Successful treatment algorithm for evaluation of early pregnancy after in vitro fertilization

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Objective: To evaluate a prospectively implemented clinical algorithm for early identification of ectopic pregnancy (EP) and heterotopic pregnancy (HP) after assisted reproductive technology (ART).
Design: Analysis of prospectively collected data.
Setting: Academic medical center.
Patient(s): All ART-conceived pregnancies between January 1995 and June 2013.
Intervention(s): Early pregnancy monitoring via clinical algorithm with all pregnancies screened using human chorionic gonadotropin (hCG) levels and reported symptoms, with subsequent early ultrasound evaluation if hCG levels were abnormal or if the patient reported pain or vaginal bleeding.
Main Outcome Measure(s): Algorithmic efficiency for diagnosis of EP and HP and their subsequent clinical outcomes using a binary forward stepwise logistic regression model built to determine predictors of early pregnancy failure.
Result(s): Of the 3,904 pregnancies included, the incidence of EP and HP was 0.77% and 0.46%, respectively. The algorithm selected 96.7% and 83.3% of pregnancies diagnosed with EP and HP, respectively, for early ultrasound evaluation, leading to earlier treatment and resolution. Logistic regression revealed that first hCG, second hCG, hCG slope, age, pain, and vaginal bleeding were all independent predictors of early pregnancy failure after ART.
Conclusion(s): Our clinical algorithm for early pregnancy evaluation after ART is effective for identification and prompt intervention of EP and HP without significant over- or misdiagnosis, and avoids the potential catastrophic morbidity associated with delayed diagnosis. (Fertil Steril® 2015;104:932–7. ©2015 by American Society for Reproductive Medicine.)
Key Words: ART, algorithm, ectopic, heterotopic, IVF

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Pregnancies conceived by in vitro fertilization (IVF) are typically monitored by reproductive endocrinologists using both serial human chorionic gonadotropin (hCG) measurements and ultrasound examinations. The purpose is to determine the viability, location, and number of implanting embryos. Of particular concern are ectopic pregnancy (EP) and heterotopic pregnancy (HP) because of the significant potential for morbidity if the diagnosis is delayed.

There is compelling evidence that EPs behave differently than viable, singleton intrauterine pregnancies, having generally lower hCG levels at the same gestational age (1). Retrospective studies of IVF-conceived pregnancies have established that pregnancies with an initial hCG value below 50 IU/L are at particularly high risk for miscarrying or being an EP (2–4). In addition to the initial hCG level, it is common practice to obtain a second hCG approximately 48 hours later to determine the percentage of rise between the two values. This is performed to identify those cases that are more likely to be nonviable; for example, a decrease, plateau, or minimal rise in hCG (<66%) is likely indicative of a failing pregnancy (5).

Multiple lines of evidence suggest that pregnancies conceived via assisted reproductive technologies (ART) with low initial hCG levels or an abnormal rise in hCG deserve special attention with early surveillance and close monitoring, as they are more commonly associated with adverse pregnancy

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outcomes (3, 6–8). Based on these retrospective data, we prospectively implemented a clinical algorithm for monitoring ART pregnancies that combined a strategy of initial and follow-up hCG monitoring as well as patient reporting of specific symptoms to time subsequent ultrasound examinations. The goal of this algorithm was to identify pregnancies at high risk for failing, particularly those that are an EP or HP, and target these pregnancies for an early ultrasound evaluation and hopefully an earlier diagnosis. Conversely, pregnancies at relatively low risk for complications were scheduled for a later ultrasound evaluation at a time when viability can be more reliably determined, thus limiting the number of visits and ultrasound examinations for these patients. Another important goal was avoiding premature intervention in these pregnancies, such as giving methotrexate to a pregnancy of unknown location that subsequently turns out to be a viable intrauterine pregnancy (IUP).

The purpose of this study was to evaluate this clinical algorithm to determine its effectiveness in meeting these clinical goals. We also sought to identify and compare early predictors of all early pregnancy failures after an ART cycle, and to determine if our current algorithm resulted in early, safe and successful treatment of EP and HP.

MATERIALS AND METHODS

Sample Selection

This study was approved by the institutional review board of the University of Iowa (no. 201305736). Any pregnancy conceived via ART between January 1995 and June 2013 at the University of Iowa's Center for Advanced Reproductive Care was included in this study, regardless of type of ART cycle, gamete source, type of embryo transfer, or embryo stage on transfer day. Additionally, we included patients who conceived more than one time in the designated time period.

Study Design

We prospectively collected data for incorporation into an institutional database on every patient undergoing ART. Data were collected on patient characteristics, cycle characteristics, clinical pregnancy details, as well as details of all pregnancy outcomes. Specific treatment details for EP and HP were extracted from a review of the medical records when needed, with data subsequently incorporated into our preexisting ART database.

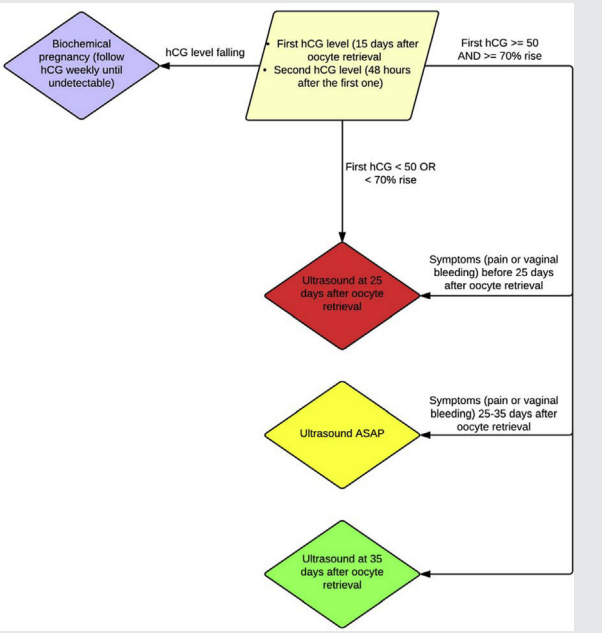
All patients were scheduled for an initial serum hCG level 15 days after oocyte retrieval (first hCG), followed by a repeat hCG level (second hCG) 48 hours later. Every attempt was made to be consistent on the day of first hCG; however, scheduling difficulties permitted some variability in the timing of this blood draw. Regardless, if the first hCG measurement was $<$50 IU/L, or if the percentage rise after 48 hours was $<$70%, an ultrasound was performed 25 days after oocyte retrieval to evaluate for pregnancy location. Alternatively, if the first hCG was $\geq$50 IU/L and the percentage rise in hCG was $\geq$70%, an ultrasound was performed 35 days after oocyte retrieval. If a patient developed pelvic pain or vaginal bleeding in the interim before the ultrasound on day 35, she was instructed to call in and an ultrasound was performed immediately. For purposes of this analysis, an "early" ultrasound was defined as being performed $<$35 days and a "late" ultrasound as $\geq$35 days from the oocyte retrieval. This clinical algorithm is demonstrated in Figure 1.

Biochemical pregnancies, characterized by hCG levels that dropped spontaneously and resolved without any treatment, were not included in this study as ultrasound examinations were not necessary. All cases of pregnancy of unknown location, where a gestational sac could not be visualized either inside or outside the uterus, were investigated with suction curettage. Diagnosis of EP was confirmed by the absence of chorionic villi in the specimen and lack of significant decrease in hCG level after the procedure. Methotrexate injection was avoided until the confirmation of EP diagnosis either as described earlier or by visualization of complex adnexal mass and/or ectopic gestational sac. Some patients elected to undergo hCG monitoring at their local laboratories for convenience; thus, there was some variability in the hCG assays used, due to the great distance that many of our patients travel for IVF treatment. However, all ultrasound examinations were performed at our center. This clinical algorithm of hCG and ultrasound monitoring has been in place at our institution for all the years included in the study.

Data Analysis

Simple statistics were used to describe the outcomes of the clinical algorithm. For testing predictors of early pregnancy

FIGURE 1



Flow diagram of clinical algorithm for early pregnancy evaluation after assisted reproduction technology. Monitoring of human chorionic gonadotropin (hCG) levels and evaluation by ultrasound was performed according to the clinical algorithm as pictorially represented.

Cookingham. Early pregnancy evaluation after IVF. Fertil Steril 2015.