Serum human chorionic gonadotropin levels on the day before oocyte retrieval do not correlate with oocyte maturity

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Objective: To evaluate the correlation of preretrieval quantitative serum hCG level with oocyte maturity.
Design: Retrospective cohort study.
Setting: Military assisted reproductive technology (ART) program.
Patient(s): Fresh autologous ART cycles.
Intervention(s): Serum hCG level the day before oocyte retrieval.
Main Outcome Measure(s): Linear regression was used to correlate serum hCG levels and oocyte maturity rates. Normal oocyte maturity was defined as $\geq$75% and the Wilcoxon rank sum test was used to compare serum hCG levels in patients with normal and low oocyte maturity. Threshold analysis was performed to determine hCG levels that could predict oocyte maturity.
Result(s): A total of 468 ART cycles were analyzed. Serum hCG level was not correlated with hCG dose; however, it was negatively correlated with body mass index (BMI). Serum hCG levels did not differ between patients with oocyte maturity of $<$75% and $\geq$75%. Serum hCG levels did not correlate with oocyte maturity rates. Receiver operator characteristic and less than efficiency curves failed to demonstrate thresholds at which hCG could predict oocyte maturity.
Conclusion(s): Serum hCG levels were not correlated with oocyte maturity. Although a positive hCG was reassuring that mature oocytes would be retrieved for most patients, the specific value was not helpful. (Fertil Steril® 2013;99:1610–4. ©2013 by American Society for Reproductive Medicine.)
Key Words: Assisted reproductive technologies, infertility, in vitro fertilization

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Human chorionic gonadotropin has been used for oocyte maturation induction during assisted reproduction cycles for more than 30 years (1). Because of the biochemical similarity between LH and hCG their cellular effects are moderated by a single polypeptide known as the LH/hCG receptor. This allows hCG to be used as a surrogate for the LH surge during the controlled ovarian hyperstimulation (COH) portion of assisted reproductive technology (ART). After administration of hCG, oocytes resume meiosis and oocyte retrieval is timed 34–36 hours later (2, 3).

Retrieving a higher percentage of mature oocytes correlates with pregnancy and live birth in ART (4). Consequently, ensuring that oocytes are mature upon retrieval is an important component of the simulation process in ART (5, 6). Oocyte maturity has been correlated with patient age,

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differences in COH dosing protocols, follicular steroid hormone levels, and duration of ovarian stimulation (7–9).

The endogenous LH surge triggers completion of the first meiotic division, follicular rupture, oocyte maturation, and ovulation. Because the hCG trigger is used as a surrogate for the LH surge in ART, serum levels of hCG after administration may be evaluated to assess whether they have an influence on clinical outcomes during ART. Previous studies have demonstrated that serum values of hCG on the day after injection are similar using different routes of injection (10) and correlated to the patient's body mass index (BMI) (11). However, there are minimal data evaluating the impact of the serum hCG level before oocyte retrieval on ART outcomes. The objective of this study was to evaluate the impact of serum hCG level on oocyte maturity during ART cycles.

MATERIALS AND METHODS

Study Design

This study was a retrospective analysis of 468 ART cycles performed at Walter Reed National Military Medical Center-Bethesda from December 2010 through April 2012. Institutional Review Board approval was obtained. All fresh autologous ART cycles proceeding to oocyte retrieval during the study period were included in the analysis. Exclusion criteria were frozen ET cycles and cycles cancelled before oocyte retrieval due to poor response. Measurement of serum hCG level on the day before oocyte retrieval was initiated in our program in December 2010 as a mechanism to insure proper hCG administration before retrieval. The study period represented the first year and a half of the new protocol.

Stimulation Protocol

All patients received a stimulation protocol of microdose flare or luteal dose lupron pituitary down-regulation with recombinant FSH and urinary hMG ovarian stimulation, as previously described (11). An evening injection of IM hCG (APP pharmaceuticals/USA) at a dose of 5,000 or 10,000 IU was administered when three or more follicles were more than 18 mm in mean diameter (12). All patients undergoing stimulation in our program received this formulation from the facility pharmacy. Patients were given the 5,000-unit dose of hCG if they had an E_2 >5,000 pg/mL or were given antagonist rescue for ovarian hyperstimulation syndrome (OHSS) risk (12). Serum hCG levels were measured by commercially available ELISA kit on the morning after hCG administration. The detection limit is 0.7 mIU/mL and the intra-assay and interassay coefficients of variation (CV) are 3.2% and 4.9%, respectively. Ultrasound-guided transvaginal oocyte retrieval was performed 36 hours after hCG injection and ET was performed either 3 or 5 days after oocyte retrieval depending on patient history and embryo quality. Luteal phase was supported with IM P in oil or vaginal P tablets depending on patient history and preference (12).

Outcomes

The primary outcome of the study was oocyte maturity. Oocyte maturity rates were calculated as the number meiosis II zygotes per patient divided by the number of oocyte retrieved, determined by the presence of a polar body to indicate that the zygote had completed meiosis II. Normal oocyte maturity was defined as ≥75% and poor oocyte maturity was defined as <75% (7, 12, 13).

Statistics

Univariate linear regression was used to correlate serum hCG levels with oocyte maturity rates. Multivariate linear regression was used to control for potential confounders to include BMI, age, and dose of hCG. The Wilcoxon rank sum test was used to compare nonparametric continuous data and the Student's *t* test to compare parametric continuous data. In addition, patients with serum hCG level below the 5th percentile (hCG ≤50 mIU/mL) were compared to patients with hCG level above the 95th percentile (≥300 mIU/mL). To determine whether there was an hCG threshold below which abnormal oocyte maturity occurred, less than efficiency curves were generated. The curves calculated the oocyte maturity below each hCG threshold beginning at <40 mIU/mL and continuing in increments of 10 mIU/mL. Thresholds values were set such that any value <75% would be considered abnormal maturity rate. Data were analyzed with SPSS software (IBM).

RESULTS

Four hundred sixty-eight ART cycles met inclusion criteria and were included in the analysis. When comparing differences between patients with normal and low oocyte maturity, there was no statistically significant difference between the two groups with respect to age, ovarian reserve, pituitary down-regulation, days of stimulation, BMI, and E_2 levels on the day of serum hCG measurement (Table 1). Mean serum hCG levels for the entire cohort were 372 ± 191 mIU/mL (range, 27–700 mIU/mL). Fifty-seven patients received a dose of 5,000 IU of hCG and 411 patients received a 10,000-IU dose. Oocyte maturity was similar between patients receiving 5,000 and 10,000 units of hCG, respectively (75.6% ± 19% vs. 76.7% ± 18%; *P*=not significant [NS]).

TABLE 1

Comparison of demographics in patients with oocyte maturity <75% and ≥75%.

	Oocyte maturity <75% (n = 180)	Oocyte maturity ≥75% (n = 288)
Age (y)	34 ± 5	35 ± 5
Days of stimulation	11 ± 2	11 ± 3
BMI (kg/m^2)	26.62 ± 4.77	25.91 ± 4.47
Day 3 FSH (IU/L)	6.9 ± 2.49	6.78 ± 2.2
Total AFC	16 ± 11	16 ± 8
E_2 on day of hCG administration +1 (pg/mL)	7,421 ± 4,648	3,953 ± 2,016
hCG peak (mIU/mL)	132 ± 86	145 ± 95

Note: There were no differences in age, days of stimulation, body mass index (BMI), ovarian reserve, E_2, and hCG levels on day of hCG administration +1. Data presented as mean ± SD. AFC = antral follicle count.

Levy. Preretrieval serum hCG. Fertil Steril 2013.