Live-Birth Rates and Multiple-Birth Risk Using In Vitro Fertilization

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Context To maximize birth rates, physicians who perform in vitro fertilization (IVF) often transfer multiple embryos, but this increases the multiple-birth risk. Live-birth and multiple-birth rates may vary by patient age and embryo quality. One marker for embryo quality is cryopreservation of extra embryos (if embryos are set aside for cryopreservation, higher quality embryos may have been available for transfer).

Objective To examine associations between the number of embryos transferred during IVF and live-birth and multiple-birth rates stratified by maternal age and whether extra embryos were available (ie, extra embryos cryopreserved).

Design and Setting Retrospective cohort of 300 US clinics reporting IVF transfer procedures to the Centers for Disease Control and Prevention in 1996.

Subjects A total of 35 554 IVF transfer procedures.

Main Outcome Measures Live-birth and multiple-birth rates (percentage of live births that were multiple).

Results A total number of 9873 live births were reported (multiple births from 1 pregnancy were counted as 1 live birth). The number of embryos needed to achieve maximum live-birth rates varied by age and whether extra embryos were cryopreserved. Among women 20 to 29 years and 30 to 34 years of age, maximum live-birth rates (43% and 36%, respectively) were achieved when 2 embryos were transferred and extra embryos were cryopreserved. Among women 35 years of age and older, live-birth rates were lower overall and regardless of whether embryos were cryopreserved, live-birth rates increased if more than 2 embryos were transferred. Multiple-birth rates varied by age and the number of embryos transferred, but not by whether embryos were cryopreserved. With 2 embryos transferred, multiple-birth rates were 22.7%, 19.7%, 11.6%, and 10.8% for women aged 20 to 29, 30 to 34, 35 to 39, and 40 to 44 years, respectively. Multiple-birth rates increased as high as 45.7% for women aged 20 to 29 years and 39.8% for women aged 30 to 34 years if 3 embryos were transferred. Among women aged 35 to 39 years, the multiple-birth rate was 29.4% if 3 embryos were transferred. Among women 40 to 44 years of age, the multiple-birth rate was less than 25% even if 5 embryos were transferred.

Conclusions Based on these data, the risk of multiple births from IVF varies by maternal age and number of embryos transferred. Embryo quality was not related to multiple birth risk but was associated with increased live-birth rates when fewer embryos were transferred.

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SINCE THE GOAL OF IN VITRO FERtilization (IVF) is pregnancy and, ultimately, live birth, clinical decision making about IVF practices is heavily focused on maximizing a woman's chances of becoming pregnant. One common practice that aims to increase the likelihood of pregnancy is to transfer multiple embryos (often more than 3) into the uterine cavity. This treatment approach also presents an important drawback, however, because it increases the risk for multiple birth. Multiple-birth infants are at significant risk for a number of adverse outcomes including preterm delivery, low birth weight, congenital malformations, fetal and infant death, and long-term morbidity and disability among survivors.[1-5] Twins are 5 times as likely, and triplet and higher-order infants 13 times as likely, as singleton infants to die during the first year of life.[2]

To curtail the multiple-birth risk, several countries have passed legislation that limits the number of embryos that can be transferred to 3.[6,7] Such a policy is not universally supported as it runs counter to the expectation of autonomy in the patient-physician relationship. In the United States, the issue of embryo transfer has thus far remained outside the legal arena; however, the American Society for Reproductive Medicine has issued practice guidelines.[8] The debate about embryo limits has increasingly focused on whether to consider prognostic factors when setting guidelines, particularly patient age, which varies inversely with a woman's chances for achieving pregnancy.[9,10] Additionally, as studies demonstrate associations between various markers of embryo quality and implantation, attention has focused on whether such data can be

See also p 1813 and Patient Page.

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translated into policy in the future. Although current grading schemes for assessing embryo quality have limitations, both embryo morphology grade and the ability to select embryos for transfer have been associated with increased pregnancy and live-birth rates in previous studies.[11-17] An especially provocative study that used population-based data from the United Kingdom suggested that elective transfer of 2 rather than 3 embryos reduced the multiple-birth risk without affecting the chance of live birth for any age group.[11]

To determine if this finding is supported by the US IVF population, we used a population-based dataset of IVF–assisted reproductive technology (ART) cycles initiated in US clinics in 1996 to examine associations between embryo number and pregnancy, live-birth, and multiple-birth rates. The large sample afforded us an opportunity to more fully explore these associations by examining several important factors, including patient age and availability of extra embryos for future ART cycles.

METHODS

Subjects

The Fertility Clinic Success Rate and Certification Act of 1992 requires that each medical center performing IVF or related ARTs report data for each ART cycle initiated to the Centers for Disease Control and Prevention (CDC) annually for the purpose of reporting clinic-specific pregnancy success rates.[18] An *ART cycle* is considered to begin when a woman begins taking fertility drugs or starts ovarian monitoring with the intent of having embryos transferred. ART centers submit data obtained from clinic records for each cycle initiated during a given reporting year (January 1 through December 31) in a standardized format. The datafile is organized with 1 record per cycle. Multiple cycles for a single patient are not linked. Data collected include patient demographics, medical history and infertility diagnoses, clinical information pertaining to the ART cycle, and information on resultant pregnancies and births. The first full year for which the CDC collected ART data was 1996. In 1996, 300 US centers reported more than 60 000 ART cycles to the CDC. Because some centers did not report their data, despite the federal mandate, this number does not represent every ART cycle performed in the United States; however, it is estimated that data on more than 95% of all cycles were reported.

We selected fresh, nondonor IVF cycles for inclusion in the current analysis (N = 44 723). This refers to cycles in which eggs were removed from a woman's ovaries, combined with sperm, and if fertilized, the resulting embryo(s) was replaced into the same woman's uterus. This selection excludes cycles in which embryos derived from a woman serving as an egg donor were transferred to the patient (n = 5162); cycles in which embryos derived from a patient were transferred into another woman serving as a gestational carrier or surrogate (n = 688); and cycles in which the embryos transferred had been retrieved and fertilized at an earlier date, frozen via cryopreservation, and thawed for use in the current cycle (n = 9290). It also excludes cycles in which embryos or oocytes were transferred into a woman's fallopian tubes rather than uterus (n = 4117), cycles in which embryos were transferred to both the uterus and the fallopian tubes (n = 619), and cycles in which both fresh and thawed embryos were transferred (n = 125). Because these cycle types may vary with respect to implantation and pregnancy rates, and also with respect to the importance of various prognostic factors, they were not combined. Separate analysis for each cycle type was precluded by small sample sizes in many key subgroups. Therefore, this analysis is restricted to the most common type of ART treatment: fresh, nondonor IVF.

Among fresh, nondonor IVF cycles that were initiated in 1996, we excluded cycles that did not progress to embryo transfer (n = 8890) and cycles for which patient age was either missing (n = 79), younger than 20 years (n = 6), or older than 44 years (n = 194). Our final sample included 35 554 fresh, nondonor IVF cycles. Because these cycles were limited to those that progressed to embryo transfer, this number actually represents 35 554 IVF transfer procedures.

Definitions of IVF Outcomes

We defined *pregnancy* as the presence of 1 or more gestational sacs observed on ultrasound (with or without the presence of a fetal heart). In rare instances (<1%), the number of fetal sacs observed on ultrasound was not recorded or was recorded as 0, but a pregnancy outcome was recorded (live birth, stillbirth, spontaneous abortion, therapeutic abortion); these cycles were also coded as pregnancies. A total of 12 115 pregnancies were reported. Since ART centers do not routinely treat patients beyond the first trimester, live births and fetal losses later than the first trimester were based on verbal or written reports from either the patient or her obstetric health care professional. ART centers often actively follow-up patients to ascertain pregnancy outcome. An outcome (live birth, stillbirth, spontaneous abortion, therapeutic abortion) was recorded for all but 457 (4%) of these pregnancies. A total of 9873 live-birth deliveries were reported. We considered each live-birth delivery as a single live birth; eg, a live-birth delivery of triplets was counted as 1 live birth.

We classified a pregnancy as a multiple gestation if either 2 or more fetal hearts were noted on an early ultrasound, or 2 or more infants were born. We defined multiple gestation based on the more stringent criterion of fetal hearts (rather than number of sacs only) because multiple gestations that do not progress to fetal hearts are generally not considered to be clinically relevant. We classified a live-birth delivery as a multiple birth if 2 or more fetuses were born and at least 1 of these was liveborn. We also separately examined triplet and higher-order gestations and triplet and higher-order births.

Data Analysis

We categorized each IVF procedure according to 2 factors: (1) the number of embryos transferred (1, 2, 3, 4, 5, 6, or ≥7), and (2) patient age at cycle start (20-29, 30-34, 35-39, or 40-44 years).

Within each age-embryo number stratum, we present the percentages of live births per transfer procedure, multiple births per live birth, triplet or higher-order births per live birth, and triplet or higher-order gestations per pregnancy. We present both triplet-birth and triplet-gestation rates because these rates were not parallel; trends for triplet and higher-order birth rates were often less pronounced than trends for triplet and higher-order gestation rates.

In addition to embryo number and patient age, we examined the effects of potential markers of patient prognosis, embryo quality, and clinic success. We evaluated trends in live-birth and multiple-birth rates after additionally stratifying on several such factors. These included previous pregnancies, previous live births, number of previous ART cycles, primary infertility diagnosis, use of intracytoplasmic sperm injection (a technique used often in male-factor infertility in which a single sperm is directly injected into the oocyte), use of assisted hatching (use of chemicals, lasers, or mechanical means to create an opening in the zona pellucida), and whether 1 or more embryos that were retrieved and fertilized during the current cycle were cryopreserved for use in later cycles. The availability of extra embryos for cryopreservation indicates that more embryos were available for transfer than were actually transferred and therefore the embryos transferred were electively chosen; this variable may be a surrogate for embryo quality. Embryo cryopreservation has been used since the early 1980s and is now a standard component of most ART programs. However, because whether or not extra embryos are cryopreserved is a function of patient choice as well as embryo availability and clinical assessment, the cryopreserved variable is a nonspecific marker. Finally, we examined all results after stratification by clinic-level characteristics. We classified each clinic as having a pregnancy rate above or below the mean pregnancy rate for all clinics combined. We analogously classified clinics as having high or low age-specific pregnancy rates. We stratified trends in live-birth rates and multiple-birth rates according to whether a cycle was performed in a clinic with low or high overall and/or age-specific pregnancy rates.

For all analyses, the statistical significance of differences in rates between categories was assessed with χ^2 tests.

This research was approved by the institutional review board at the CDC.

Table 1. Percent Distribution of In Vitro Fertilization (IVF) Transfer Procedures by Patient Age and Factors Related to Patient Medical History or IVF Procedure*

	Patient Age at IVF Cycle Start, y			
	20-29 (n = 4590)	30-34 (n = 12 774)	35-39 (n = 13 174)	40-44 (n = 5016)
Previous pregnancies, No.				
0	64.2	54.3	44.5	38.1
1	19.6	24.4	26.1	25.4
2	9.0	11.1	15.0	15.3
≥3	7.1	10.2	14.4	21.2
Previous live births, No.				
0	88.0	82.0	74.8	70.3
1	8.9	13.6	18.1	20.2
≥2	3.0	4.4	7.1	9.5
Previous IVF cycle, No.				
0	70.7	59.4	53.9	48.2
1	17.4	21.3	22.3	23.3
2	7.4	10.4	11.6	12.7
≥3	4.5	8.9	12.3	15.7
Primary infertility diagnosis				
Endometriosis	12.2	16.3	14.9	12.2
Tubal factor	32.3	32.5	34.5	27.1
Male factor	33.8	27.8	25.2	22.4
Ovulatory dysfunction	11.5	9.8	8.6	11.9
Uterine factor	0.7	1.2	1.9	3.4
Idiopathic infertility	4.3	6.5	7.6	9.9
Other	5.1	5.9	7.2	13.2
Embryos transferred, No.				
1	3.4	4.4	6.6	10.3
2	8.9	8.6	10.8	14.6
3	33.2	28.0	18.4	17.1
4	33.2	34.3	34.0	20.7
5	12.0	14.3	17.4	18.3
6	6.4	7.4	8.6	11.4
≥7	2.9	3.0	4.2	7.5
Cryopreservation of ≥1 embryos retrieved during cycle				
No	56.4	63.0	74.5	89.3
Yes	43.6	37.0	25.5	10.7
Use of intracytoplasmic sperm injection				
No	56.1	61.1	63.0	66.1
Yes, with some embryos	9.3	8.5	7.6	5.0
Yes, with all embryos	34.6	30.4	29.5	29.0
Use of assisted hatching				
No	72.9	69.0	56.4	38.4
Yes, with some embryos	6.7	8.1	10.4	12.0
Yes, with all embryos	20.4	22.9	33.2	49.6

*$P<.01$, χ^2 to test for differences in distributions by age. Sample size was reduced for some analyses due to missing values; maximum number of missing values was 3.5% for intracytoplasmic sperm injection.

RESULTS

Patient medical history and IVF procedural factors varied significantly by patient age (TABLE 1). Both previous

pregnancies and previous live births increased with each successive increase in patient age. Older women were also more likely to have undergone IVF previously; younger women were more likely to be diagnosed as having infertility related to tubal or male factors. The distribution of the number of embryos transferred also varied by age; older women were more likely to be in both of the outlying categories (1 or ≥7 embryos transferred) than women in the younger age groups. Additionally, use of both cryopreservation for extra embryos and intracytoplasmic sperm injection declined with age, while use of assisted hatching procedures increased.

Pregnancy rates declined from 41% among women aged 20 to 29 years to 20% among women aged 40 to 44 years. Live-birth rates declined from 35% to 13% in these same categories. In addition to age, live-birth rates varied significantly by the number of embryos transferred (TABLE 2). Among the 2 youngest age groups, the live-birth rate increased considerably with increasing number of embryos transferred up to 3; beyond 3 embryos, there was no additional increase and, in fact, declines were noted in a few categories. Among women aged 35 to 39 years, the live-birth rate continued to increase with up to 4 embryos transferred and then declined slightly. Among women aged 40 to 44 years, the live-birth rate continued to increase with up to 5 embryos transferred. However, even at this maximum rate, the live-birth rate among women in the oldest age group was still substantially lower than the maximum rate observed among women in the youngest age group (20.3% vs 37.7%).

Similar patterns were observed for multiple births, triplet and higher-order gestations, and triplet and higher-order births. In general, younger women were at greater risk for each of these outcomes given the same number of embryos transferred. Among women aged 20 to 29 years, the proportion of live births that were multiple increased substantially with each embryo transferred up to 3 when it reached 46%. The multiple-birth rate continued to increase beyond 3 embryos, although the magnitude of the increase was much smaller. Among women aged 30 to 34 years and 35 to 39 years, increases in the multiple-birth rate were observed with up to 4 embryos transferred (45% and 38% for women aged 30-34 years and 35-39 years, respectively). Increases in the multiple-birth rate among women aged 40 to 44 years were less striking and did not reach the high levels noted for other groups until 7 or more embryos were transferred (39%).

The triplet-gestation and triplet-birth rates were substantially elevated among women in the 2 youngest age groups when 3 or more embryos were transferred. Among women 20 to 29 years of age with 3 embryos transferred, the triplet-gestation and triplet-birth rates both reached 10%. Among women 30 to 34 years of age with 3 embryos transferred, the triplet-gestation rate reached 10%; the triplet-birth rate was near 7%. Among women 40 years of age or older, the risk for triplets was greatly reduced; both triplet-gestation and triplet-birth rates were less than 2% when 4 embryos were transferred and less than 5% when 5 embryos were transferred. Triplet rates among women aged 35 to 39 years were intermediate between the younger and older age groups.

The basic patterns in live-birth and multiple-birth rates apparent in Table 2 persisted after further stratification on previous pregnancies, previous live births, previous ART cycles, infertility diagnosis, use of intracytoplasmic sperm injection, use of assisted hatching, and clinic-level pregnancy and age-specific pregnancy rates (data not shown). For all age groups, however, trends in live-birth rates varied markedly between cycles in which 1 or more embryos had been cryopreserved and cycles in which no embryos were cryopreserved (TABLE 3). Women in the cryopreserved group achieved higher live-birth rates with fewer embryos transferred. Among women aged 20 to 29 years and 30 to 34 years, those with cryopreserved embryos achieved live-birth rates of 43% and 36%, respectively, when 2 embryos were transferred; these rates were more than double the rates observed among women in these age groups for whom 2 embryos were transferred and no embryos were cryopreserved. Further, among the cryopreserved group, live-birth rates were not significantly greater when 3 or more embryos were transferred than when 2 embryos were transferred. Among women aged 35 to 39 years, live-birth rates were substantially increased for both 2 and 3 embryo transfers (25% and 33%, respectively) when additional embryos were cryopreserved. Among women aged 40 to 44 years, the cryopreserved group achieved notably higher live-birth rates when 3 embryos were transferred (19%); additionally, the live-birth rate continued to increase slightly when more than 3 embryos were transferred (24% with 5 embryos). Among all age groups, small sample sizes impeded evaluation of procedures in which 1 embryo was transferred and additional embryos were cryopreserved; among women aged 40 to 44 years, there were also too few procedures in which 2 embryos were transferred and additional embryos were cryopreserved. Although whether embryos were cryopreserved had a large impact on live-birth rates, trends in multiple-birth rates did not vary by the cryopreserved variable. Within each age group, the trends in multiple birth presented in Table 2 were similar to both the trends in multiple birth among women with 1 or more embryos cryopreserved and the trends among women with no embryos cryopreserved (data not shown).

COMMENT

Since the first successful IVF procedure in 1978,[19] the field of ART has grown rapidly. In the United States alone, more than 60 000 ART cycles were initiated in 1996, which resulted in more than 17 000 clinical pregnancies and more than 14 000 live births.[20] The majority of these were achieved using fresh, non-

donor IVF treatments. We examined these population-based data, and in keeping with prior studies,[11-17,21-23] we found that 3 factors—patient age, number of embryos transferred, and the ability to select embryos for transfer—had a pronounced effect on the success of an IVF procedure and the risk for multiple birth. The large sample size allowed us to explore the interrelationships between these 3 factors.

Although we did not have specific laboratory data to classify embryo quality, we found that among women younger than 35 years, when the number of embryos transferred was elective limited to 2, as indicated by 1 or more available embryos being cryopreserved, the live-birth rates achieved were comparable to those achieved with transfer of 3 embryos; however, the multiple-birth risk was halved and the risk for triplet and higher-order pregnancies and births was virtually eliminated. In contrast, women aged 35 to 39 years appeared to receive some benefit from elective transfer of 3 rather than 2 embryos; although not statistically significant at the .05 level, the live-birth rate increased by 8 percentage points. While multiple-birth rates were also increased with 3 embryos transferred (29.4%), these risks were much smaller than those seen in women aged 20 to 29 years with 3 embryos transferred (45.7%). There were too few procedures to compare elective transfer of 2 vs 3 embryos among women aged 40 to 44 years; however, we observed a trend of increasing birth rates with elective transfer of up to 5 embryos. Additionally, the multiple-birth rate among women aged 40 to 44 years with 5 embryos transferred (24.6%) was comparable to the multiple-birth rate seen among women aged 20 to 29 years with only 2 embryos transferred (22.7%) and the triplet-birth rate was relatively low at 2.1%.

When embryos were not cryopreserved, we observed increases in the live-birth rate when up to 3 embryos were transferred for women aged 20 to 29 years and 30 to 34 years, when up to 4 embryos were transferred for women aged 35 to 39 years, and when up to 5 embryos were transferred for women aged 40 to 44 years. The increased embryo number needed to maximize success rates for women younger than 40 years also presented important drawbacks, however, as commensurate increases in multiple- and triplet-birth rates were noted.

Our findings for patients younger than 35 years are supported by prior studies,[11,12,14,15,17] most notably the analysis of the British IVF registry by Templeton and Morris.[11] This population-based study of British IVF cycles found that when more than 4 eggs had

Table 2. Key Indicators of Live Birth and Multiple Birth by Number of Embryos Transferred and Patient Age

	Embryos Transferred, No.						
Age, y	1	2	3	4	5	6	≥7
Live Births per In Vitro Fertilization Transfer Procedure, %							
20-29	10.4	23.7*	37.7*	37.3	36.6	37.5	31.3
30-34	9.1	19.4*	35.1*	36.4	33.0†	34.6	28.6†
35-39	6.3	14.0*	23.0*	33.3*	29.8*	30.1	28.3
40-44	2.1	5.0*	8.3†	14.4*	20.3*	20.2	15.1†
Multiple Births per Live Birth, %							
20-29	. . .	22.7†	45.7*	48.1	47.8	54.6	50.0
30-34	. . .	19.7*	39.8*	45.4*	44.1	48.0	50.0
35-39	. . .	11.6†	29.4*	37.5*	38.4	42.4	42.4
40-44	. . .	10.8	11.3	20.0	24.6	24.1	38.6†
Triplet or Higher Gestations per Pregnancy, %							
20-29	. . .	. . .	13.0*	18.1†	17.9	24.0	24.5
30-34	. . .	. . .	10.8*	15.8*	17.4	23.2†	18.8
35-39	. . .	. . .	4.0*	11.5*	13.4	16.3†	22.3
40-44	. . .	. . .	0	1.8	4.2	5.9	12.5
Triplet or Higher-Order Births per Live Birth, %							
20-29	. . .	. . .	9.9*	12.0	10.5	16.4	7.1
30-34	. . .	. . .	6.7*	10.0*	8.8	9.5	10.2
35-39	. . .	. . .	2.2†	5.4*	6.5	8.5	11.4
40-44	. . .	. . .	0	0.7	2.1	0.9	5.3

*$P<.01$ for comparison between the proportion in a given embryo category to the proportion in the preceding embryo category within the same age group.
†$P<.05$ for comparison between the proportion in a given embryo category to the proportion in the preceding embryo category within the same age group.

Table 3. Live-Birth Rate by Number of Embryos Transferred, Patient Age, and Whether Extra Embryos Were Cryopreserved for Later Use

	Embryos Transferred, No.					
	2	3	4	5	6	≥7
Age 20-29 y						
0 embryos cryopreserved	17.9	34.3*	34.2	34.1	35.4	28.3
≥1 embryos cryopreserved	42.7	41.1	40.3	40.5	40.0	42.9
Age 30-34 y						
0 embryos cryopreserved	17.2	30.4*	34.3*	30.3†	33.3	28.5
≥1 embryos cryopreserved	36.0	41.5	38.8	38.0	37.1	28.8
Age 35-39 y						
0 embryos cryopreserved	13.3	19.9*	30.8*	28.6	29.3	27.6
≥1 embryos cryopreserved	24.7	33.0	37.6†	33.2	31.9	32.9
Age 40-44 y						
0 embryos cryopreserved	5.1	7.7†	13.8*	19.6*	18.8	14.8
≥1 embryos cryopreserved	. . .	18.8	17.5	24.0	25.9	18.4

*$P<.01$ for comparison between the proportion in a given embryo category to the proportion in the preceding embryo category within the same age-cryopreserved group.
†$P<.05$ for comparison between the proportion in a given embryo category to the proportion in the preceding embryo category within the same age-cryopreserved group.

been fertilized, the odds of a live birth were no different with elective transfer of 2 embryos compared with elective transfer of 3 embryos; however, the multiple-birth risk was increased when 3 embryos were transferred. Although our findings among patients older than 35 years are supported by a previous clinical study,[12] our results for this age group are not consistent with the British data. While we noted an improvement in the birth rate among women aged 35 to 39 years with elective transfer of 3 embryos, the British study showed no difference in live-birth rates between elective transfer of 2 and elective transfer of 3 embryos.

Differences in IVF practice between the United Kingdom and the United States might partially explain the disparity between our results and the British data. The United Kingdom limits the number of embryos transferred to 3,[6] while in the United States it is not uncommon to transfer 4, 5, or even 6 embryos, particularly in women aged 35 years or older. Thus, even in the elective transfer group, differential decision making by US and UK practitioners about whether to transfer 2, 3, or more embryos in women 35 years of age or older may have affected comparability between patients included in various embryo-number groups. In fact, in the United States, there were very few cycles among women aged 40 years or older in which embryo transfer had been electively limited to 2. Although this rendered us unable to compare elective transfer of 2 and elective transfer of 3 embryos for this oldest age group, we were able to examine elective transfer of higher numbers of embryos and found that live-birth rates improved when more than 3 embryos were transferred, whether or not additional embryos had been cryopreserved. Embryo transfers beyond 3 could not be evaluated with the British data.

A further difference between the 2 studies is the definition of elective transfer. We defined *elective transfer* on the basis of whether embryos had been cryopreserved, whereas the comparable category in the British study was based on the number of embryos fertilized. Our definition may have been a more specific indicator of embryo quality as not only did an excess of fertilized embryos need to be available, but 1 or more of them had to be deemed acceptable for cryopreservation. Thus, our cryopreserved group may have represented a more select group of cycles. If this is true, it also follows that our group of cycles for which no embryos were cryopreserved included a heterogeneous mix of cycles. That is, our "nonelective transfer" group included cycles for which embryo transfer was truly limited because additional embryos were not available, as well as cycles in which additional embryos that were available for transfer were neither transferred nor cryopreserved for any number of reasons related to clinical assessment and practice or patient choice. We do not have data on the number of embryos fertilized and therefore cannot subdivide this group further.

The unit of analysis for this study was the IVF transfer procedure. Women who underwent more than 1 transfer procedure in 1996 are therefore represented in multiple procedures. Although we did not have the necessary data to link cycles from the same woman, we did have medical history data for each procedure, including whether a woman had undergone previous ART cycles (in 1996 or earlier). Therefore, we repeated our analysis after limiting the sample to women who were undergoing their first cycle and found no difference in comparison to our original findings (data not shown).

We focused this presentation on the most relevant outcomes, live birth and multiple birth. We also examined the more proximal outcomes, pregnancy and multiple-gestation pregnancy. Because the trends observed for live-birth rates and multiple-birth rates were parallel to the trends for pregnancy rates and multiple-gestation rates, respectively, we presented only the former here. However, because trends for triplet-gestation rates were in some instances more pronounced than triplet-birth rates, we presented both. The differences in the pattern of results for triplet gestation and birth rates may reflect an effect due to spontaneous or therapeutic fetal reduction. Patients and health care professionals may consider being faced with the choice of therapeutic fetal reduction as an additional undesirable consequence of a triplet or greater gestation. The trends in triplet-gestation rates provide an indication of the total triplet risk—the potential for having a triplet birth with associated infant and maternal health risks and the potential of being faced with the decision for a therapeutic reduction. The trends in triplet-birth rates provide a sense of the realized public health impact of triplets in 1996.

This study was based on observational data. Although we were able to stratify on age and availability of embryos for transfer, we cannot completely discount the possibility that women who had 3 embryos transferred had poorer quality embryos than those who had 2 embryos transferred or differed on some other unmeasured determinant of success. Given the limitations of current embryo grading methods, only a large randomized trial would ensure complete comparability between women with different numbers of embryos transferred.

Although these findings are based on observational data, they strongly suggest that embryo transfer can be limited in many women undergoing IVF, thereby reducing the risk of multiple birth without reducing the chance of pregnancy and live birth. Adverse fetal and infant outcomes associated with multiple pregnancy and birth have been identified as the greatest potential hazard associated with IVF therapies. As technology advances, we look to developments in embryo culture techniques, such as blastocyst culture, to eliminate the need for high-order embryo transfers for all age groups.[24] Until then, however, persons undergoing IVF and their physicians need to carefully consider the trade-offs between benefit and risk in deciding how many embryos to transfer. This is particularly critical for younger patients.

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The precondition of any fruitful relationship between literature and science is knowledge.
—Aldous Huxley (1894-1963)