Cycle day, estrogen level, and lead follicle size: analysis of 27,790 in vitro fertilization cycles to determine optimal start criteria for gonadotropin-releasing hormone antagonist

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Objective: To determine the optimal criteria at which to start GnRH antagonists during controlled ovarian hyperstimulation (COH) for in vitro fertilization (IVF).
Design: Retrospective clinical cohort.
Setting: IVF clinics.
Patient(s): Women undergoing fresh autologous IVF using GnRH antagonist for ovulation suppression during COH.
Intervention(s): Measurement of lead follicle size, E_2 level, and cycle day of stimulation on day of antagonist initiation.
Main Outcome Measure(s): Clinical pregnancy rate (PR).
Result(s): The highest clinical PR was achieved when the antagonist was started when a lead follicle reached 14–15.9 mm in size (mean clinical PR 21.3; 95% confidence interval [CI] 19.3, 23.6) on cycle day 6 (mean clinical PR 22.2; 95% CI 17, 28.4), or when the E_2 level was between 500 and 599 pg/mL (mean clinical PR 25.4; 95% CI 19.5, 32.4). Starting antagonists when the E_2 level was <300 or $>1,100$ pg/mL reduced the odds of clinical pregnancy by 40% (odds ratio 0.60, 95% CI 0.5, 0.7).
Conclusion(s): Cycle day, E_2 level, and follicle size at time of antagonist start are all independent predictors of a clinical pregnancy after IVF. Initiating antagonists when the E_2 level is extremely low (<300 pg/mL) or extremely high ($>1,100$ pg/mL) significantly reduces the odds of pregnancy. (Fertil Steril® 2018;109:633–7. ©2017 by American Society for Reproductive Medicine.)
Key Words: GnRH antagonist, in vitro fertilization, pregnancy outcomes

Gonadotropin-releasing hormone antagonists were introduced in the 1990s as a novel way of inhibiting the premature LH surge during ovarian hyperstimulation (1). Despite widespread use, few aspects of antagonist administration have been standardized and significant variation in practice patterns exist. Although some practitioners standardize administration and begin the antagonist on a predetermined cycle day of stimulation (known as a fixed start), others rely on feedback from each cycle, including size of the lead follicle to individualize timing of antagonist start (known as a flexible start) (1, 2). Results from studies comparing these two protocols have been mixed (3–5). However, early evaluation comparing the fixed and flexible protocol strategies focused on reducing unnecessary use of the GnRH antagonist (GnRH-a) instead of more efficiently preventing premature LH surge or improving IVF outcomes (4).

Criteria as to when to start an antagonist during flexible start protocols are also not standardized. Practitioners use various parameters such as

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cycle day (CD), lead follicle size (FS), and E_2 levels and within each parameter criteria vary.

Given emerging evidence that altered levels of P and E_2 are associated with poor pregnancy outcomes, hormone profiles during IVF stimulation might represent one area requiring further exploration (6, 7). The American Society for Reproductive Medicine (8) and a Cochrane review (9) have concluded that the decrease in clinical PR when using a GnRH-a protocol is not attributable to chance, and more study is needed to determine the ideal timing of GnRH-a start during IVF cycles (1).

The objective of our study was to use a large multicenter database of >27,000 IVF cycles to determine the optimal criteria at which to start GnRH-a during controlled ovarian hyperstimulation (COH) for IVF. We hypothesized that E_2 levels, lead FS, and CD on day of antagonist initiation would all be independent and important predictors of IVF success.

MATERIALS AND METHODS

This study was considered to be exempt for review by the University of North Carolina Institutional Review Board. We conducted a retrospective cohort study of 34,862 antagonist IVF cycles from 20 IntegraMed clinics performed between 2013 and 2015 in the United States. Cycles were included if they were antagonist IVF cycles intended for fresh transfer at cycle start. Cycles were excluded from analyses if they were converted to a freeze all. Primary outcome was clinical pregnancy rate (PR) defined as a positive fetal cardiac activity on first trimester ultrasound. All data were provided to the research team deidentified. Demographic information provided included maternal age at cycle start, nulliparity, race, primary diagnosis, number of prior IVF cycles, and method of fertilization.

Statistical Analysis

Descriptive statistics for CD, E_2, and lead FS on day of antagonist start were first performed to assess distributions and aid in categorization of parameters for all statistical analyses. Estradiol (in picograms per milliliter) on day of antagonist start was modeled in 13 categories: 0–99, 100–199, 200–299, 300–399, 400–499, 500–599, 600–699, 700–799, 800–899, 900–999, 1,000–1,099, 1,100–1,199, and ≥1,200. Lead FS (in millimeters) on day of antagonist start was modeled in six categories: 0–4.9, 5–9.9, 10–11.9, 12–13.9, 14–15.9, 16–19.9, and ≥20. Cycle day on day of antagonist start was modeled in seven categories: CD 1–4, CD5, CD6, CD7, CD8, CD9, and ≥CD10. Subsequently the frequency and PR for each combination of start parameters was determined.

A multivariate regression model was created including the antagonist start parameters (CD, E_2, and lead FS) and covariates (maternal age at cycle start, primary diagnosis, race, nulliparity, method of fertilization) to determine the range of values for each parameter where clinical PR was optimized. Maternal age at cycle start was modeled as a continuous variable; all other covariates were categorized to aid in interpretation: primary diagnosis (diminished ovarian reserve, endometriosis, tubal disease, male factor infertility, ovulatory disorder, uterine factor, unexplained, other/unknown); race (white, black, Asian, other); nulliparous (yes/no), method of fertilization (intracytoplasmic sperm injection [ICSI], conventional, mixed ICSI/conventional).

Based on the findings of the adjusted multivariate regression model, which determined the range of values for each parameter where clinical PR was maximized, categories for CD, E_2, and FS were further collapsed into dichotomous variables. These dichotomous variables for each of CD, E_2, and FS were subsequently analyzed in a multivariate regression model to determine whether there was a single parameter that resulted in a significantly higher clinical PR when compared with the other two parameters.

RESULTS

Observations from 27,790 IVF cycles from 20 IntegraMed IVF clinics were included in the final analyses. Fifty-five percent of cycles (n = 15,360) had complete observations for E_2, lead FS, and CD at time of antagonist start. Data were missing for E_2 and FS on day of antagonist start in 44% of cycles (n = 12,231 and n = 12,115, respectively) and for CD in 6% (n = 1,816) of cycles. This was most likely because some women were not seen the day they were instructed to begin GnRH-a and therefore did not have ultrasound or laboratory data recorded. The mean maternal age was 35 ± 5 years, with most participants of white race (54%), multiparous (52%), and undergoing their first IVF cycle (58%). The most common diagnoses for couples were male factor infertility (20%), diminished ovarian reserve (18%) and unexplained infertility (17%). Intracytoplasmic sperm injection was performed in 45% of IVF cycles (Table 1).

The mean E_2 and FS values were 734 pg/mL (SD 548) and 14.8 mm (SD 3.2) with a median CD7 (interquartile range CD6, 8) on day of antagonist start. The average number of oocytes retrieved was 15.1 (SD 9.9), and the overall unadjusted clinical

TABLE 1

Antagonist cycle baseline characteristics (n = 27,790).

Mean age at start of stimulation (y)	**35 (SD 5.4)**
Primary diagnosis, n (%)	
Male infertility	5,548 (20)
Diminished ovarian reserve	5,120 (18)
Unexplained	4,677 (17)
Ovulation disorder	2,785 (10)
Tubal disease	2,098 (7)
Endometriosis	1,065 (4)
Uterine factor	497 (2)
Other/unknown	6,000 (22)
Nulliparous (%)	13,336 (48)
Cycles with prior fresh cycle, n (%)	11,659 (42)
Race, n (%)	
White	15,073 (54)
Asian	4,065 (15)
Black	2,554 (9)
Other/unknown	6,098 (22)
Mode of insemination, n (%)	
Conventional	11,879 (43)
Intracytoplasmic sperm injection	12,647 (45)
Other/unknown	3,264 (12)

Schumacher. Criteria for initiation of GnRH-a. Fertil Steril 2017.