How low is too low? Cycle day 28 estradiol levels and pregnancy outcomes

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Objective: To determine the utility of cycle day 28 estradiol (E_2) levels in predicting pregnancy outcomes after IVF.
Design: Retrospective, cohort study.
Setting: Academic medical center.
Patient(s): All IVF cycles resulting in a positive pregnancy test result at our center between January 2007 and December 2012 were included.
Intervention(s): In vitro fertilization with fresh embryo transfer.
Main Outcome Measure(s): A total of 5,471 IVF cycles were identified. Cycles were stratified by day-28 E_2 level (pg/mL) into three groups: A: $\leq$50; B: 51–100; and C: >100. Outcomes measured were live birth, clinical pregnancy, biochemical, ectopic, and spontaneous abortion rates.
Result(s): There were 806, 588, and 4,077 IVF pregnancies in groups A, B, and C, respectively. Live birth rates were lower in groups A (15.4%) and B (41.2%) compared with group C (77.4%), representing decreased odds of live birth in patients with E_2 levels of $\leq$50 pg/mL (odd ratio 0.05, 95% confidence interval 0.04–0.07) and in patients with levels of 51–100 pg/mL (odds ratio 0.20, 95% confidence interval 0.17–0.25) compared with patients with levels >100 pg/mL. Rates of biochemical and ectopic pregnancies were higher in groups A (66.5%, 6.20%) and B (30.7%, 3.57%) compared with group C (7.31%, 0.66%). An hCG level <50 mIU/mL was associated with increased odds of a biochemical pregnancy and decreased odds of a live birth.
Conclusion(s): Low E_2 levels early in IVF pregnancies are associated with poorer pregnancy outcomes. Estradiol can be used alone or in conjunction with hCG levels to predict the odds of a live birth. (Fertil Steril® 2016;105:905–9. ©2016 by American Society for Reproductive Medicine.)
Key Words: Early pregnancy, estradiol level, IVF, predictive value

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The role of the corpus luteum before and after implantation has been well described. Estradiol (E_2) and progesterone (P) produced by the corpus luteum regulate pregnancy's initial stages and sustain pregnancy until the luteal–placental shift (1). Therefore, early luteal phase hormone levels may be useful in predicting the likelihood of conception as well as pregnancy outcome.

Several studies have examined the use of luteal E_2 to predict pregnancy in assisted reproductive technology cycles. Its role, however, remains controversial. Significant differences in luteal phase E_2 levels between conception and nonconception cycles have been described, and early luteal phase increases in E_2 have been observed in pregnant women (2–4). In contrast, other studies have failed to show a correlation between luteal phase E_2 levels and IVF cycle outcomes (5). This variation in the literature highlights the poorly understood clinical relevance of E_2 levels after controlled ovarian stimulation protocols. Although high E_2 levels are generally thought to signify a healthy pregnancy, little has been published regarding the prognostic value of a low level. The purpose of this study was to determine whether low E_2 level at the time of a first positive pregnancy test after IVF can be used to predict pregnancy outcomes.

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MATERIALS AND METHODS

Cycle Inclusion Criteria

This study was approved by the Weill Cornell Medical College Institutional Review Board. Cycles selected for inclusion were identified after review of all IVF cycles performed from January 2007 through December 2012 at The Ronald O. Perelman and Claudia Cohen Center for Reproductive Medicine of Weill Cornell Medical College. All fresh IVF cycles that resulted in a cycle day 28 β-hCG (hCG) level >5 mIU/mL were included. Exclusion criteria included cycles that resulted in a negative day-28 pregnancy test result, cycles for which day-28 hCG and/or E_2 measurement was not performed or a result was not documented, canceled cycles, donor oocyte recipient cycles, and cycles in which a fresh embryo transfer (ET) did not occur. Cycles using luteal phase E_2 supplementation of any variety were also excluded. Cycles were stratified a priori into three groups by day-28 E_2 level: group A ($E_2 \leq 50$ pg/mL), group B (E_2 51–100 pg/mL), and group C ($E_2 > 100$ pg/mL). A total of 16,084 IVF cycles were analyzed for inclusion.

Clinical Protocols

Controlled ovarian hyperstimulation (COH), oocyte retrieval, and ET were performed per our standard protocols (6, 7). Patients were down-regulated with either GnRH agonist (Lupron, Abbott Pharmaceuticals) followed by stimulation with gonadotropins (Follistim, Merck; Gonal-F, EMD-Serono; and/or Menopur, Ferring) or were stimulated with gonadotropins until criteria were met for pituitary suppression with a GnRH antagonist (0.25 mg Ganirelix acetate, Organon; 0.25 mg Cetrotide, EMD-Serono). The GnRH agonists were used in either long or short protocols. Luteal suppression with GnRH agonist was started 8 days after an LH surge. For GnRH-antagonist cycles, Ganirelix or Cetrotide were administered at either a lead follicle diameter of 13 mm or an E_2 level >300 pg/mL. Luteal suppression for antagonist-based protocols, when used, was achieved with E_2 patches started 8–10 days after LH surge or oral contraceptive pills. All protocols were selected with reference to age, weight, ovarian reserve, and prior response to COH, as well as individual physician preference. Patients were monitored with serial E_2 measurements and transvaginal ultrasounds. Human chorionic gonadotropin (3,300–10,000 IU) (Profasi, EMD-Serono; Novarel, Ferring Pharmaceuticals; or Pregnyl, Schering-Plough) was administered when deemed clinically appropriate, most often when two follicles reached 17 mm in diameter. Because of the need for E_2 luteal phase support, cycles using GnRH agonist trigger either alone or in conjunction with low-dose hCG were excluded. Retrieval was performed in the standard fashion 35 to 36 hours after trigger administration. Day of oocyte retrieval was considered cycle day 14, irrespective of length of COH. Luteal P supplementation was begun 1 day after oocyte retrieval with the use of 25–50 mg P (IM), depending on E_2 response. Embryo transfers were performed 3 or 5 days after oocyte retrieval (cycle day 17 or 19, respectively) via a Wallace catheter (Marlow/Cooper Surgical). On the morning of cycle day 28, patients' blood was drawn at our center, and serum was analyzed for E_2, P, and hCG concentrations. All hormone measurements were performed on site at the Center for Reproductive Medicine's Reproductive Endocrinology Laboratory using a Siemens Immulite 2000 immunoassay system. Analyzers in our laboratory undergo daily quality control monitored by the New York State Department of Health, and clinical validation between machines is performed every 6 months. The sensitivity of the E_2, hCG, and P assays are 20 pg/mL, 0.4 mIU/mL, and 0.2 ng/mL, respectively, and all intra- and interassay variation coefficients are $<10\%$. All samples with E_2 levels $>1{,}200$ pg/mL are diluted before repeating the assay to obtain results within the range of maximum accuracy.

Outcome Variables Assessed

The primary outcome studied was live birth rate. Secondary outcomes included clinical pregnancy, biochemical, ectopic, and abortion rates. Live birth rate was defined as the proportion of cycles resulting in at least one live-born child delivered at >24 weeks' gestation out of all included pregnancy cycles. Clinical pregnancy rate was defined as the proportion of included cycles resulting in at least one intrauterine gestational sac with yolk sac, fetal pole, and fetal cardiac activity. Biochemical pregnancy rate was defined as the proportion of cycles resulting in a transient elevation in hCG level without ultrasound confirmation of a gestational sac per all included cycles. Abortion rate was defined as number of anembryonic pregnancies, missed abortions, or spontaneous abortions before 20 weeks' gestation per included cycles. Ectopic pregnancy rate was defined as the proportion of cycles resulting in a sonographically or surgically confirmed extrauterine gestation or a pregnancy of unknown location treated empirically with methotrexate. Baseline patient demographic and IVF characteristics were collected for all included cycles. Primary and secondary outcomes were compared between groups A and C and groups B and C. Groups A, B, and C were then substratified by cycle day 28 hCG level. Pregnancy outcomes within these groups were compared between cycles with day-28 hCG levels of ≤ 50 mIU/mL and >50 mIU/mL for secondary analysis.

Statistical Analysis

Categorical variables were expressed as number of cases (n) and percentage of occurrence (%). Continuous variables were checked for normality and expressed as mean $\pm$ SD. Chi-squared (χ^2) with Mantzel-Hansel correction and Fisher's exact test were used for categorical variables. One-sided analysis of variance with Bonferroni correction was used for continuous variables. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated for outcomes in groups A and B compared with group C. Analyses were implemented in STATA version 13 (StataCorp).

RESULTS

Of the 16,084 fresh IVF cycles performed during the study period, 5,471 cycles met inclusion criteria. The numbers of cycles in groups A, B, and C were 806, 588, and 4,077, respectively. Demographic and IVF characteristics of the three