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Risk of Multiple Birth Associated with In Vitro Fertilization using Donor Eggs

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Multiple birth, which is associated with adverse fetal, infant, and maternal outcomes, is increasingly related to the use of in vitro fertilization (IVF). Among women undergoing IVF who use their own eggs, greater maternal age is associated with decreased risk of multiple birth; using donor eggs from younger women may negate this age effect. Data from 6,936 IVF procedures performed in the United States in 1996–1997 on women aged 35–54 years who used donor eggs were analyzed to assess the effect of maternal age, number of embryos transferred, and cryopreservation of extra, nontransferred embryos (an indicator of higher embryo quality) on risk of multiple birth. Greater maternal age did not decrease multiple-birth risk. Rates of multiple birth were related to number of embryos transferred and whether extra embryos had been cryopreserved, and they were high compared with those of IVF patients the same age who had used their own eggs. Among women who had extra embryos cryopreserved, transferring more than two embryos increased multiple-birth risk, with no corresponding increase in the chance for a livebirth. These results highlight the need to consider the age of the donor and embryo quality when making embryo transfer decisions involving use of donor eggs. *Am J Epidemiol* 2001;154:1043–50.

embryo transfer; fertilization in vitro; multiple birth offspring; pregnancy, multiple; reproduction techniques

The rate of twin birth among liveborn infants has increased in the United States over the past 20 years, from 18.9 per 1,000 in 1980 to 26.8 per 1,000 in 1997 (1). Rates of triplet or higher-order (triplet+) births also increased during the same period, from 37.0 per 100,000 to 173.6 per 100,000 (1). Much of this increase is thought to be due to the increased use of in vitro fertilization (IVF) and other forms of assisted reproductive technology (ART), which often involve the transfer of more than one embryo into a woman's uterus. One study estimated that by 1997 over 43 percent of triplet+ births in the United States involved conceptions resulting from ART (2).

Multiple-gestation pregnancies are associated with adverse fetal and infant outcomes (3–8), and they also pose increased risks of maternal morbidity and mortality (9). The public health burden of these births is compounded by the fact that the advancing technology of ART, combined with the use of eggs donated by young women, increasingly allows women beyond the traditional reproductive ages (15–44 years) to achieve pregnancy and livebirth. Older women are more likely to have underlying chronic medical conditions that may be exacerbated by pregnancy. Additionally, advanced maternal age has been associated with higher rates of infant morbidity and mortality, even after controlling for maternal complications (10). Thus, it is especially important to minimize the risk of multiple birth among older women undergoing ART.

A recent study of 33,554 IVF procedures performed on women using their own eggs (11) demonstrated that risk of multiple birth decreased as a function of maternal age, even when the number of embryos transferred was held constant. The association between maternal age and lower risk of multiple birth could be driven by factors associated with the uterus, the egg, or both; and these factors, in turn, may operate at the level of initial embryo implantation and/or retention. If uterine factors underlie the age association, then older women using donor eggs should also have a decreased risk of multiple birth. However, if egg factors drive this association, older women using eggs from younger donors would be expected to have an increased risk of multiple birth in comparison with older women using their own eggs.

Previous studies of IVF procedures using donor eggs have generally focused on patient age and its relation to overall rates of pregnancy and livebirth; they typically have not directly evaluated the relation between patient age and multiple gestation or multiple birth (12–23). In most studies, small sample sizes have precluded analysis of the risks of multiple gestation and multiple birth, in terms of both maternal age and number of embryos transferred. Analyses of

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Abbreviations: ART, assisted reproductive technology; IVF, in vitro fertilization.

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rates of pregnancy and livebirth, while more complete, have also been limited by investigators' having data only on eggs donated by women with known fertility problems. Results from these studies have been inconsistent. Some studies found no association between patient age and rates of pregnancy, pregnancy loss, or livebirth when donor embryos were used, which suggests that egg factors play the primary role in embryo implantation (14–16, 20, 21); other studies documented associations with patient age, indicating that uterine factors may be important (12, 13, 17, 18).

We used population-based data on ART procedures performed in the United States to assess risk of multiple birth among ART patients using donor eggs and to investigate factors related to this risk, focusing on maternal age, number of embryos transferred, and embryo quality.

MATERIALS AND METHODS

The Fertility Clinic Success Rate and Certification Act of 1992 (24) requires every medical center in the United States that performs ART procedures to report its pregnancy success rates annually to the Centers for Disease Control and Prevention. Each year, the Society for Assisted Reproductive Technology creates a database of ART procedures performed in US clinics and, per contract, shares these data with the Centers for Disease Control and Prevention. A more detailed description of this database has been published elsewhere (11). For the present study, available data included ART procedures initiated in 1996 and 1997, which are estimated to represent 95 percent of all procedures performed in the United States during that time. Only procedures using embryos derived from donor eggs were considered. Additionally, only procedures using fresh embryos (i.e., embryos that had never been frozen) and procedures using IVF with transcervical embryo transfer (the most common ART method) were included. This refers to procedures in which eggs were removed from the ovaries of a donor and fertilized in the laboratory and the resulting embryo(s) were transferred into the patient's uterus. Because of insufficient sample sizes at the extremes of the age spectrum, analyses were restricted to procedures in which the embryo recipient was aged 35–54 years. Although the exact ages of the donors were not available, it is standard practice to use donors in their early thirties or younger. Of the 135,862 ART procedures performed in the United States in 1996 and 1997, 6,936 were IVF procedures in which fresh embryos derived from donor eggs were transferred to patients aged 35–54 years; these comprised our final sample.

We defined pregnancy as the presence of one or more gestational sacs observed via ultrasound. Livebirth delivery was defined as the delivery of one or more live infants; as such, the number of livebirth deliveries is not equivalent to the number of infants born. A livebirth delivery was classified as a multiple-birth delivery if two or more fetuses were delivered and at least one of them was liveborn. We examined the percentage of livebirth deliveries per IVF transfer procedure, the percentage of livebirth deliveries that were multiple births, and the percentage of livebirth deliveries that were triplet+ births. Because procedures resulting in pregnancies with more than two fetuses are more likely to involve spontaneous or medical reductions in the number of fetuses, we also examined the percentage of pregnancies that had been triplet+ gestations as the total potential for triplet+ births. We examined each of these indices after stratifying the data according to key patient and IVF procedural factors, most notably patient age at the start of the procedure, number of embryos transferred, and whether any extra embryos not transferred during the procedure had been frozen or cryopreserved for possible future use (an indicator of higher embryo quality).

The cryopreservation of extra, nontransferred embryos for future use following a given IVF procedure indicates that the number of embryos available to the patient for that procedure exceeded the number she chose to have transferred. This means that 1) her clinician was able to select the highest-quality embryos (based on visual inspection of embryo morphology) from all available embryos and 2) the remaining embryos were deemed to be of sufficient quality to save for possible future use. Because most egg donors receive high doses of ovulation stimulation drugs, resulting in the retrieval and fertilization of multiple eggs, virtually all patients using donor eggs have multiple embryos available for any given IVF procedure. Although current standardized embryo-quality grading schemes have limitations, both embryo morphology grade and the ability to choose embryos for transfer have been associated with increased rates of pregnancy and livebirth (11, 25–31).

Embryo grading scores are not included in the ART data set. We relied on cryopreservation of nontransferred embryos as our best measure of embryo quality, and we stratified all outcomes according to this variable. Note that this variable did not allow us to identify procedures in which nontransferred embryos were simply discarded. Despite this, for ease of presentation we refer to procedures in which nontransferred embryos were cryopreserved (the group with presumed higher embryo quality) as the "embryo-choice" group and all other procedures as the "no-embryo-choice" group. We expect that these two groups are more comparable in terms of livebirth and multiple-birth rates than would be the case if the no-embryo-choice group could have been subdivided into those procedures that truly transferred all available embryos and those that transferred a subset but did not cryopreserve the nontransferred embryos. Thus, our findings for differences between the embryo-choice subgroups are likely conservative.

Bivariate associations and analyses of trends were evaluated using χ^2 tests. Multivariable adjustment was performed using sets of logistic regression models, with the first using livebirth delivery (yes/no) as the dependent variable and including all 6,936 IVF procedures with donor eggs. The second examined multiple livebirth delivery (yes/no) as the dependent variable and included the 2,740 IVF procedures in which two or more embryos had been transferred and a livebirth had resulted. We constructed separate models for each dependent variable by embryo-choice group, because bivariate analyses of livebirth delivery rates suggested effect modification between this variable and the number of embryos transferred. All models included patient age, number of

embryos transferred, prior livebirth, use of intracytoplasmic sperm injection (in which a single sperm is injected directly into an egg), and assisted hatching (using chemicals, lasers, or mechanical means to create an opening in the zona pellucida of the embryo) as independent variables. We constructed separate models to conduct trend analyses by age for the logistic regression. Procedures in which only one embryo had been transferred were excluded from the logistic regression models because of insufficient sample size. Finally, we compared rates of livebirth delivery and multiple livebirth by patient age, controlling for number of embryos transferred, between the current sample of donor-egg procedures and a previous sample of non-donor-egg IVF procedures (11).

This study was approved by the institutional review board of the Centers for Disease Control and Prevention.

RESULTS

Three fourths (74.8 percent) of the IVF procedures in our final sample were performed on women aged ≥40 years (table 1). Approximately half (54.1 percent) of the procedures were performed on women who had had previous pregnancies, but only 24.9 percent of patients had had a prior livebirth. Almost half of the procedures (48.6 percent) were performed on patients who had previously undergone ART. Nearly all procedures involved the transfer of multiple embryos: In 54.8 percent of the procedures, at least four embryos had been transferred. In almost half (46.8 percent) of the procedures, more embryos were available than were transferred; these procedures comprised the embryo-choice group. Intracytoplasmic sperm injection and assisted hatching were each used in approximately one fourth of procedures.

Patient age showed little association with key IVF procedural factors. The average number of embryos transferred was near four for each age group (3.73–4.13), although the average was slightly increased for the oldest age group (table 2). There was no variation by patient age in the proportion of procedures categorized as involving embryo choice; approximately 47 percent of procedures in each age group were classified in the embryo-choice group.

Of the 6,936 IVF procedures in the sample, 3,320 (47.9 percent) resulted in a pregnancy and 2,761 (39.8 percent) in a livebirth delivery. Over 40 percent (42.9 percent) of the livebirth deliveries were multiple-birth deliveries (n = 1,185), usually twin deliveries (n = 1,028). Rates of livebirth and multiple birth varied little by patient age (table 3). While there appeared to be slight declines in rates of livebirth and multiple birth for the oldest age group, neither decline was statistically significant when compared with the rate in the preceding age group. Additionally, tests for trend did not produce significant results for either livebirth rates or multiple-birth rates. Rates of triplet+ gestation and birth were significantly lower among women aged 40–44 years than among women aged 35–39 years. Results of trend tests were statistically significant for both triplet+ measures. All groups had rates of triplet+ gestation above 8 percent and rates of triplet+ birth above 3 percent.

The relations among the variables "number of embryos transferred," "embryo choice," and livebirth, multiple-birth, and triplet+ gestation rates are presented in table 4. A significant trend in livebirth rates by number of embryos transferred was observed, but these results varied by embryo choice. For those procedures with known embryo choice, livebirth rates approached or exceeded 40 percent regardless of the number of embryos transferred. Additionally, livebirth rates declined slightly with increasing number of embryos transferred. In contrast, in the no-embryo-choice group, livebirth rates increased significantly with increasing

TABLE 1. Characteristics of in vitro fertilization procedures performed on patients aged 35–54 years in the United States using fresh embryos derived from donor eggs, 1996–1997

	% at start of IVF* procedure (n = 6,936)
Maternal age (years)	
35–39	25.2
40–44	50.3
45–49	21.9
50–54	2.6
Previous pregnancies	
0	45.9
1	21.9
2	15.0
≥3	17.2
Previous livebirths	
0	75.1
1	16.1
2	5.8
≥3	3.0
Previous ART* procedures	
0	51.4
1	18.3
2	11.6
≥3	18.7
No. of embryos transferred	
1	1.7
2	8.0
3	35.5
4	32.6
5	13.0
6	6.5
≥7	2.7
Embryo choice†	
Yes	46.8
No	53.2
Use of intracytoplasmic sperm injection	
Yes	28.5
No	71.5
Use of assisted hatching	
Yes	24.5
No	75.5

* IVF, in vitro fertilization; ART, assisted reproductive technology.
† Known embryo choice for an IVF procedure was determined by the cryopreservation of extra, nontransferred embryos following the procedure.

TABLE 2. Relation between maternal age, number of embryos transferred, and embryo choice for in vitro fertilization procedures performed on patients aged 35–54 years in the United States using fresh embryos derived from donor eggs, 1996–1997

Maternal age (years)	Average no. of embryos transferred	% of procedures with known embryo choice†
35–39	3.73	45.6
40–44	3.83	47.4
45–49	3.78	46.6
50–54	4.13*	47.5

* $p < 0.01$ for comparison between the average number of embryos transferred in the given age group and all preceding age groups in the column.

† Known embryo choice for an in vitro fertilization procedure was determined by the cryopreservation of extra, nontransferred embryos following the procedure.

numbers of embryos transferred. For the no-embryo-choice group, procedures in which one or two embryos were transferred had particularly low success rates compared with procedures in which three or more embryos were transferred.

An overall trend of increasing multiple-birth rates with increasing numbers of embryos transferred was found for both embryo-choice groups. For procedures in which more than one embryo was transferred, the largest increase in multiple-birth rates was seen in the change from two embryos to three embryos. This was true regardless of embryo choice, but the rates were generally lower overall in the no-embryo-choice group.

Rates of triplet+ gestation approached or exceeded 10 percent regardless of embryo choice. For both embryo-choice groups, there was a significant trend toward increasing rates of triplet+ gestation with increasing numbers of embryos transferred. Rates of triplet+ birth were near 5 percent when three embryos were transferred. Triplet+ birth rates also tended to increase with increasing numbers of embryos transferred; however, these increases were not as marked as those for triplet+ gestation rates, and the test for trend produced a nonsignificant result. There was little variation in triplet+ birth rates on the basis of embryo choice.

The fact that a trend was found for increasing triplet+ gestations with increasing numbers of embryos transferred, while the trend for triplet+ births was not significant, is indicative of spontaneous or medical reductions in the number of fetuses. We were not able to differentiate spontaneous reductions from medical reductions.

Data from logistic regression analyses of livebirth and multiple livebirth, stratified by embryo choice, are presented in table 5. Increasing age was associated with a decreased chance of livebirth among women in the embryo-choice group. Age was not associated with risk of multiple birth for either embryo-choice group. For women in the embryo-choice group, transferring more than two embryos was not associated with livebirth but was associated with multiple birth. In contrast, in the no-embryo-choice group, transferring more than two embryos was associated with both livebirth and multiple birth. Neither prior livebirth, prior ART, nor assisted hatching was independently associated with either outcome variable. Intracytoplasmic sperm injection was associated with a decreased chance of livebirth and multiple birth in the no-embryo-choice group. This may reflect the differential use of intracytoplasmic sperm injection for patients with a poorer prognosis. Data with which to explore this hypothesis were not available.

Results from models examining triplet+ gestations among both embryo-choice groups and triplet+ births among procedures without embryo choice generally confirmed the results of the stratified analyses presented in tables 3 and 4 (data not shown). (We were unable to evaluate a multivariable model for triplet+ births among procedures with embryo choice because of small sample sizes in some subgroups.)

Results from our sample of donor egg procedures are presented in table 6 alongside rates of livebirth and multiple birth among women of various ages who used IVF with their own eggs. This presentation is limited to those procedures with known embryo choice—a more homogeneous

TABLE 3. Rates of livebirth and multiple livebirth, by maternal age, for in vitro fertilization procedures performed on patients aged 35–54 years in the United States using fresh embryos derived from donor eggs, 1996–1997

Maternal age (years)	Livebirth deliveries per IVF† transfer procedure		Multiple livebirths per LBD†,‡		Triplet or higher-order gestations per pregnancy§		Triplet or higher-order births per LBD§	
	No. of transfers	%	No. of LBDs‡	%	No. of pregnancies§	%	No. of LBDs§	%
35–39	1,749	39.5	684	45.5	746	18.6	641	9.2
40–44	3,489	40.8	1,410	42.5	1,561	15.4*	1,319	5.0**
45–49	1,517	38.8	586	43.2	665	14.4	552	5.4
50–54	181	33.2	60	36.7	68	8.8	55	3.6
χ^2 (test for trend)/ p value	1.26	NS†	1.49	NS	7.00	$p < 0.01$	8.5	$p < 0.01$

* $p < 0.05$; ** $p < 0.001$ (comparison between the proportion in a given age group and the proportion in the preceding age group within the same data column).

† IVF, in vitro fertilization; LBD, livebirth delivery; NS, not significant.

‡ Excludes cycles in which only one embryo was transferred.

§ Excludes cycles in which only one or two embryos were transferred, since these cycles are extremely unlikely to result in triplet or higher-order pregnancies or births.

TABLE 4. Rates of livebirth delivery, multiple livebirth, triplet or higher-order livebirth, by number of embryos transferred and embryo-choice group,† for in vitro fertilization procedures performed on patients aged 35–54 years in the United States using fresh embryos derived from donor eggs, 1996–1997

No. of embryos transferred	Livebirth deliveries per IVF‡ transfer procedure (%) (*n* = 6,936)			Multiple livebirths per livebirth delivery§ (%) (*n* = 2,761)			Triplet or higher-order gestations per pregnancy¶ (%) (*n* = 3,040)			Triplet or higher-order births per livebirth delivery¶ (%) (*n* = 3,040)		
	Total	Embryo choice: Yes	Embryo choice: No	Total	Embryo choice: Yes	Embryo choice: No	Total	Embryo choice: Yes	Embryo choice: No	Total	Embryo choice: Yes	Embryo choice: No
1	17.0	40.0	15.9									
2	31.0**	46.3	21.2	23.1	30.7	12.5						
3	42.2***	45.0	38.8***	41.0***	42.9*	38.4***	11.4	13.1	9.0	4.7	5.2	4.1
4	40.0	42.8	37.1	46.5*	50.1*	42.2	16.9***	19.6**	13.9*	7.5**	9.3**	5.5
5	38.7	39.2	38.4	49.9	57.1	45.0	20.8	25.7	17.5	6.9	7.9	6.2
6	44.3	41.2	46.0*	44.2	50.8	41.2	20.2	23.5	18.4	4.5	7.9	2.9
≥7	41.6	38.6	42.6	48.1	47.1	48.3	25.2	18.5	27.6	9.1	5.9	10.0*
χ^2 (test for trend)	11.2	4.7	39.0	19.8	15.6	11.6	33.1	15.8	25.5	1.9	2.4	1.1
p value	<0.001	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	NS‡	NS	NS

* $p < 0.05$; ** $p \le 0.01$; *** $p \le 0.001$ (comparison between the proportion in a given "no. of embryos transferred" group and the proportion in the preceding embryo transfer group within the same data column).

† Known embryo choice for an in vitro fertilization procedure was determined by the cryopreservation of extra, nontransferred embryos following the procedure.

‡ IVF, in vitro fertilization; NS, not significant.

§ Excludes cycles in which only one embryo was transferred.

¶ Excludes cycles in which only one or two embryos were transferred, since these cycles are extremely unlikely to result in triplet or higher-order pregnancies or births.

group with respect to embryo quality. (The analyses of nondonor procedures were performed as part of a previous study (11).) Among patients using their own eggs, a definite age trend of decreased livebirth rates with increasing age was found, even when the number of embryos transferred was held constant (two-embryo group: $\chi^2 = 6.33$, $p < 0.05$; three-embryo group: $\chi^2 = 13.3$, $p < 0.001$). In contrast, no age trend was found for livebirth rates among patients using donor eggs (two-embryo group: $\chi^2 = 2.0$, not significant; three-embryo group: $\chi^2 = 0.001$, not significant). Notably, the livebirth rates for these patients were comparable to, and even higher than, the rates for the youngest patients who used their own eggs. Multiple-birth rates among donor and nondonor procedures showed patterns that were similar to the livebirth trends, albeit less pronounced.

DISCUSSION

In 1996–1997, a total of 6,936 IVF procedures using fresh embryos derived from donor eggs were reported among women aged 35–54 years in the United States. These procedures resulted in over 3,000 pregnancies and more than 2,500 livebirth deliveries. Rates of multiple birth in this population generally exceeded 40 percent; this is higher than the rate found in the general population (2.9 percent in 1997 (1)) and significantly higher than that previously reported for IVF patients of the same age who used their own eggs (11).

Our finding that maternal age was not associated with multiple birth suggests that egg factors are more important than uterine factors in assessing risk of multiple birth. The absence of an age effect on multiple-birth risk for patients using donor eggs contrasts sharply with the striking age trends found for IVF patients who used their own eggs (11). Thus, if our assumption that most US egg donors are in their early thirties or younger is correct, the age of the woman providing the eggs is an important variable to factor into embryo transfer decisions.

Nonetheless, this study suggests that uterine factors may also play a role in multiple-birth risk, albeit secondary to the role of egg factors. When we examined separately the risks for triplet+ gestation and triplet+ birth, we observed a modest trend toward decreasing risk with patient age. Additionally, there was a modest decline in the livebirth rate in the oldest patient age group. We presumed that the ages of the egg donors were similar across patient age groups, and anecdotal reports from IVF clinicians indicate that IVF patients usually use young egg donors, regardless of patient age. However, in a small number of procedures, a woman selects a friend or family member to serve as an egg donor. We did not have sufficient data to evaluate whether there was a correlation in these cases between donor age and patient age and, if so, whether there were enough such cases in the current data set to have impacted the rates of livebirth and triplet+ birth.

Both number of embryos transferred and embryo quality, as measured by cryopreservation of nontransferred embryos or "embryo choice," were important in assessing risk of multiple birth. Among those procedures with known embryo

TABLE 5. Adjusted* odds ratios for livebirth delivery and multiple livebirth among in vitro fertilization procedures performed on patients aged 35–54 years in the United States using fresh embryos derived from donor eggs, 1996–1997

	Livebirth delivery				Multiple livebirth			
	Embryo choice		No embryo choice		Embryo choice		No embryo choice	
	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval	Odds ratio	95% confidence interval
Maternal age (years)†								
35–39	1.0‡		1.0‡		1.0‡		1.0‡	
40–44	1.0	0.8, 1.2	1.1	0.9, 1.3	0.8	0.6, 1.1	0.9	0.7, 1.2
45–49	0.8	0.7, 1.0	1.0	0.8, 1.2	0.9	0.6, 1.2	1.0	0.7, 1.4
50–54	0.6	0.3, 0.9	0.7	0.4, 1.2	1.1	0.5, 2.5	0.7	0.3, 1.8
No. of embryos transferred§								
2	1.0‡		1.0‡		1.0‡		1.0‡	
3	1.0	0.7, 1.3	2.5	1.8, 3.3	1.7	1.1, 2.7	4.2	2.0, 8.7
4	0.8	0.6, 1.1	2.2	1.6, 2.9	2.2	1.4, 3.5	5.2	2.5, 10.7
5	0.7	0.5, 1.0	2.3	1.7, 3.2	3.1	1.8, 5.4	5.5	2.6, 11.8
6	0.7	0.4, 1.1	2.8	1.9, 4.0	2.0	1.0, 4.1	4.1	1.9, 9.2
≥7	0.7	0.4, 1.5	2.3	1.4, 3.6	1.9	0.6, 5.9	5.5	2.2, 13.9
Prior livebirth	1.2	1.0, 1.4	1.1	0.9, 1.3	1.1	0.9, 1.5	1.0	0.8, 1.3
Prior assisted reproductive technology procedure	0.9	0.8, 1.1	0.9	0.8, 1.1	1.1	0.9, 1.4	1.2	0.9, 1.5
Intracytoplasmic sperm injection	1.0	0.8, 1.2	0.8	0.7, 0.98	0.9	0.7, 1.2	0.7	0.6, 0.96
Assisted hatching	1.0	0.9, 1.2	1.0	0.9, 1.2	0.8	0.6, 1.1	1.2	1.0, 1.6

* Adjusted for all variables shown in the table.
† We repeated all analyses with age used as an ordinal variable. Results indicated a significant trend of declining livebirth with increasing age for the embryo-choice group ($\chi^2 = 5.3$, $p < 0.05$). Results for age from all other models were not significant.
‡ Reference group.
§ Procedures in which only one embryo was transferred were excluded from the models.

choice, moving from the transfer of two embryos to the transfer of three embryos had no effect on the chance of a livebirth (46 percent vs. 45 percent), but it significantly increased the risk of multiple birth (from 31 percent to 43 percent). This suggests that for donor egg procedures, there is little additional benefit but significant risk in transferring more than two embryos when the embryos are assessed as being of reasonable quality. Even limiting embryo transfer to two among these women was still associated with a 31 percent rate of multiple birth. The number of women who elected to have only one embryo transferred was too small ($n = 5$) to provide stable results; still, it is noteworthy that

TABLE 6. Rates of livebirth delivery and multiple livebirth, by egg type, number of embryos transferred, and maternal age, for in vitro fertilization procedures with known embryo choice* performed in the United States, 1996–1997

Maternal age (years)	Livebirth delivery (%)				Multiple livebirth (%)			
	Two embryos transferred		Three embryos transferred		Two embryos transferred		Three embryos transferred	
	Donor egg	Nondonor egg	Donor egg	Nondonor egg	Donor egg	Nondonor egg	Donor egg	Nondonor egg
20–29		42.7		41.1		24.4		47.8
30–34		36.0		41.5		31.1		47.1
35–39	54.6	24.7	43.8	33.0	25.0	19.1	45.4	31.4
40–44	47.8	—†	46.4	18.8	30.2	—†	43.1	11.1
45–49	35.7		43.1		40.0		39.1	
50–54	57.1		45.7		—†		43.4	
χ^2 (test for trend)/p value	NS‡	$p < 0.05$	NS	$p < 0.001$	NS	NS	NS	$p < 0.001$

* Known embryo choice for an in vitro fertilization procedure was determined by the cryopreservation of extra, nontransferred embryos following the procedure.
† Insufficient sample size.
‡ NS, not significant.

two of these five women had a livebirth. This may indicate, as recent European studies have suggested, that using just one high-quality embryo can result in pregnancy rates comparable to those achieved with multiple embryos (32, 33). Although this is difficult to assess in the United States, since so few women in this country elect to transfer a single embryo (less than 2 percent of procedures performed in 1996–1997 involved the transfer of a single embryo), it is important to further investigate outcomes for the transfer of one high-quality embryo, since the transfer of a single embryo virtually eliminates the risk of multiple birth.

In contrast to women in the embryo-choice group, those in the no-embryo-choice group achieved a significantly higher rate of livebirth when transferring three embryos rather than two (39 percent vs. 21 percent). In this group, transferring more than three embryos bestowed little additional benefit. The increased chance of a livebirth associated with transferring a third embryo for these women, while significant, must be considered in light of the accompanying threefold increase in the rate of multiple birth (from 13 percent to 38 percent).

These data were not derived from a randomized trial but rather were observational and were based on patient choice regarding how many embryos to transfer and whether nontransferred embryos would be cryopreserved for future use. We used information on embryo choice (extra embryos cryopreserved) to control for potential differences in embryo quality, since embryo choice has been associated with increased rates of pregnancy and livebirth (11, 25–31). Procedures in which nontransferred embryos were cryopreserved for future use are presumably a much more homogeneous group with respect to embryo quality than procedures in which embryos were not cryopreserved. The latter group includes procedures in which all available embryos were transferred, as well as those in which nontransferred embryos were not cryopreserved for a variety of reasons (patient objection, lack of cryopreservation facilities, embryos judged not to be of sufficient quality, etc.). Only a large randomized trial could ensure complete comparability between women with different numbers of embryos transferred.

Few studies have been conducted with randomized assignment of donor eggs, and these have followed the oocyte donation model, in which eggs from a single donor are randomly allocated to two recipients from different age groups (e.g., ≤40 years and >40 years). This research design is more methodologically sound for investigating the effect of patient age on livebirth rate and multiple-birth risk among patients using donor eggs, but studies using this design have been small and have produced inconsistent results. Both Abdalla et al. (14) and Navot et al. (16) found no difference in pregnancy or delivery rates between older and younger donor egg recipients. However, Cano et al. (12) found that older recipients experienced significantly more miscarriages, and Borini et al. (13) found that older recipients had lower rates of pregnancy and implantation. All of these studies had sample sizes that were insufficient to consider multiple-birth risk or to compare groups on the basis of number of embryos transferred. These studies also used eggs donated by women undergoing IVF. It is difficult to ascertain the degree to which results from these studies might be generalizable to patients using eggs donated by women without known fertility problems.

Additional limitations of the present study stem from the fact that the ART database we used is designed for surveillance and therefore does not include detailed clinical information on each procedure. Specifically, no information on donor age or embryo quality, apart from whether nontransferred embryos were cryopreserved for possible future use, is collected.

The unit of analysis in this study was an IVF transfer procedure. Therefore, women who underwent more than one IVF procedure in 1996–1997 were multiply represented. This lack of independence could have affected the analyses of livebirth rates, for which the denominator is IVF procedures. It would not have affected the analyses of multiple-birth rates, because it is unlikely that a woman would achieve two livebirth deliveries from IVF procedures performed during a 2-year period. Although we did not have the necessary data to link multiple procedures from the same woman, we did have medical history data for each procedure, including prior ART procedures. Therefore, we repeated our analysis of livebirth rates after limiting the sample to women who were undergoing their first ART procedure. We found no difference in comparison with our original findings (data not shown).

Use of donor eggs continues to rise in the United States, and it is increasingly popular among older women. In 1997, donor eggs were used in less than 5 percent of ART procedures for women younger than 37 years but in more than 70 percent of procedures for women older than 46 years (34). The findings of this study support current guidelines from the American Society for Reproductive Medicine and the Society for Assisted Reproductive Technology for making embryo transfer decisions (35). These guidelines regarding the number of embryos to transfer vary by the age of the recipient for women using their own eggs. For women under age 35 years who have embryos deemed to be of high quality, it is recommended that no more than two embryos be transferred, whereas for women over age 40, the guidelines recommend limiting transfers to five embryos. The guidelines further recommend that when donor eggs are used, the age criterion for selecting the number of embryos to transfer should be the donor's age rather than the recipient's age. In the current study, we did not have data on the exact ages of the donors, but most ART clinics limit egg donation to women in their twenties and early thirties. Thus, it is reasonable to assume that the vast majority of donors who provided eggs for the procedures investigated in this study fell into that age range. Therefore, we believe that these results support the current guidelines' recommendation to consider the age of the donor when making embryo transfer decisions (35). Further research should examine success rates for electively transferring a single, high-quality donor embryo in order to assess whether embryo transfers may be limited to one for certain recipients without significantly jeopardizing their chance of a livebirth.

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