopausal gonadotropin (hMG) [16].

Controversy exists regarding whether or not the use of OCP pretreatment with antagonist protocols affects cycle outcome, including live birth and clinical pregnancy rates [1,17], ovarian response, and early pregnancy loss [18-20], with published studies producing a conflicting view of the impact of OCP pretreatment and suppression of endogenous LH. Further studies on which to base more solid conclusions are needed [21,22]. The aim of this retrospective cohort study was to evaluate the effect of profound pituitary suppression after OCP pretreatment in GnRH antagonist cycles supplemented with LH activity.

Materials and Methods

Study design and patient population

This was a retrospective database analysis of GnRH antagonist cycles that utilized OCP pretreatment in an academic IVF center (Reproductive Medicine Associates of New York) from January 2008 to January 2010. This analysis was conducted in accordance with the principles described in the Declaration of Helsinki, and institutional review board approval was obtained from the Western Institutional Review Board.

Women aged 20 to 46 years who had undergone an initial IVF cycle (with or without intracytoplasmic sperm injection) utilizing OCP pretreatment were included. Patients must have had an infertility diagnosis of tubal factor, male factor, diminished ovarian reserve, polycystic ovary syndrome, endometriosis, or idiopathic.

All patients received OCP pretreatment with 35 μg ethinyl estradiol and 1 mg norethindrone (Ortho-Novum® 1/35 [Janssen Pharmaceuticals, LLC, Titusville, NJ, USA]) for a duration of approximately 21 days (range, 8-41 days). Ovarian stimulation with a 2:1 combination of recombinant FSH (rFSH; Gonal-F® [EMD Serono, Rockland, MA, USA] or Follistim® [Merck & Co., Inc., Kenilworth, NJ, USA]) and highly purified hMG (Menopur® [Ferring Pharmaceuticals, Inc., Parsippany, NJ, USA]) was initiated 4 days after OCP discontinuation. When the lead follicle was >14 mm in diameter, GnRH antagonist treatment (0.25 mg/day; Cetrotide® [EMD Serono] or Ganirelix [Merck & Co., Inc.]) was initiated, the hMG dose was increased by 75 IU/day. Human chorionic gonadotropin (hCG; 250 mcg Ovidrel® [EMD Serono]) was administered upon confirmation of ≥2 follicles that were ≥18 mm in diameter. Oocyte retrieval occurred 36 hours after hCG administration, and embryo transfer followed 3 to 5 days later. Patients received intramuscular progesterone (50 mg/day) for luteal phase support starting the night of oocyte retrieval.

Study assessments

Patients were retrospectively assigned to groups based on endogenous LH levels (≤1.5 vs. >1.5 mIU/mL) on day 1 of stimulation (i.e., 4 days after OCP discontinuation), which were determined using an Immulite® instrument (Siemens Medical Solutions Diagnostics, Flanders, NJ, USA). Peak serum estradiol levels, durations of stimulation, total gonadotropin dose, oocyte yields, fertilization and implantation rates, clinical pregnancies, live births, and spontaneous abortions were assessed in each group from patient medical records. Separate analyses were performed to determine the correlation between endogenous LH level on day 1 of stimulation and the duration of OCP pretreatment, total gonadotropin dose, days of stimulation, and number of oocytes retrieved. LH levels were also assessed in subgroups based on duration of OCP pretreatment (<19 days, 19-23 days, and >23 days).

Statistical analyses

Sample size determination was based on the comparison of clinical pregnancy rates in the LH ≤1.5 mIU/mL and LH >1.5 mIU/mL groups. An estimated 259 patients were required in the LH ≤1.5 mIU/mL group and 777 patients in the LH >1.5 mIU/mL group to detect a 5% difference in clinical pregnancy rates at a power of 80%, assuming failure rates of 40% and 50%, respectively. In this pilot study of 318 patients, the likelihood of detecting an 18% difference in pregnancy rate was 80%. Differences in patient demographics, cycle characteristics, cycle outcomes were assessed using chi-square and Student *t* tests. The relationships between LH level and duration of OCP pretreatment, total gonadotropin dose, days of stimulation, and number of oocytes retrieved were assessed using Pearson's correlation coefficient and Student *t* test. An analysis of variance model was used to evaluate differences in LH levels in subgroups based on duration of OCP pretreatment. *P* values <0.05 were considered statistically significant.

Results

Patients and cycle characteristics

A total of 318 patients were assigned to groups based on endogenous LH level on Day 1 of stimulation: 75 women with LH levels ≤1.5 mIU/mL and 243 women with LH levels >1.5 mIU/mL. In the LH ≤1.5 mIU/mL groups, there were 12 cycle cancellations and 63 patients (84%) underwent embryo transfer. In the LH >1.5 mIU/mL group, there were 31 cycle cancellations and 212 patients (87%) underwent embryo transfer. Of the patients with cycle cancellations, 2 of 12 patients in the low LH group and 11 of 31 patients in the normal LH group had no embryos for transfer despite oocyte retrieval. The remaining cancellations occurred prior to oocyte retrieval. Patient demographic and cycle characteristics were generally comparable between the 2 groups, except that patients in the LH ≤1.5 mIU/mL group tended to have a longer duration of OCP pretreatment (by approximately 1 day) and had significantly lower baseline (pre-OCP) LH levels (4.3 vs. 5.2 mIU/mL for patients in the LH >1.5 mIU/mL group; Table 1). Patients in the LH ≤1.5 mIU/mL group also had significantly lower FSH (1.8 vs. 7.4 mIU/mL) and LH (0.6 vs. 4.8 mIU/mL) levels after OCP pretreatment.

Stimulation, fertilization, and pregnancy outcomes

The mean number of days of ovarian stimulation and the mean total gonadotropin dose were significantly greater in the LH ≤1.5 mIU/mL group versus the LH >1.5 mIU/mL group (Table 2). Additionally, significantly more oocytes were retrieved in the LH ≤1.5 mIU/mL group compared with the LH >1.5 mIU/mL group (17.7 vs. 14.9 oocytes). However, no differences in fertilization, implantation, pregnancy, live birth, and spontaneous abortion rates were detected between the LH ≤1.5 mIU/mL and LH >1.5 mIU/mL groups (Table 2).

Duration of OCP pretreatment and LH suppression

Longer durations of OCP pretreatment were correlated with lower post-OCP LH levels on the first day of gonadotropin stimulation (*r*=–

Characteristics	LH ≤1.5 mIU/mL (n=75)	LH >1.5 mIU/mL (n=243)	*P* value
Mean (SD) age, years	35.9 (4.2)	36.5 (4.5)	NS
Intracytoplasmic sperm injection rate, n*	27/63 (42.9%)	102/212 (48.1%)	NS
Mean (SD) days on OCP	22.4 (4.5)	21.3 (4.2)	0.052
Mean (SD) baseline FSH, mIU/mL	7.7 (6.5)	7.2 (2.6)	NS
Mean (SD) post-OCP FSH	1.8 (1.7)	7.4 (3.6)	<0.0001
Mean (SD) baseline LH, mIU/mL	4.3 (2.2)	5.2 (2.5)	0.006
Mean (SD) post-OCP LH	0.6 (0.4)	4.8 (2.7)	<0.0001

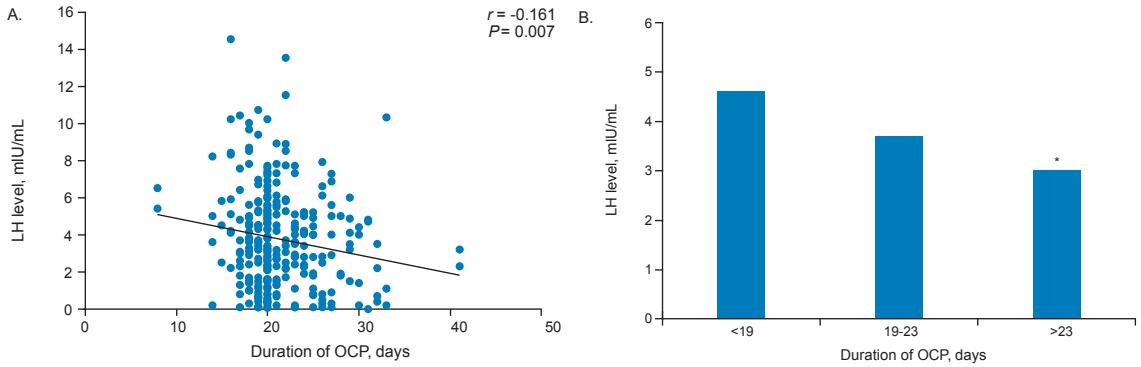
*Out of completed *in vitro* fertilization cycles. Abbreviations: LH: Luteinizing Hormone; SD: Standard Deviation; NS: Non-significant; OCP: Oral Contraceptive Pill; FSH: Follicle-stimulating Hormone

Table 1: Demographic and infertility characteristics.

Parameters	LH ≤1.5 mIU/mL (n=75)	LH >1.5 mIU/mL (n=243)	*P* value
Mean (SD) no. of days of stimulation*	10.9 (0.8)	9.5 (1.1)	<0.0001
Mean (SD) gonadotropin dose, IU*	4328 (1266)	3543 (1283)	<0.0001
Mean (SD) peak estradiol on day of hCG, pg/mL	2091 (827)	2049 (990)	NS
Mean (SD) no. of oocytes retrieved*	17.7 (9.4)	14.9 (7.8)	0.019
Fertilization rate/oocyte, n	632/1119 (56.5%)	1742/3172 (54.9%)	NS
Day 5 embryo transfer rate, n*	16/63 (25.4%)	44/212 (20.8%)	NS
Mean (SD) no. of embryos transferred	2.8 (1.7)	2.8 (1.2)	NS
Implantation rate/embryo, n	48/179 (26.8%)	153/597 (25.6%)	NS
Clinical pregnancy rate/embryo transfer, n	31/63 (49.2%)	98/212 (46.2%)	NS
Ongoing pregnancy rate/embryo transfer, n	25/63 (39.7%)	86/212 (40.6%)	NS
Live birth rate/started cycle, n	26/75 (34.7%)	83/243 (34.2%)	NS
Spontaneous abortion rate/clinical pregnancy, n	6/31 (19.4%)	12/98 (12.2%)	NS
Cycle cancellation rate/started cycle, n	12/75 (16.0%)	31/243 (12.8%)	NS

*Out of completed *in vitro* fertilization cycles. Abbreviations: LH: Luteinizing Hormone; SD: Standard Deviation; hCG: Human Chorionic Gonadotropin; NS: Non-significant

Table 2: Summary of stimulation, fertilization, and pregnancy outcomes.



**P*=0.005
Abbreviations: OCP: Oral Contraceptive Pill; LH: Luteinizing Hormone
Figure 1: OCP duration and LH suppression. (A) Correlation between post-OCP LH level and OCP duration. (B) Post-OCP LH level for subgroups of patients by OCP duration.

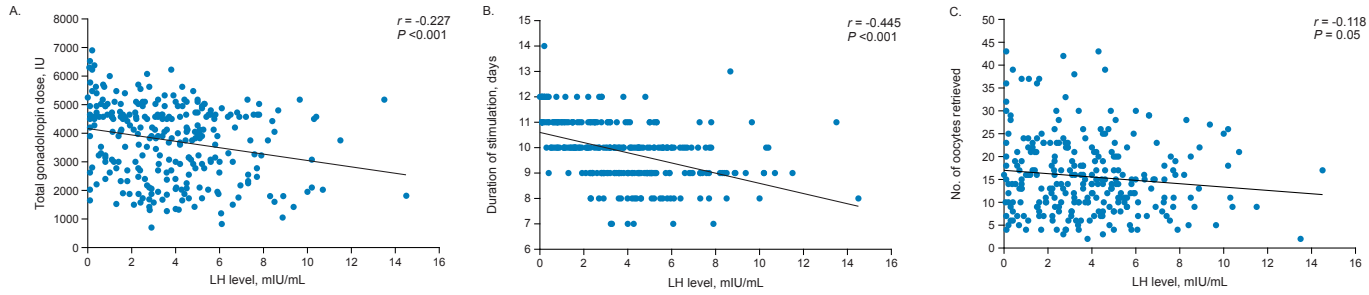
0.161, *P*=0.007; Figure 1A). An analysis of post-OCP LH suppression in subgroups of patients who had received OCP pretreatment (<19 days, 19-23 days, or >23 days) showed greater LH suppression among individuals who had received >23 days of OCP pretreatment versus <19 days (*P*=0.005; Figure 1B).

Effects of LH suppression

Greater LH suppression following OCP pretreatment correlated with increases in the total gonadotropins administered (r=–0.227, P <0.001; Figure 2A) and the number of days of stimulation (r=–0.445, P <0.001; Figure 2B). However, the level of post-OCP LH suppression did not significantly impact the total number of oocytes retrieved (r=–0.118, P=0.05; Figure 2C).

Discussion

In this retrospective study, patients with significant LH suppression after OCP pretreatment in GnRH antagonist cycles required a longer duration of ovarian stimulation and a higher cumulative dosage of gonadotropins to reach follicular maturity, consistent with previous studies [5,18-20,23,24]. A longer duration of OCP pretreatment resulted in lower endogenous LH levels, with LH suppression significantly greater in patients who had received >23 days of OCP pretreatment compared with those who had received <19 days of OCP pretreatment. More oocytes were retrieved in patients with greater LH suppression, which may have resulted from better synchronization of the early follicular cohort and thus a greater number of follicles responsive to



Abbreviations: OCP: Oral Contraceptive Pill; LH: Luteinizing Hormone

Figure 2: Effects of post-OCP LH suppression. Correlations between post- OCP LH level and (A) total gonadotropin dose, (B) stimulation duration, and (C) oocytes retrieved.

gonadotropin stimulation [2,3]. Fertilization rate, implantation rate, and pregnancy outcomes, including clinical pregnancy and live birth rates, were similar in patients with LH levels ≤1.5 mIU/mL and those with LH levels >1.5 mIU/mL on the first day of stimulation.

The outcomes of the current study are consistent with those in another study that assessed OCP pretreatment in GnRH antagonist cycles with additional LH supplementation [20]. Patients with greater suppression of endogenous LH (≤1.2 mIU/mL) required a longer duration of stimulation compared with patients who had post-OCP LH levels of >1.2 mIU/mL (10.2 vs. 9.4 days; *P*=0.028), but demonstrated a higher clinical pregnancy rate (50% vs. 20%; *P*=0.026). However, the small sample sizes (n=17 and n=60, respectively) of the study impeded any clinically meaningful conclusions. Nevertheless, the data suggest that LH supplementation may help improve outcomes in patients following profound suppression of LH after OCP pretreatment. A separate study showed that LH supplementation in oocyte donors undergoing OCP pretreatment prior to a GnRH antagonist cycle improved implantation rates in these recipients [25]. Furthermore, the addition of recombinant LH has been shown to improve outcomes in poor responders in GnRH agonist cycles [26].

Several clinical studies have reported similar live birth rates and/or ongoing pregnancy rates in GnRH antagonist protocols with or without OCP pretreatment [5,9,14,27], with these cumulative findings further supported by systematic reviews and meta-analyses [4,21]. In contrast, a Cochrane review evaluating the use of oral contraceptives in ovarian stimulation protocols reported lower clinical pregnancy rates, a longer duration of stimulation, and higher gonadotropin consumption with OCP pretreatment in GnRH antagonist cycles. However, the authors acknowledged that most of the studies included in the review were small and of poor quality [28]. A meta-analysis of 6 randomized controlled trials also reported significantly lower ongoing pregnancy rates in GnRH antagonist cycles utilizing OCP pretreatment compared with antagonist cycles without pretreatment (–5% difference) [22]. OCP pretreatment was also found to be associated with significant increases in the duration of stimulation (1.3 days) and gonadotropin consumption (360 IU). Of note, only rFSH (without the addition of LH activity) was used for ovarian stimulation in all 6 of the included studies, and it is possible that, had a mixed protocol (i.e., FSH+LH) been used, these studies may have found similar outcomes between the OCP pretreatment and non-pretreatment groups.

OCP pretreatment has also been associated with profound suppression of endogenous LH (<0.5 mIU/mL) in a subset of women and may be associated with reduced ovarian response and early pregnancy loss [18-20]. A randomized controlled study reported significantly higher early pregnancy loss in GnRH antagonist cycles with OCP pretreatment compared with cycles without pretreatment (36.4% vs. 21.6%) [14]. In contrast, a separate retrospective study found that OCP pretreatment in GnRH antagonist cycles did not result in increased rates of early pregnancy loss when the majority of cycles (83%) were supplemented with hMG or LH. Outcomes were not reported for the 17% of patients who did not receive supplementation [29].

In the previously mentioned meta-analysis of 6 clinical studies, stimulation was initiated at varying times after cessation of OCP pretreatment (2-5 days) [22], which may have also affected outcomes. Another study demonstrated that, within 5 days following OCP treatment cessation, endogenous FSH and LH returned to levels similar to those of a natural cycle, although the follicular cohort remained homogeneous [6]. Initiating stimulation within 5 days of OCP pretreatment may result in a poorer and slower response [1,6] and may increase the duration of stimulation and the amount of gonadotropin required. Thus, it is recommended that OCP pretreatment be stopped 5 or even 6 days prior to initiating ovarian stimulation in patients who are expected to be high responders and in those with hypothalamic amenorrhea. Conversely, patients with an infertility diagnosis of diminished ovarian reserve may benefit from a very short OCP duration and cessation of OCP pretreatment just 3 to 4 days before initiating ovarian stimulation. Further research will help determine if stimulation should be initiated in patients regardless of LH suppression status, or if it is best to delay stimulation until LH levels have normalized.

In our study, hCG was administered to induce final follicular maturation. The use of an hCG trigger has been associated with an increased risk of OHSS in some patients [30]. GnRH antagonist protocols that utilize a GnRH agonist, either alone or in combination with a low dose of hCG (dual trigger) to induce ovulation, have been shown to minimize the risk of OHSS [31]. A recent retrospective study of GnRH antagonist cycles identified long-term OCP use (i.e., OCP use upon the patient's initial clinical visit), a practice often utilized with egg donors, as a risk factor for suboptimal response to a GnRH agonist or dual trigger (defined as serum LH <15 mIU/mL on the morning after trigger) [32]. These findings suggest that a GnRH agonist or dual trigger may not be appropriate for use in patients with profound pituitary suppression. A prospective cohort study evaluating the use of OCP pretreatment in GnRH antagonist cycles reported reduced risk of OHSS with OCP pretreatment in high-responder patients, even with the use of an hCG trigger [33], suggesting that alternative trigger methods may not be needed to prevent OHSS when OCP pretreatment is used in GnRH antagonist cycles. Additional studies are needed to establish the relationship between OCP pretreatment and reduced risk of OHSS in both GnRH agonist and antagonist cycles.

Limitations of this study include the retrospective design,

relatively small sample size, and the lack of a control group in which no patients received OCP pretreatment. Furthermore, this study was conducted prior to the routine use of advanced preimplantation genomic screening techniques, which have been shown to improve IVF outcomes [34]. Prospective studies in a greater number of patients, including those who undergo embryo biopsy and genetic screening, are needed to better characterize the impact of OCP pretreatment in GnRH antagonist cycles.

Conclusion

In summary, women with profound LH suppression following OCP pretreatment demonstrated comparable prognosis compared with women who did not, despite requiring a longer duration of stimulation and a higher total gonadotropin dose. The addition of LH activity with highly purified hMG during stimulation may have helped to improve outcomes in patients with greater LH suppression. Larger prospective studies are needed to better define the effects of profound pituitary suppression following OCP pretreatment and to optimize the use of OCP pretreatment in GnRH antagonist cycles.

Declarations

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Competing interests

Jane Ruman was a full-time employee of Ferring Pharmaceuticals, Inc. at the time of manuscript development. Gerardo Vela, Martha Luna, Benjamin Sandler and Alan B Copperman have no relevant competing interests to disclose.

Author contributions

Gerardo Vela, Jane Ruman, and Alan B Copperman participated in the study conception and design, and with the collection, analysis, and interpretation of the data. Martha Luna and Benjamin Sandler participated in the study conception and design. All authors participated in the development of the manuscript and approved the final version of the manuscript for publication.

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