

# Trends in Multiple Births Conceived Using Assisted Reproductive Technology, United States, 1997–2000

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**ABSTRACT.** *Objective.* To examine trends in multiple births conceived using assisted reproductive technology (ART) in the United States between 1997 and 2000 and to estimate the proportion of all US multiple births attributable to ART use.

*Methods.* We analyzed population-based data of 109 519 live-born infants who were conceived in the United States using ART and born between 1997 and 2000 and population-based data of 15 856 809 live-born infants who were delivered in the United States between 1997 and 2000. Multiple birth rates (the number of live-born infants delivered in multiple gestation pregnancies per 1000 live births) and the proportion of all US multiple births attributable to ART were evaluated.

*Results.* The twin rate for ART patients increased between 1997 and 2000, reaching 444.7 per 1000 live births in 2000, whereas the triplet/+ rate declined substantially from 134.3 to 98.7 per 1000 live births from 1997–2000. From 1997–2000, the proportion of multiple births in the United States attributable to ART increased from 11.2% to 13.6%, whereas the proportion attributable to natural conception decreased from 69.9% to 64.5%. In 2000, the proportion of triplet/+ births attributable to ART and to natural conception was 42.5% and 17.7%, respectively. The contribution of ART to multiple births increased substantially with maternal age, from 11.6% for triplet/+ infants born to women aged 20 to 24 to 92.8% for women aged 45 to 49 years.

*Conclusions.* The contribution of ART to twin birth rates continues to increase, but the contribution of ART to triplet/+ birth rates has declined. *Pediatrics* 2003;111:1159–1162; assisted reproductive technology, fertilization in vitro, embryo transfer, multiple-birth offspring, multiple pregnancy.

ABBREVIATIONS. ART, assisted reproductive technology; CDC, Centers for Disease Control and Prevention.

Rates of multiple births rose substantially in the 1980s and 1990s in the United States.<sup>1</sup> From 1980–1997, the twin birth rate increased 42% from 18.9 to 26.8 per 1000 births, whereas the triplet and higher order (triplet/+) rate increased 5-fold

from 0.37 to 1.74 per 1000 births. Although the triplet/+ rate seems to have stabilized in the past few years, the rate for twins continues to increase.<sup>2</sup> Multiple birth is associated with poor infant and maternal health outcomes, including pregnancy complications, preterm delivery, low birth weight, congenital malformations, and infant death.<sup>3–9</sup>

The increasing use of assisted reproductive technology (ART) procedures (defined as any procedure that entails the handling of both eggs and sperm or of embryos for the purpose of establishing a pregnancy; it therefore does not include the use of fertility drugs when there is no intention of removing eggs and does not include intrauterine insemination) and other non-ART fertility treatments (eg, intrauterine insemination, use of ovulation-inducing drugs) in the past 2 decades has been implicated in the increase in multiple births. It is widely known that pregnancies conceived through the use of ART and non-ART fertility treatments are more likely to result in multiple births than naturally conceived pregnancies.<sup>10,11</sup> However, another factor that might be causing the increase is the concurrent shift in the maternal age distribution as more women delay childbearing into their late 30s and 40s. The risk for multiple birth among naturally conceived pregnancies increases with maternal age. Although risk for naturally conceived multiple births increases with maternal age, so does the risk for fertility problems that may necessitate the use of fertility treatments to achieve conception. Thus, it is important to disentangle these potential effects when evaluating trends.

We used population-based surveillance data of ART procedures performed in the United States and US birth certificate data to estimate the percentage of multiple births in the United States annually from 1997 through 2000 that are attributable to natural conception and the percentage attributable to ART. The remaining percentage is primarily thought to be the result of non-ART fertility treatments (eg, use of ovulation drugs without ART or intrauterine insemination).

## METHODS

The total number of live births and multiple births born in the United States in 1997 through 2000 were derived from birth certificate data (US natality files) from the Centers for Disease Control and Prevention's (CDC's) National Center for Health Statistics.<sup>12</sup> These data represent 100% of births registered in the United States during the study period. The total number of liveborn infants and multiple infants in 1997 through 2000 who were conceived using ART was derived from the CDC's registry of ART procedures

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performed in the United States. The Fertility Clinic Success Rate and Certification Act of 1992<sup>13</sup> mandates that every clinic in the United States that performs ART procedures report pregnancy success rate data annually to the CDC. 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 CDC. A detailed description of this database has been published.<sup>10</sup> We estimate that the database includes >95% of ART procedures performed in the United States each year.

A multiple birth was defined as a live birth delivered in a multiple-gestation pregnancy. Although only liveborn infants were included in this study, the assignment of plurality was based on the total number of liveborn and stillborn infants delivered. Thus, a liveborn infant delivered from a pregnancy that also included a stillbirth is considered a multiple-birth infant.

Because data on whether births were conceived naturally or using infertility treatments are not available in the natality files, it was not possible to calculate directly the percentage of multiple births attributable to natural conception. Instead, these figures were estimated by applying 1971 age-specific ratios of multiple births<sup>12</sup> to the maternal age distributions for each birth cohort 1997–2000. We chose 1971 as the reference because this was before the widespread use of ovulation-inducing drugs and ART. Standardization was not performed separately by ethnicity of mother (Hispanic mothers composed 20% of all births for 2000) because data on maternal ethnicity were not available for the early 1970s.

The percentage of multiple births attributable to ART was estimated by dividing the total number of ART-conceived multiple births reported in the ART registry by the total number of US multiple births reported in the natality files. Because residency data for the ART registry was incomplete, it was not possible to exclude ART births to non-US residents. Thus, total US births also include births to non-US residents and differ slightly from those published.<sup>2</sup> The remaining percentage of multiple births unexplained by either natural conception or ART is presumed to be the result of non-ART fertility treatments such as the use of ovulation medications without ART.

We estimated secular trends in the distributions of naturally conceived, ART-conceived, and unexplained multiple births. Trends were examined for total birth cohort and separately by maternal age. The expected number of naturally conceived multiple births to women 50 years of age and older could not be

estimated because maternal age was edited for quality control purposes for ages 10 to 49 years in the national birth files for 1964–1997. However, there were fewer than 200 total births to women 50 years and older in 2000. This study was approved by the Institutional Review Board at the CDC.

## RESULTS

A total of 109 519 liveborn infants conceived from ART procedures performed in the United States were delivered between 1997 and 2000. The annual number of ART infant births increased 44% during this period, from 21 943 in 1997 to 31 582 in 2000. Table 1 displays the characteristics of these infants. Most were multiple births, primarily twins. The proportion of singletons and twins both increased during the study period, whereas the proportion of infants who were triplets decreased. In all years, most infants conceived using ART were born to women aged 30 to 39 years, with few born to women younger than 25 or older than 49 years. More than 75% of the infants were conceived using their mothers' eggs, rather than those donated by other women, and were conceived from newly fertilized embryos rather than embryos that had been previously frozen and thawed.

Table 2 presents the number and rate of twin and triplet/+ birth rates for the US and ART patients for 1997–2000. The twin birth rate in the United States increased from 26.8 to 29.3 per 1000 births during the study period. The twin birth rate for ART patients also increased from 434.5 to 444.7. In contrast, the triplet/+ birth rate peaked in 1998 at 1.9 per 1000 for total US live births and 140.5 per 1000 for ART births and declined thereafter.

The proportion of twin births in the United States

**TABLE 1.** Characteristics of Infants Who Were Born Between 1997 and 2000 and Were Conceived Using ART in the United States

	1997	1998	1999	2000
Number of liveborn infants conceived using ART	21 943	26 418	29 576	31 582
Plurality (%)				
Singleton	43.1	42.1	44.3	45.7
Twin	43.5	43.8	44.4	44.5
Triplet	12.2	12.8	10.6	9.3
Quadruplets/+	1.3	1.2	0.6	0.6
Maternal age distribution (%)				
<20	0.0	0.0	0.0	0.0
20–24	1.0	1.0	1.1	1.2
25–29	12.5	14.1	14.5	14.5
30–34	38.3	38.5	37.8	36.9
35–39	33.7	32.4	31.8	32.3
40–44	11.4	11.1	11.6	11.7
45–49	2.9	2.6	2.8	3.0
50–54	0.3	0.3	0.3	0.4
>54	0.0	0.1	0.0	0.0
Type of ART procedure*				
Fresh, nondonor	77.5	77.5	76.9	76.2
Fresh, donor	9.4	8.6	8.5	8.5
Frozen, nondonor	10.6	10.8	11.5	11.8
Frozen, donor	1.4	2.0	1.9	2.3
Gestational carrier	1.1	1.2	1.2	1.2

Numbers may not add to 100% because of rounding.

\* ART procedures are typically classified according to whether the woman used her own eggs (nondonor) or those donated by another woman (donor) and whether the embryos transferred were newly fertilized (fresh) or previously fertilized, frozen, and then thawed (frozen).

In addition, a woman other than the ART patient may carry or gestate the pregnancy (gestational carrier) with the intention of returning the infant to the ART patient.

**TABLE 2.** Number and Rate of Twin and Triplet/+ Births for the US and ART Patients, by Year 1997–2000

Year	Twins				Triplet/+ Infants			
	Total US*		ART†		Total US*		ART†	
	No. of Births	Birth Rate (per 1000)	No. of Births	Birth Rate (per 1000)	No. of Births	Birth Rate (per 1000)	No. of Births	Birth Rate (per 1000)
1997	104 208	26.8	9535	434.5	6752	1.7	2946	134.3
1998	110 743	28.1	11 580	438.3	7631	1.9	3711	140.5
1999	114 412	28.9	13 136	444.2	7327	1.8	3331	112.6
2000	118 997	29.3	14 043	444.7	7328	1.8	3118	98.7

\* Source: US natality files.

† Source: CDC ART registry.

estimated to have been conceived naturally declined from 73.2% to 67.3% from 1997–2000, whereas the proportion attributable to ART increased from 9.1% to 11.8% (Table 3). The remaining proportion, presumed to have been conceived using non-ART fertility treatments, increased from 17.7% to 20.9%. The estimated contribution of ART to the triplet/+ birth rate showed a different pattern. After an initial increase from 43.6% in 1997 to 48.6% in 1998, the proportion declined to 42.5% in 2000.

The proportion of twin and triplet/+ infants estimated to have been conceived naturally decreased substantially with maternal age, whereas the proportion attributable to ART generally increased with age in 2000 (Table 4). Although 0.8% of twins and 11.6% of triplet/+ infants born to women aged 20 to 24 were estimated to have been conceived using ART, 65.4% of twins and 92.8% of triplet/+ infants born to women aged 45 to 49 years were estimated to be attributable to ART. Only 8 of the 23 triplet/+ infants born to women older than 49 years were estimated to have been conceived using ART. Given the low probability of women this age conceiving either naturally or using non-ART infertility treatments, it should be noted that some or all of the remaining 15 infants may have been conceived using ART at clinics that did not report their data to the CDC. Similar patterns were found for 1997–1999 in terms of substantially larger proportions of twin and triplet/+ infants who were born to older women being attributable to ART compared with natural conception (data not shown).

### DISCUSSION

The total number of infants conceived using ART continues to increase. Although the proportion of these infants who are triplet/+ is declining, the total

proportion who are multiple births remains above 50%. The twin and triplet/+ birth rates for ART patients are 14-fold and 54-fold higher, respectively, than for the United States as a whole. ART and non-ART fertility treatments are accounting for an increasingly larger proportion of all multiple births and twin births in the United States. In contrast, after increasing from 1997–1998, the contribution of ART to triplet/+ births in the United States seems to be declining. Despite this decline, ART accounted for >40% of all triplet births in 2000. This is approximately double the proportion of triplet/+ births that were estimated to have been conceived using ART in 1990.<sup>14</sup>

The contribution of ART to twin and triplet/+ births increased dramatically with maternal age, reflecting that few women early in their reproductive life turn to these techniques to achieve pregnancy, whereas the use of these techniques is often necessary for most women beyond 45 years to achieve a pregnancy. That only 8 of the 23 triplet/+ infants born to women older than 49 years in 2000 were known to have been conceived using ART highlights an important limitation of this study: ART births are not completely reported to the registry. Each year 4% to 8% of ART clinics do not report their data to the CDC as required by law, and among clinics that did report data, a small number of pregnancies (256 [0.8%] in 2000) were lost to follow-up. This may result in an underestimation of the contribution of ART to multiple births in the United States.

Two additional limitations with a potential opposite effect stem from the fact that the ART data set does not have adequate residency data before 2000 and does not include information on where infants were born. Thus, we cannot determine how many of the ART-conceived infants were born outside the

**TABLE 3.** Proportion of Multiple Births Attributable to Natural Conception and to ART Procedures, United States, 1997–2000

Year	All Multiple Births			Twins			Triplet/+		
	% Natural Conception	% ART	% Unexplained	% Natural Conception	% ART	% Unexplained	% Natural Conception	% ART	% Unexplained
1997	69.9	11.2	18.9	73.2	9.1	17.7	18.4	43.6	38.0
1998	66.5	12.9	20.5	70.0	10.5	19.5	16.5	48.6	34.9
1999	65.1	13.5	21.4	68.2	11.5	20.4	17.3	45.5	37.3
2000	64.5	13.6	21.9	67.3	11.8	20.9	17.7	42.5	39.7

Natural conception refers to the multiple-birth infants who are expected to be conceived naturally, i.e., conceived without the use of any type of fertility treatment, ART or non-ART. Natural conception rates were estimated indirectly by applying maternal age-specific multiple birth rates from 1971 to age strata for each birth cohort, 1997–2000.

Numbers may not sum to 100% because of rounding.

**TABLE 4.** Proportion of Twin and Triplet/+ Births Attributable to Natural Conception and to ART Procedures, by Maternal Age, United States, 2000

Age	Twins				Triplet/+			
	N*	% Natural Conception	% ART	% Unexplained	N*	% Natural Conception	% ART	% Unexplained
20–24	22 393	73.9	0.8	25.4	450	57.4	11.6	31.2
25–29	30 655	70.5	6.8	22.7	1776	26.8	33.0	40.3
30–34	33 892	65.1	16.0	18.8	2859	11.8	44.6	43.6
35–39	19 659	62.7	22.3	15.0	1666	9.7	53.5	36.8
40–44	4073	49.4	36.3	14.3	374	6.7	64.4	28.9
45–49	668	11.7	65.4	22.9	69	†	92.8	†
>49	80	‡	65.0	‡	23	‡	34.8	‡

Natural conception refers to the multiple-birth infants who are expected to be conceived naturally, ie, conceived without the use of any type of fertility treatment, ART or non-ART. Natural conception rates were estimated indirectly by applying maternal age-specific multiple birth rates from 1971 to age strata for each birth cohort, 1997–2000.

Numbers may not sum to 100% because of rounding. The age group <20 years was not included because of the small number of women of this age using ART.

\* Source: US natality files.

† The proportion of triplet/+ births attributable to women 45 to 49 years could not be estimated because no triplet/+ births were reported to women in this age group in 1971, the year for which age-adjusted triplet/+ birth rates were applied to the 2000 maternal age distribution.

‡ The proportion of twin and triplet/+ attributable to natural conception for women older than 49 and the remaining unexplained proportion could not be estimated because birth records for mothers reported to be aged 50 and older in 1971 were edited and imputed to ages 10 to 49 years for the 1971 birth file.

United States or the number who were born to non-US residents. However, residency data available for ART procedures performed in 2000 suggest that only 1% of procedures are performed on women who are not US residents.

Despite these limitations, it is clear that ART continues to exert a powerful influence on birth plurality in the United States, particularly for older women. The declining contribution of ART to triplet/+ births may be attributable to a number of different factors. Additional analysis of the ART registry data revealed that the proportion of ART procedures that involved the transfer of 3 or more embryos, a predictor of triplet/+ birth outcome, decreased from 82% in 1997 to 67% in 2000. Changes in the distribution of the types of patients who received these higher order transfers may have also changed. Additional research is needed to investigate the decline in triplet/+ births to ART patients and their contribution to triplet/+ births in the United States.

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#### REFERENCES

- Martin JA, Park MM. Trends in twin and triplet births: 1980–97. *Natl Vital Stat Rep.* 1999;47:1–16
- Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM. Births: final data for 2000. *Natl Vital Stat Rep.* 2002;50:1–101
- Kiely JL. What is the population-based risk of preterm birth among twins and other multiples? *Clin Obstet Gynecol.* 1998;41:3–11
- Guyer B, Martin JA, MacDorman MF, et al. Annual summary of vital statistics—1996. *Pediatrics.* 1997;100:905–918
- Pharoah PO, Cooke T. Cerebral palsy and multiple births. *Arch Dis Child Fetal Neonatal Ed.* 1996;75:F174–F177
- Gardner MO, Goldenberg RL, Cliver SP, et al. The origin and outcome of preterm twin pregnancies. *Obstet Gynecol.* 1995;85:553–557
- Spellacy WN, Handler A, Ferre CD. A case-control study of 1,253 twin pregnancies from a 1982–1987 perinatal data base. *Obstet Gynecol.* 1990;75:168–171
- Kinzler WL, Ananth CV, Vintzileos AM. Medical and economic effects of twin gestations. *J Soc Gynecol Investig.* 2000;7:321–327
- Senat MV, Ancel PY, Bouvier-Colle MH, et al. How does multiple pregnancy affect maternal mortality and morbidity? *Clin Obstet Gynecol.* 1998;41:78–83
- Schieve LA, Peterson HB, Meikle SF, et al. Live-birth rates and multiple-birth risk using in vitro fertilization. *JAMA.* 1999;282:1832–1838
- Reynolds MA, Schieve LA, Jeng G, Peterson HB, Wilcox LS. Risk of multiple birth associated with in vitro fertilization using donor eggs. *Am J Epidemiol.* 2001;154:1043–1050
- National Center for Health Statistics. *Natality Public-Use Tapes and CD-ROMs 1971, 1997, 1998, 1999, and 2000.* Hyattsville, MD: National Center for Health Statistics
- Fertility Clinic Success Rate and Certification Act of 1992 (FCSRCA), P.L. 102–493, October 24, 1992
- Centers for Disease Control and Prevention. Contribution of assisted reproductive technology and ovulation-inducing drugs to triplet and higher-order multiple births—United States, 1980–1997. *MMWR Morb Mortal Wkly Rep.* 2000;49:535–538

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