ORIGINAL ARTICLE: ASSISTED REPRODUCTION

# Adverse perinatal outcomes associated with crown-rump length discrepancy in in vitro fertilization pregnancies

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**Objective(s):** To determine whether an association exists between small crown-rump length (CRL) and adverse obstetrical outcomes in pregnancies conceived by IVF and to compare a CRL reference based on IVF pregnancies to a reference based on spontaneous pregnancies.
**Design:** Retrospective cohort study. CRL was classified as small by comparing it with the local university hospital maternal fetal medicine standard and the Monash IVF reference chart.
**Setting:** University-affiliated fertility center.
**Patient(s):** Singleton pregnancies conceived by IVF with ultrasounds performed between 7+0 and 8+6 weeks of gestational age.
**Intervention(s):** None.
**Main Outcome Measure(s):** Pregnancy loss, preterm birth, and low birth weight.
**Result(s):** Included were 940 clinical pregnancies. The overall and CRL-discrepant miscarriage rates were 12.7% and 41%, respectively. When CRL was small, the maternal age-adjusted odds of miscarriage were 13.8 times higher (95% confidence interval [CI], 8.9–21.6). At age 30, small CRL was associated with a 30% risk of miscarriage, versus 61% at age 45. There was no association between small CRL and preterm birth or low birth weight. The sensitivity and specificity for predicting miscarriage from the optimal Monash cut point were 0.69 (95% CI, 0.61–0.77) and 0.84 (95% CI, 0.82–0.87), which were similar to those of the CRL reference based on spontaneous pregnancies.
**Conclusion(s):** Small CRL in IVF pregnancy was strongly associated with miscarriage, especially in the context of advanced maternal age. Small CRL was not associated with preterm birth or low birth weight. A CRL reference based on IVF pregnancies was equivalent to the standard reference for predicting miscarriage. (Fertil Steril® 2017;■:■–■. ©2017 by American Society for Reproductive Medicine.)
**Key Words:** In vitro fertilization, crown-rump length, miscarriage, preterm birth, low birth weight

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A first trimester ultrasound is recommended in naturally conceived pregnancies by the Society of Obstetricians and Gynaecologists of Canada and the American College of Obstetricians and Gynecologists (ACOG) (1, 2). Potentially affected by factors such as ovulatory irregularity, human errors in recalling the last menstrual period, or contraceptive failures, menstrual dating can be unreliable (1, 3, 4). First trimester ultrasound is the most accurate way to establish a pregnancy due date that will better inform obstetrical monitoring and management (1, 2). With in vitro fertilization (IVF), the gestational age (GA) of a pregnancy is irrefutable. This age is calculated from the embryo age and the date of embryo transfer (ET) (2). First trimester ultrasounds are routinely performed after 6–7 weeks of GA in these patients to confirm the viability, growth, location, and amnionicity/chorionicity of the pregnancies (5).

The crown-rump length (CRL) is the measured length of the embryo in the midsagittal plane from the head to rump (2). The CRL is measured at the first ultrasound in both IVF and natural pregnancies. There are multiple CRL references used internationally, each describing a

Received June 29, 2017; revised and accepted September 22, 2017.
K.C. has nothing to disclose. C.D. has nothing to disclose. A.Y.K.A. has nothing to disclose. J.C.H. has nothing to disclose.
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Fertility and Sterility® Vol. ■, No. ■, ■ 2017 0015-0282/$36.00

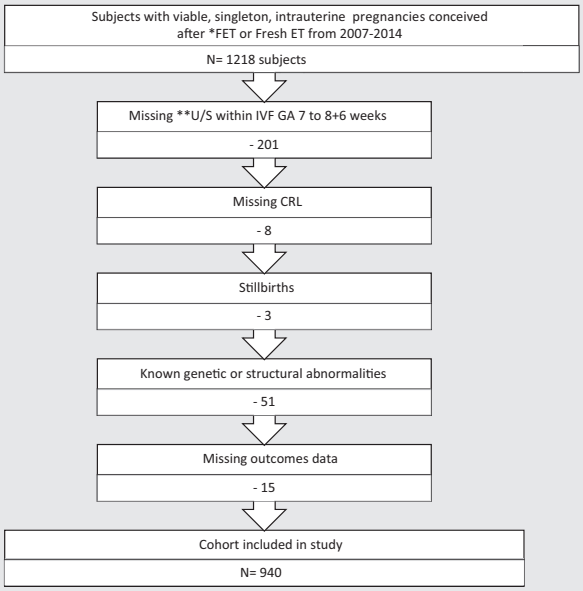
https://doi.org/10.1016/j.fertnstert.2017.09.026

slightly different standard CRL value for each GA (6). In British Columbia (BC), the university hospital CRL reference is published by a government organization, Perinatal Services BC (PSBC). The published values are based on a 1998 study of 1,396 pregnancies that used menstrual dating and were measured by lower resolution ultrasound technology (7, 8).

Early identification of pregnancy risks can be useful for patient counseling and to better monitor a pregnancy. Two studies have demonstrated differences in the CRL references based on IVF populations compared with those based on menstrual dating (6, 9). Smaller than expected CRL has been reported as a risk factor for adverse perinatal outcomes such as miscarriage (10–13), preterm birth (14), and low birth weight (3, 14). Slow fetal heart rate (FHR) at first trimester ultrasound is also associated with an increased risk of miscarriage (12, 15). The present study aimed to investigate whether first trimester ultrasound findings were associated with adverse perinatal outcomes in our IVF population.

We believe this is the first study to evaluate whether the discrepancy in CRL measurement from established standards can predict adverse pregnancy outcomes, such as miscarriage, preterm birth, or low birth weight infants in the IVF patient population. We also aimed to determine whether a CRL reference based on IVF pregnancies would be more predictive compared with an older reference constructed from spontaneously conceived pregnancies.

**FIGURE 1**




Patients with viable, singleton, intrauterine pregnancies conceived after fresh or frozen ET, 2007–2014. *Frozen ET. **Ultrasound.

*Cho. CRL discrepancy in IVF. Fertil Steril 2017.*

## MATERIAL AND METHODS

### Data Collection

A retrospective chart review was performed at a university-affiliated fertility center in Burnaby, Canada. Ethics approval was obtained from the University of British Columbia's clinical research ethics board before data collection (H16-01886). We included patients with a singleton, viable, intrauterine pregnancy conceived via fresh or frozen ET between January 1, 2007, and December 31, 2014. Patients were excluded if they conceived with donor eggs, were diagnosed with multiple gestations, underwent therapeutic termination, presented with undetectable FHR, or were diagnosed with fetal structural/genetic anomalies (Fig. 1). When a biochemical pregnancy was diagnosed, first trimester ultrasound was routinely performed in house or at an outpatient accredited imaging facility. These records were reviewed to identify the CRL and FHR from the first ultrasound performed between 7+0 and 8+6 weeks of GA. The IVF GA was calculated using the formula suggested by ACOG (2). Transvaginal ultrasounds were performed at our facility by physicians specializing in reproductive endocrinology and infertility with GE Logiq 3 or Voluson 730 ultrasound machines. Lastly, the patient demographics and primary outcomes, including live-birth rate, GA at birth, and birth weights, were prospectively collected by the clinic staff as part of the mandatory national reporting of IVF outcomes. These records were linked to each included pregnancy.

### Data Analysis

We compared the recorded CRL to the provincial CRL reference published by PSBC (8) and to the Monash IVF CRL reference published by Delpachitra et al. in 2012 (6). PSBC is a publicly funded provincial organization that publishes best practice guidelines for perinatal care (16). The PSBC reference provides the CRL measurement at the 10th percentile, 50th percentile, and 90th percentile for each GA. As mentioned, the PSBC reference is based on GA calculated from women with regular menstrual cycles (8). The Monash reference is based on the CRL measured at 6–9 weeks GA from 1,268 singleton pregnancies conceived via IVF (6). The Monash chart provides a reference CRL for each GA (6). When comparing with the PSBC reference, a PSBC small CRL was defined as a measurement less than that corresponding to the 10th percentile for GA. Relative to the Monash data, a Monash small CRL was smaller than the reference value >2 days younger than the known IVF GA.

To determine whether the PSBC or the Monash reference was the optimal model to predict pregnancy loss in our population, we constructed a receiver operating characteristic (ROC) curve for the Monash reference by calculating the difference in days between the IVF GA and the Monash GA linked to the measured CRL. The area under the curve (AUC) from the ROC analysis was calculated, and Youden's index (17) was used to determine the optimal cut point for the difference in GA.

We used logistic regression analysis to predict the probability of miscarriage by assigning miscarriage or live birth as independent outcome variables and measurements corresponding to PSBC <10th percentile and Monash >2 days, >3 days, and >4 days smaller as predictors. Given the association of advanced maternal age with miscarriage, age was included as a covariate in the adjusted models for each