Occult abnormal pregnancies after first post–embryo transfer serum beta-human chorionic gonadotropin levels of 1.0–5.0 mIU/mL

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Objective: To assess the occult pregnancy rate after "negative" first post−embryo transfer (ET) serum β-hCG results.
Design: Two-part retrospective cohort study and nested case series.
Setting: University-based fertility center.
Patient(s): A total of 1,571 negative first post-ET serum β-hCG results were included in the study; 1,326 results (primary cohort, June 2009–December 2013) were initially reported as <5 mIU/mL and 245 results (secondary cohort, January 2014–March 2015) were reported as discrete values from 1.0 to 5.0 mIU/mL.
Intervention(s): None.
Main Outcome Measure(s): Rates of occult pregnancy, ectopic pregnancy, and complications after negative first post-ET serum β-hCG results.
Result(s): A total of 88.8% (1,178/1,326) of the negative first post-ET results reported as <5 were actually <1.0 mIU/mL. Occult pregnancy was incidentally identified in 1.2% (12/1,041) of subjects with follow-up. Six had ectopic pregnancies, and seven experienced serious complications; 11 (91.7%) of the 12 occult pregnancies had a first post-ET serum β-hCG level of 1.0–5.0 mIU/mL and 1 (8.3%) <1.0 mIU/mL. All pregnancies with serious complications had initial β-hCG levels of 1.0–5.0 mIU/mL. Of the 245 results reported as discreet values, occult pregnancies were diagnosed in 5.5% (9/163) of subjects with follow-up. One had an ectopic pregnancy, which was treated with methotrexate. There were no serious complications in the secondary cohort.
Conclusion(s): The majority of negative first post-ET serum β-hCG levels are <1.0 mIU/mL. Results from 1.0 to 5.0 mIU/mL may fail to exclude abnormal pregnancy and are associated with poor outcomes compared with β-hCG levels <1.0 mIU/mL. Serial serum β-hCG may be warranted in this population. (Fertil Steril® 2016;105:938–45. ©2016 by American Society for Reproductive Medicine.)
Key Words: Ectopic pregnancy, serum β-hCG, in vitro fertilization

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In assisted reproductive technology (ART) cycles, pregnancy is routinely diagnosed with the use of serum β-hCG testing 11 days after cleavage-stage embryo transfers (ETs) and 9 days after a blastocyst ET (1–5). A serum β-hCG level of <5.0 mIU/mL is widely accepted to be a negative result and specific values <5 mIU/mL are typically not reported (6). Although many have studied the predictive value of serum β-hCG levels >5 mIU/mL after ET (7–10), limited data exist on the accuracy of a "negative" serum β-hCG result, especially after an ET.

Assisted reproductive technology (ART) is associated with an increased risk of ectopic pregnancy, estimated to be ~2% of all ETs (11). Failure to diagnose ectopic pregnancy can result in serious complications requiring medical or surgical intervention. Reliability

Received October 16, 2015; revised and accepted November 25, 2015; published online December 15, 2015.
B.-S.L.M. has nothing to disclose. A.B. has nothing to disclose. C.S. has nothing to disclose. L.E. has nothing to disclose. C.B. has nothing to disclose. J.C.N. has nothing to disclose.
Initial results presented as a poster at the American Society for Reproductive Medicine Annual Meeting, October 18–22, 2014, Honolulu, Hawaii. Nested case series presented as a poster at the Pacific Coast Reproductive Society Annual Meeting, March 19–23, 2014, Indian Wells, California.
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Fertility and Sterility® Vol. 105, No. 4, April 2016 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2015.11.049

of the first post-ET serum β-hCG result to exclude occult pregnancy is paramount in ensuring proper patient care.

The primary aim of the present study was to investigate the rate at which an occult pregnancy was recognized after a first post-ET serum β-hCG level <5 mIU/mL and the rate of resulting complications. Our secondary aim was to evaluate whether a change in reporting policy to discrete serum β-hCG values ≥1.0 mIU/mL decreased complications from occult pregnancies. We hypothesized that negative first post-ET serum β-hCG values from 1.0 to 5.0 mIU/mL may not exclude occult pregnancies, particularly ectopic pregnancies, which without close follow-up are associated with poor outcomes.

MATERIALS AND METHODS

We conducted a two-part retrospective cohort study of all negative first post-ET serum β-hCG results <5.0 mIU/mL after fresh or frozen ETs performed at the University of Connecticut's Center for Advanced Reproductive Services from June 2009 (when in-house testing began) through March 2015. The Institutional Review Board at the University of Connecticut School of Medicine (Farmington) approved this study by expedited board review (IRB no. 14-127-3). All in-house serum β-hCG results <5.0 mIU/mL from tests performed either 11 days after a cleavage-stage ET or 9 days after a blastocyst ET (index hCG) were included in the study. For the initial study cohort (June 2009–December 2013), the electronic medical record reported all negative results as <5 mIU/mL. All included subjects during this time period were clinically managed as not pregnant. However, in the course of this study, we retrospectively unmasked the discrete serum β-hCG values of all included results. For each included index hCG, we also collected the immediate next serum β-hCG value (follow-up hCG) documented in the medical record. Follow-up hCG results were obtained from studies ordered during the course of routine clinical care, typically from baseline serum β-hCG measurements in a subsequent in vitro fertilization (IVF) or frozen embryo transfer (FET) cycle. Patients who did not return for a subsequent cycle or had no additional documented serum β-hCG values after the index hCG were considered to be lost to follow-up.

A second study cohort consisted of all negative first post-ET serum β-hCG results from January 2014 through March 2015. During this time period, the electronic medical record was reprogrammed to report discrete values for all serum β-hCG ≥1.0 mIU/mL. The same retrospective process for collecting follow-up hCG levels was followed, except index hCG results of 1.0–5.0 mIU/mL were routinely repeated 2 days later. Again, patients who did not return for a subsequent cycle or had no additional documented serum β-hCG values after the index hCG were considered to be lost to follow-up.

We queried the electronic medical records for clinical data including demographic information, medical history, cycle type, number and stage of embryos transferred, and pregnancy outcomes from all included subjects. Given the hypothesis that serum β-hCG values from 1.0 to 5.0 mIU/mL may not necessarily exclude pregnancy, we examined all subjects with follow-up hCG results ≥1.0 mIU/mL for potential occult pregnancies. The lead author verified all abstracted data, reviewed the electronic medical records for all subjects with follow-up hCG results ≥1.0 mIU/mL, and categorized each result as either a subsequent unrelated conception or potential occult pregnancy. Subsequent unrelated conceptions were defined by one of the following criteria: 1) documentation of a pregnancy resulting from a new treatment cycle (e.g., insemination cycles, where serum β-hCG is not routinely measured at the baseline); 2) pregnancy arising after a documented ovulation event that occurred after the index hCG; or 3) fetal biometry placing the time of conception after the index hCG. Although the term "occult pregnancy" has previously been used to describe a similar phenomenon (12), for the purpose of this study we defined potential occult pregnancy as a serum β-hCG level ≥1.0 mIU/mL after a negative serum β-hCG that could not be attributed to a subsequent unrelated conception by one of the above criteria. We considered those with serum β-hCG levels that continued to rise beyond the follow-up hCG to be true occult pregnancies. Rates of potential and true occult pregnancies were calculated only from subjects with available follow-up data.

Clinical outcomes for all potential and true occult pregnancies were identified in the electronic medical record. Gestations with an initially rising serum β-hCG that spontaneously declined were categorized as biochemical pregnancies. Subjects were considered to have a spontaneous abortion if a gestational sac was visualized on ultrasound before the loss or chorionic villi were identified on pathology after loss. Ectopic pregnancies were identified based on clinical diagnoses documented in the electronic medical record. These included visualization of an extrauterine gestational sac on ultrasound or pathologic identification of chorionic villi surgically removed from an extrauterine location.

All serum β-hCG testing was performed in house with the use of a Siemens Immulite 2000 (interassay coefficient of variation [CV] 7.4, intra-assay CV 6.2). Differences between groups were analyzed with the use of χ^2, Fisher exact test, or Student *t* test as appropriate. Nonparametric analysis was performed using Mann-Whitney *U* testing. Negative predictive value was calculated by dividing the true negative outcomes by the total negative test results. Significant findings in the bivariate analyses were further analyzed with the use of a logistic regression model for potentially confounding covariables. Statistical analyses were performed with the use of IBM SPSS Statistics v. 21. A two-tailed *P* value of <.05 was considered to be significant.

RESULTS

A total of 1,571 first post-ET negative serum β-hCG test (index hCG) results were included in the study. The primary cohort, where all negative results were reported as <5 mIU/mL and discrete values were retrospectively revealed, included 1,326 results. Figure 1 classifies all of the included results for the primary cohort. The index hCG level was <1.0 mIU/mL in 1,178/1,326 (88.8%) of the results and 1.0–5.0 mIU/mL in 148/1,326 (11.2%) of the results. Table 1 summarizes the demographic and cycle data for the index hCG <1 and the index hCG 1–5 groups. There were no significant