

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 repro-

ductive 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 \geq 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

TABLE 1

A. Patient (n = 10,169) characteristics at the start of cycle 1.

Characteristic	Data
Age (y) mean \pm SD	35.7 \pm 4.7
Age no. (%)	
<35 y	4,458 (43.8)
35 to <38 y	2,243 (22.1)
38 to <40 y	1,380 (13.6)
\geq 40 y	2,088 (20.5)
Body mass index (kg/m ²) mean \pm SD	25.3 \pm 5.4
Gravity no. (%)	
0	5,176 (50.9)
1	2,435 (24.0)
\geq 2	2,333 (22.9)
Unknown	225 (2.2)
Parity no. (%)	
0	6,301 (62.0)
1	1,882 (18.5)
\geq 2	552 (5.4)
Unknown	1,434 (14.1)
CD3 FSH (mIU/L) mean \pm SD	6.8 \pm 4.1

B. Cycle characteristics.

Characteristic	Cycle 1 n = 10,169	Cycle 2 n = 6,227	Cycle 3 n = 3,752	Cycle 4 n = 2,060	Cycle 5 n = 1,121	Cycle 6 n = 579
Fresh cycles n (%)	10,169 (100.0)	5,239 (84.1)	3,190 (85.0)	1,755 (85.2)	936 (83.5)	461 (79.6)
Total gonadotropins (IU) (mean \pm SD) ^a	2,748.8 \pm 1,505.5	3,451.2 \pm 1,744.5	3,617.1 \pm 1,758.0	3,845.3 \pm 1,779.6	4,064.3 \pm 1,827.1	3,734.6 \pm 1,974.2
Peak E ₂ (pg/mL) (mean \pm SD) ^a	1,477.5 \pm 1,220.2	1,274.2 \pm 1,053.6	1,309.2 \pm 1,072.6	1,415.0 \pm 1,261.2	1,334.9 \pm 1,161.1	1,312.1 \pm 1,119.7
Eggs retrieved (mean \pm SD) ^a	10.4 \pm 6.6	9.8 \pm 6.1	10.2 \pm 6.4	10.7 \pm 6.6	11.2 \pm 7.0	11.8 \pm 8.0
Embryos cryopreserved (mean \pm SD) ^a	1.2 \pm 2.4	0.8 \pm 1.9	0.8 \pm 2.0	0.9 \pm 2.1	1.0 \pm 2.3	1.1 \pm 2.6
Intracytoplasmic sperm injection cycles n (%) ^a	2,693 (26.5)	1,879 (35.9)	1,228 (38.5)	746 (42.5)	419 (44.8)	207 (44.9)
Assisted hatching cycles n (%) ^a	348 (3.4)	463 (8.9)	544 (17.1)	551 (31.4)	321 (34.3)	179 (38.8)
Embryos transferred ^{b,c}	2.1 \pm 1.1	2.3 \pm 2.1	2.5 \pm 1.4	2.6 \pm 1.5	2.6 \pm 1.5	2.6 \pm 1.5
Blastocyst transfer ^c	911 (7.3)	439 (6.0)	343 (6.5)	294 (8.4)	208 (9.1)	129 (9.5)

Note: CD3 FSH = follicle-stimulating hormone on cycle day 3.

^a Calculated only for fresh IVF cycles.

^b Plus-minus values are means \pm SD.

^c Calculated from all IVF cycles (both fresh and frozen cycles).

Malizia. Cumulative multiple live birth after IVF. Fertil Steril 2013.

TABLE 2

Cycle outcomes.									
Cycle	Cycle cohort N	Did not return to care N (%) ^a	Retrieval N (%) ^b	Transfer N (%) ^b	Chemical pregnancy N (%) ^b	Live birth N (%) ^b	Singleton deliveries N (%) ^c	Twin deliveries N (%) ^c	Triplet deliveries N (%) ^c
1	10,169	n/a	9,020 (88.7)	8,141 (80.1)	3,563 (35.0)	2,675 (26.3)	1,905 (71.2)	736 (27.5)	34 (1.3)
2	6,227	1,267 (16.9)	5,676 (91.2)	5,097 (81.9)	1,890 (30.4)	1,283 (20.6)	915 (71.3)	350 (27.3)	18 (1.4)
3	3,752	1,192 (24.1)	3,457 (92.1)	3,107 (82.8)	1,152 (30.7)	754 (20.1)	544 (72.1)	199 (26.4)	11 (1.5)
4	2,060	938 (31.3)	1,931 (93.7)	1,753 (85.1)	606 (29.4)	372 (18.1)	265 (71.2)	98 (26.3)	9 (2.4)
5	1,121	567 (33.6)	1,053 (93.9)	952 (84.9)	339 (30.2)	190 (17.0)	134 (70.5)	51 (26.8)	5 (2.6)
6	579	352 (37.8)	540 (93.3)	498 (86.0)	159 (27.5)	102 (17.6)	75 (73.5)	24 (23.5)	3 (2.9)

Note: n/a = not available.

^a Denominator is the number of patients eligible to return for the next IVF cycle (calculated by the previous cycle N minus those achieving live birth).

^b Denominator is the number in the cycle cohort.

^c Denominator is the number of live births in that cycle.

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embryos. Among fresh cycles, the proportion that used intracytoplasmic sperm injection (ICSI) and assisted hatching increased with each subsequent cycle. The mean number of embryos transferred increased from 2.1–2.6 from the first to the sixth cycle, and the proportion of fresh cycles in which blastocyst transfer occurred ranged from 6.0%–9.5%. These and other cycle characteristics are shown in Table 1B.

Among the 10,169 women presenting for a first cycle at our center, there were 5,433 deliveries of a liveborn infant(s). There were 3,838 (71.4%) singletons, 1,458 (27.1%) sets of twins, and 80 (1.5%) sets of triplets. Table 2 shows the incidence of a liveborn infant(s), as well as the proportion of women in each cycle that underwent oocyte retrieval and ET.

Among 1,737 pregnancies that began with two heartbeats noted on ultrasound approximately 4 weeks after ET, 76.5% resulted in liveborn twins, whereas 17.7% resulted in a singleton live birth. Of the 221 triplet pregnancies, 33.9% of women delivered triplets, 48.9% delivered twins, and 10.9% delivered a singleton infant. Only 12 pregnancies had four fetal heartbeats at the first ultrasound; 66.7% resulted in liveborn twins and 25.0% in liveborn triplets. No pregnancies began with more than four fetal heartbeats. The number of heartbeats per pregnancy and the number of resulting liveborn infants are shown in Table 3.

After six cycles, the cumulative live birth rate was 73.8% (95% CI 72.3%–75.2%). The corresponding values were 52.8% (95% CI 51.3%–54.2%) for singletons, 19.8% (95% CI 18.7%–20.8%) for twins, and 1.3% (95% CI 0.9%–1.6%) for triplets. For any cycle, the cumulative probability of delivering liveborn singletons, twins, and triplets sums to the cumulative

probability of delivering a liveborn infant. The cumulative live birth rate at each cycle, overall and stratified by the number of liveborn infants, is shown in Figure 1A. The cumulative probability of a *singleton* birth stratified by the woman's age at her first cycle is displayed in Figure 1B; the age-stratified cumulative probability of liveborn *multiples* is shown in Figure 1C.

DISCUSSION

The overall cumulative live birth rate in our population of more than 10,000 women undergoing up to six IVF cycles, with a median of two cycles, was 73.8%. When stratifying by the number of liveborn infants, the cumulative live birth rate was 52.7% for a singleton live birth, 19.8% for twins, and 1.3% for triplets. The twin cumulative live birth rate doubled from 7.2%–14.5% in cycles 1 to 3, with the rate of increase slowing from cycles 3 through 6 (14.5% to 19.8%). Although very low in absolute terms, the triplet cumulative live birth rate doubled from cycles 1 through 3 and doubled again from cycles 3 through 6. Importantly, there were no births of more than three infants; only 12 pregnancies had more than three fetal heartbeats on first ultrasound, and 66.7% of these women delivered twins.

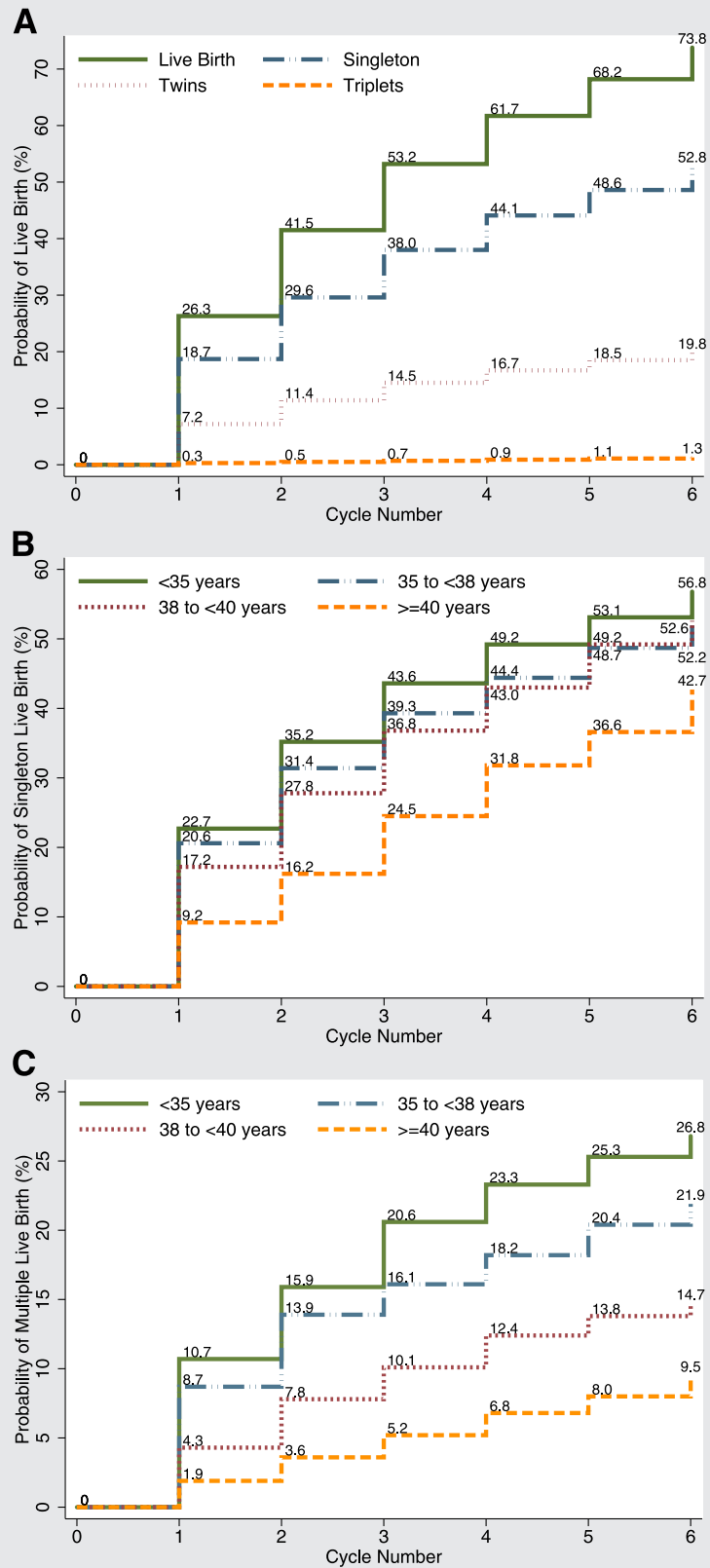
Consistent with our previously reported findings, in the present study of women using their own oocytes for IVF treatment, the overall cumulative live birth rate (2) decreased as women's age increased. A similar pattern was seen with the incidence of liveborn multiples. Women less than 35 years of age had the highest absolute risk of liveborn multiples;

TABLE 3

Number of ultrasound-confirmed fetuses and number of liveborn infants.					
No. of heartbeats	N	Clinical pregnancy loss N (%)	Singleton deliveries N (%)	Twin deliveries N (%)	Triplet deliveries N (%)
1	4,050	543 (13.4)	3,495 (86.3)	12 (0.3)	0 (0)
2	1,737	98 (5.6)	308 (17.7)	1,329 (76.5)	2 (0.12)
3	221	14 (6.3)	24 (10.9)	108 (48.9)	75 (33.9)
4	12	1 (8.3)	0 (0)	8 (66.7)	3 (25.0)
Unknown	12	0 (0)	11 (91.7)	1 (8.3)	0 (0)
Total	6,032	656 (10.9)	3,838 (63.6)	1,458 (24.2)	80 (1.3)

Malizia. Cumulative multiple live birth after IVF. *Fertil Steril* 2013.

FIGURE 1



The cumulative probability of multiple live birth is presented. The overall cumulative live birth rate in our study population of more than 10,000 patients is presented in (A). The cumulative live birth rate is stratified by patient age at the start of the first fresh, nondonor IVF cycle. This rate is presented as the cumulative singleton live birth rate (B) and the cumulative multiple live birth rate (C).

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yet they had a cumulative rate of liveborn multiples of only 20.6% after three IVF cycles and 26.8% after six IVF cycles. The lowest absolute risk was seen in women age 40 years and older, who had a 5.2% risk of delivering multiples after three cycles and a 9.5% risk after six cycles. According to American Society for Reproductive Medicine guidelines (21), there are no data to justify a limit on the number of embryos transferred in women 43 years of age and older, as the incidence of pregnancy is low and the incidence of multiple-gestation pregnancy is extremely small.

Despite the increased maternal and fetal complications that liveborn multiples entail (3, 5, 22), many infertility patients actually desire twins or triplets. Given that multifetal reduction procedures involve ethical and legal issues and may not be acceptable to some couples (23–25), efforts continue in the IVF community to decrease the number of embryos transferred. In our cohort, liveborn multiples accounted for 32.1% of live births among women less than 35 years of age and 18.2% of live births among women 40 years of age and older. These proportions are considerably lower than what was found using national data from 1996 (26), perhaps as a result of national guidelines to limit the number of embryos for transfer in IVF that were introduced in the United States in 1999 and revised multiple times since (21).

For women who achieve pregnancy after an IVF cycle, the potential reduction of pregnancies with more than one heartbeat on ultrasound is an important issue. There are reports of a 15%–30% incidence of “vanishing twins” after ART and an even higher incidence of spontaneous loss when three or more fetal heartbeats are present (3, 5, 16, 17, 27–31). In our population of 5,203 clinical pregnancies, 17.7% of twin pregnancies resulted in a singleton delivery, but we do not have data to distinguish between spontaneous and medically induced reductions. Among triplet pregnancies, nearly half resulted in liveborn twins, and 10.9% resulted in a singleton birth. Among pregnancies that began with four fetal heartbeats, it is important to note that there were no quadruplet deliveries and, whereas 25.0% of women delivered triplets, the majority (66.7%) delivered twins.

Various methods to predict the occurrence of a multiple live birth after IVF treatment have been published. Three studies used mathematical models to predict the probability of singleton and multiple live birth (4, 32, 33). Another group used the number of early cleaving embryos in their prediction of multiple pregnancy (34). These studies aimed to estimate per cycle rates and do not reflect cumulative risk.

The cumulative live birth rates reported in our study are not directly comparable to the per cycle pregnancy and live birth rates reported nationally and abroad (1, 35, 36). Statewide data demonstrate that the per cycle rates for pregnancy, live birth, and multiple live birth are lower in Massachusetts than national summary data for 2009 (35), likely due to insurance coverage for infertility care in our state. Insurance coverage has been found to encourage the transfer of fewer embryos during IVF treatment (36–38). Although great strides have been made to decrease the incidence of multiple-gestation pregnancy and liveborn multiples after IVF in the past 20 years (38), the increased use of elective single ET cycles (14, 39) and expanded insurance

coverage would allow for the potential to decrease the incidence of multiple-gestation pregnancy and liveborn multiples and the high costs associated with them even further.

A limitation of our study is the lack of data available on the type of reduction, whether spontaneous or medically induced, that occurred in pregnancies with multiple fetal heartbeats. With current practice patterns in mind, women with quadruplet pregnancies are the most likely to opt for multifetal pregnancy reduction (23), whereas women with twin pregnancies are the least likely (24).

An additional limitation is the statistical method used to estimate the cumulative live birth rates, which censors women who do not return for a subsequent IVF cycle, thereby assuming that women who did not return to care have the same probability of live birth as those who did. Given that women may end treatment secondary to a poor response, as we reported previously, this method may overestimate the cumulative probability of a live birth (2). Characteristics of the population of women who did not return to care at our center are reported previously (2). In our previous report of cumulative live birth using Massachusetts data (2) and in a later report of cumulative live birth using similar methods and national data (40), the cumulative probability curves are presented as optimistic/optimal and conservative estimates. We chose not to present both curves in this article to maintain simplicity and readability of the figures. Given the additional stratification of curves in this article to present the cumulative probability of singleton, twin, and triplet live birth, we chose instead to provide confidence intervals for all outcomes.

Another limitation of the statistical method used in this article is that the data cannot be stratified by cycle variables such as ET number. However, the ET number increases only slightly from the cycle 1 average of 2.1 to a cycle 6 average of 2.6 embryos transferred. The reported cumulative probability of singleton and multiple live birth including the increase in ET number through the progression of cycles, maintains the goal of presenting the “real-life” experience of the patient entering her first fresh IVF cycle.

A major strength of this study is the use of a large cohort of all women presenting for their first fresh IVF cycle and followed during more than a decade without exclusion based on ovarian reserve testing, diagnosis, or other prognostic factors, thereby maximizing generalizability. Unlike some studies that excluded frozen ET cycles from the calculation of live birth rates (18, 19, 24, 41, 42), we included these cycles to represent a woman’s entire treatment experience. Furthermore, we provided an estimate of the cumulative risk of liveborn multiples for a woman entering her first IVF cycle, rather than simply the per cycle PR, thus providing an estimate of the risk of liveborn multiples during the entire course of treatment. The large sample size allowed us to stratify the estimates by a woman’s age and to report the incidence of reduction of multiple-gestation pregnancies.

We conducted this study to provide meaningful evidence-based estimates of the cumulative risk of liveborn multiples for couples presenting for IVF. We are encouraged by the low incidence of liveborn multiples, especially for triplets, resulting from IVF treatment found in our study. The results provided here may be useful in counseling patients on their

risk of liveborn multiples and encouraging steps to continue to lower the risk of liveborn multiples after IVF.

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