The cumulative probability of liveborn multiples after in vitro fertilization: a cohort study of more than 10,000 women

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Objective: To estimate the cumulative probability of liveborn multiples after IVF to improve patient counseling regarding this significant morbidity.
Design: Retrospective cohort study.
Setting: Large academic-affiliated infertility practice.
Patient(s): A total of 10,169 women were followed from their first fresh, nondonor IVF cycle through up to six fresh and frozen IVF cycles from 2000–2010.
Intervention(s): None.
Main Outcome Measure(s): Delivery of a liveborn infant(s).
Result(s): After three IVF cycles the cumulative live birth rate (CLBR) was 53.2%. The singleton, twin, and triplet CLBRs were 38.0%, 14.5%, and 0.7%. After six IVF cycles the CLBR was 73.8%, with 52.8%, 19.8%, 1.3% for singletons, twins, and triplets. Of the 5,433 live births, 71.4% were singletons, 27.1% were twins, and 1.5% were triplets. Women more than 39 years had the lowest incidence of liveborn multiples with CLBRs of 5.2% after three cycles and 9.5% after six cycles. The twin CLBR doubled from cycles 1 through 3 with the rate of increase slowing from cycles 3 through 6. Although very low in absolute terms, the triplet CLBR also doubled from cycles 1 through 3 and doubled again from cycles 3 through 6. Of the 1,970 pregnancies that began as multifetal on ultrasound, 77.4% resulted in liveborn multiples.
Conclusion(s): Providers should be aware of the cumulative probability of liveborn multiples to effectively counsel patients on this important issue. With nearly three-quarters of all women having live birth after up to six IVF cycles, it is encouraging to report a low incidence of liveborn multiples. (Fertil Steril® 2013;99:393–9. ©2013 by American Society for Reproductive Medicine.)
Key Words: In vitro fertilization, multiple live birth, multiple-gestation pregnancy, cumulative

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Twin, triplet, and higher-order multiple pregnancies are the most significant morbidity after IVF. Although the incidence of multiple-gestation pregnancies and liveborn multiples from assisted reproductive technology (ART) has been declining steadily since 1997 (1), multiple-gestation pregnancies remain a significant portion of pregnancies after ART and are both a joy and a strain on the parents, physicians, and health systems who care for them. Liveborn multiples are sensationalized by the media, which distorts public perception about the true incidence of these births after ART.

An estimate of the incidence of liveborn multiples after ART that can be used to meaningfully counsel patients remains elusive. The majority of national reporting systems throughout the world report the per cycle pregnancy rate (PR) as the primary outcome after IVF, mainly due to the ease with which this measure can be calculated. Unfortunately, women who present for IVF treatment are not primarily

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interested in the per cycle PR. Per cycle PRs do not account for differences in success between the women undergoing their first cycle and those who did not become pregnant in previous attempts, nor do they account for the risk of pregnancy loss or multiple-gestation pregnancy. From the patient perspective, the cumulative probability of live birth (previously reported by our group) and the cumulative probability of liveborn multiples are more informative because they estimate the patient's ultimate outcome through her entire course of treatment (2).

There are multiple studies that report the incidence of liveborn multiples after a single IVF cycle (3–6), the complications and cost of these pregnancies (7–11), and discussions of the appropriate embryo number to transfer (12–15). However, to our knowledge, no published studies follow a population of women entering IVF treatment to estimate the cumulative risk of multiple-gestation pregnancy or liveborn multiples after a series of treatment cycles. Although a few studies report the incidence of spontaneous and selective pregnancy reduction in multiple-gestation pregnancies (3, 16, 17), there are no data in the literature on a large cohort of women with the number of fetuses identified on the first ultrasound and outcomes of those pregnancies. This is an important counseling issue for physicians and patients who are faced with a multiple-gestation pregnancy after IVF treatment.

We report the cumulative probability of liveborn multiples among a large cohort of women through their entire course of treatment including both fresh and frozen IVF cycles at a single center. Our objective is to provide data on multiple-gestation pregnancy and estimate the cumulative probability of liveborn multiples to assist physicians and fertility centers to improve patient counseling on this important issue.

MATERIALS AND METHODS

Patients

All women undergoing their first fresh, nondonor IVF cycle from January 1, 2000 through June 30, 2010 at Boston IVF (Waltham, MA) were included in this retrospective cohort study. We followed women for at least 1 year after their first IVF cycle, until discontinuation of treatment or until delivery of a live infant(s), whichever occurred first. The primary outcome was the delivery of two or more live infants in up to six IVF cycles. We chose this time period based on insurance benefits in Massachusetts, the diminishing numbers of women who continue treatment beyond six cycles, and the decreasing success rates beyond six cycles (2, 18, 19).

Any woman who did not deliver at least one live infant in a given cycle was eligible to return to care for the subsequent cycle, including women with a canceled cycle or those who achieved a pregnancy that did not result in a live birth. The group who did not return to care included women who transferred to another IVF center, used oocyte donation or a gestational carrier, or discontinued IVF treatment. The Committee on Clinical Investigations at Beth Israel Deaconess Medical Center approved this study.

Fresh and Frozen Embryo Transfer Cycle

The protocol is described in detail elsewhere (2). Women underwent standard ovarian stimulation protocols, monitoring, and oocyte retrieval. In general, the embryo transfer (ET) took place 3 days after the oocyte retrieval. The number of embryos transferred reflected national guidelines, with some variation according to an individual woman's needs. Cryopreservation was generally performed 3 days after oocyte retrieval and included only embryos that were deemed viable by morphologic criteria. Cycles using cryopreserved embryos were performed after priming the uterus with estrogen and used progesterone for luteal phase support. With the exception of the first cycle, which was limited to fresh ET, frozen ET cycles were included as distinct treatment cycles thereafter (2).

Data Collection

We collected patient characteristics, details of each IVF cycle, and pregnancy outcomes from the medical record. Pregnancies were confirmed with levels of β-hCG, and the number of gestational sacs and fetal heartbeats were obtained by transvaginal ultrasound approximately 4 weeks after ET, with a range of 3–6 weeks (or 5–8 weeks gestation).

Statistical Analysis

All analyses were conducted using Statistical Analysis System (SAS 9.3; SAS Institute). Descriptive data are reported as mean ($\pm$SD), median (interquartile range), or proportion, depending on data type and distribution.

We calculated the cumulative probability of the first live birth during the study period using IVF cycle number as the time metric. This outcome is referred to as the cumulative live birth rate. The cumulative live birth rate and 95% confidence intervals (CI) were estimated separately for singleton, twin, and triplet live births using a SAS macro to compute the cumulative incidence function in the setting of competing risks (20). We acknowledge that the cumulative live birth rate is a proportion and not a rate, but we chose to use this terminology to remain consistent with what is commonly used in the literature.

We chose the categories for the age-stratified estimates based on the following strata used by the Centers for Disease Control and Prevention and the Society for Assisted Reproductive Technologies: <35, 35 to <38, 38 to <40, and ≥ 40 years. The strata were constructed using each woman's age at the start of her first cycle.

RESULTS

There were 10,169 women who underwent 27,668 cycles during the study period. The number of cycles per woman ranged from 1–14, with a median of 2.0 (1.0–3.0) cycles per woman. This analysis was limited to the first six cycles per woman, which amounted to 23,908 consecutive cycles. The baseline characteristics of the women at the start of their first cycle are displayed in Table 1A.

In the first cycle, all embryos were fresh; in all subsequent cycles the proportion using fresh embryos ranged from 80%–85%, with the remainder involving transfer of frozen