SPECIAL ARTICLE

Trends in Embryo-Transfer Practice and in Outcomes of the Use of Assisted Reproductive Technology in the United States

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ABSTRACT

BACKGROUND

During the past decade in the United States, increasing attention has been paid to lowering the incidence of multiple gestations resulting from the use of assisted reproductive technology. To determine whether such efforts have been successful, we assessed national trends in embryo-transfer practice patterns and in outcomes after the use of assisted reproductive technology.

METHODS

We analyzed data on outcomes of assisted reproductive technology procedures as reported to the Centers for Disease Control and Prevention from 1995 to 2001 by fertility clinics in the United States. We also analyzed data from the National Center for Health Statistics on the rates of twin births and triplet or higher-order multiple births.

RESULTS

From 1995 to 2001 in the United States, the number of infertility clinics, the number of fresh-embryo cycles initiated, and the number of fresh-embryo transfers increased steadily. The average number of embryos transferred per cycle began decreasing in 1997, with the steepest decline (an 11.1 percent decrease) between 1998 and 1999. In contrast, the number of pregnancies and live births per cycle during the period from 1995 to 2001 steadily increased. Even though the percentage of pregnancies with twins did not change significantly between 1997 and 2001, the percentage of pregnancies with three or more fetuses significantly decreased every year, with the steepest decline (a 20.8 percent decrease) between 1998 and 1999, after the publication in 1998 of the American Society for Reproductive Medicine guidelines for embryo transfer.

CONCLUSIONS

Since 1997 in the United States, there have been consistent decreases in both the number of embryos transferred per cycle and the percentage of pregnancies with three or more fetuses, as well as a consistent increase in the percentage of live births per cycle.

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THE INCREASING AVAILABILITY AND USE of assisted reproductive technology in the United States has given thousands of infertile couples the opportunity to conceive and bear children.[1] To achieve successful outcomes while minimizing the number of assisted-reproduction attempts, in many cases multiple embryos are transferred into the uterus. The ultimate result is increases in the rates of twin gestations and triplet or higher-order gestations.[2,3] It is well known that multiple births are associated with serious short- and long-term health risks for women and their children and hence pose a public health problem.[4] Furthermore, the economic burdens for the parents and for society are substantial.[5]

Recognizing multiple gestations as an undesirable complication of assisted reproductive technology, many countries (such as Brazil, Denmark, Germany, Hungary, Saudi Arabia, Singapore, Sweden, Switzerland, and the United Kingdom) have enacted strict laws limiting the number of embryos (from two to four) that can be transferred per cycle.[6] In nations with such legislation, the penalties for violation of the laws may be severe; they include withdrawal of the license to practice medicine (in the United Kingdom and Sweden), fine or imprisonment (in Germany), and imprisonment with a substantial fine (in Switzerland).[6,7] The United States, however, has no such federal regulation of the practice of assisted reproduction, in part because of the basic belief that such decisions should be left to couples and their physicians.[8]

The incidence of multiple births in the United States is increasing, and there is a growing body of evidence that the transfer of fewer embryos helps to prevent multiple gestations while maintaining the pregnancy rate.[9-13] For these reasons, the American Society for Reproductive Medicine (ASRM), in conjunction with the Society for Assisted Reproductive Technology (SART), approved of and published (in June 1997 and January 1998, respectively) guidelines recommending maximal numbers of embryos for transfer, according to the woman's age, the quality of the embryos, and the opportunity for embryo cryopreservation.[14] The maximal numbers of embryos to transfer for women with an "above-average" prognosis (those less than 35 years of age who do not have cryopreserved embryos), an "average" prognosis (those 35 to 40 years of age), and a "below-average" prognosis (those more than 40 years of age or those who have had several failed cycles) are three, four, and five, respectively. These guidelines were later amended and republished in November 1999[15] on the basis of further evidence supporting the transfer of fewer embryos.[2,16] The amended guidelines include a new prognosis called "most favorable" (for those less than 35 years of age who have good-quality embryos and a sufficient quantity for cryopreservation), a category for which the transfer of no more than two embryos is recommended.

The clinical effect of the growing emphasis on reducing the incidence of multiple gestations attributable to assisted reproductive technology in the United States is not yet clear.[17] Some authors have suggested that the ASRM guidelines are "ineffective"[18] or "have failed to control the multiple-pregnancy problems"[7]; others have further suggested that the guidelines are insufficient and recommend that "a federal law be adopted limiting the number of embryos transferred per cycle."[19] Before legislation that would control embryo-transfer practice is considered, however, it is important to assess trends in the patterns of embryo-transfer practice and the associated outcomes. We analyzed national data on outcomes of the use of assisted reproductive technology from 1995 to 2001 in order to identify trends in embryo-transfer practices in relation to these outcomes.

METHODS

COLLECTION OF DATA

In accordance with the Fertility Clinic Success Rate and Certification Act of 1992, the Centers for Disease Control and Prevention (CDC) compiles and publishes annual data on success rates at fertility clinics throughout the United States.[20] Each year, SART (which is an affiliate of the ASRM) collects data from individual clinics and, per contract, shares these data with the CDC. To date, the CDC has published data on the success rates of fertility clinics for the years 1995 through 2001.

Pertinent data from the 1995 to 2001 success-rate reports were downloaded from the CDC Web site for analysis.[21] Only cycles involving fresh embryos from women's own eggs were analyzed, since these are used in the majority of cycles. The reports from most years provided age-group–specific summary data, expressed in percentages, for several variables of interest: cycles resulting in pregnancies, cycles resulting in live births, pregnancies with twins, and pregnancies with three or more fetuses. (The exceptions were the reports from 1995 and 1996,

which did not include data on the latter two variables.) All pregnancies in the CDC data set were confirmed by evidence of one or more gestational sacs in the uterus on first-trimester ultrasound examination. For purposes of calculating total percentages, we converted the age-specific percentages to raw numbers, added them, and then reconverted the data into percentages (as previously reported).[1] A new variable, singletons per pregnancy, was calculated by first determining the number of singletons (by subtracting the number of twin and higher-order multiple pregnancies from the total number of pregnancies) and then dividing by the total number of pregnancies.

The CDC data were organized according to the age of the women: for the 1995 and 1996 data, three age groups were used (less than 35, 35 to 39, and more than 39 years); for the 1997 and 1998 data, four age groups were used (less than 35, 35 to 37, 38 to 40, and more than 40 years); and for the 1999, 2000, and 2001 data, five age groups were used (less than 35, 35 to 37, 38 to 40, 41 to 42, and more than 42 years). Because these age distributions are not uniform, we chose the distribution based on four age groups (less than 35, 35 to 37, 38 to 40, and more than 40 years) to use in our analyses. This allowed us to present age-specific data for the years 1997 to 2001.

Data on the birth of twins and of triplets or infants from higher-order multiple gestations, as well as on the total number of live births in the United States from 1980 to 2001, were abstracted from National Vital Statistics Reports, published by the National Center for Health Statistics.[22,23]

STATISTICAL ANALYSIS

We calculated 95 percent confidence intervals for the cumulative rates of incidence of cycle outcomes and used the normal-distribution approximation formula to quantify random error around the measurements.[24] Linear regression analysis was used to compare age-adjusted trends in the number of embryos transferred per cycle and specific outcomes of the use of assisted reproductive technology from 1995 through 2001. All reported P values are two-sided. Linear regression analyses were performed with the use of SAS statistical software (version 8.2).

RESULTS

Table 1 shows U.S. trends for several outcomes related to the use of assisted reproductive technology. Despite the federal requirement to report success rates, each year approximately 5 to 9 percent of the fertility clinics either failed to submit their data to SART and the CDC or did not provide verification from the clinic's medical director that the tabulated success rates were correct. The number of infertility clinics, the number of fresh-embryo cycles initiated, and the number of fresh-embryo transfers performed steadily increased from 1995 to 2001. The mean number of embryos transferred per cycle began decreasing in 1997, with the steepest decline (an 11.1 percent decrease) occurring between 1998 and 1999. In contrast, the numbers of pregnancies and live births per cycle steadily increased from 1995 to 2001. Even though the rate of twin gestation (expressed as a percentage of pregnancies) did not change significantly between 1997 and 2001, the percentage of pregnancies involving three or more fetuses decreased every year, with the steepest decline (a 20.8 percent decrease) occurring between 1998 and 1999.

An examination of trends in the United States from 1980 to 2001 in the birth of twins and triplets or infants from higher-order multiple gestations, relative to the total number of live births (Fig. 1),[4,22,23] reveals a consistent increase in the rate of twin births. However, the birth rates of triplets or infants from higher-order multiple gestations stabilized from 1999 to 2001, after a steady rise from 1980 to 1998.

We subsequently performed a comparative trend analysis of the mean number of embryos transferred per cycle during the periods from 1995 to 1997 and from 1998 to 2001. The mean number of embryos transferred per cycle declined significantly during these two periods ($P<0.001$).

DISCUSSION

Our study shows that the mean number of embryos transferred per cycle in the United States has been decreasing since 1997. This decrease was associated with a significant decline in the rate of pregnancies with three or more fetuses, while overall rates of pregnancy and live birth were maintained. Furthermore, starting in 1999, the national rate of triplet and higher-order multiple births began to stabilize for the first time in at least 18 years.

The observed improvements in embryo-transfer practice coincide temporally with the publication of ASRM embryo-transfer guidelines in 1998. Although our study cannot prove a cause-and-effect

Table 1. Trends in and Outcomes of Assisted Reproductive Technology in the United States from 1995 to 2001, According to Women's Age.*

Variable and Age Group	1995	1996	1997	1998	1999	2000	2001	P Value†
Assisted reproductive technology clinics — no.	300	315	354	390	399	408	421	
Clinics reporting outcome data — no. (%)	281 (93.7)	300 (95.2)	335 (94.6)	360 (92.3)	370 (92.7)	383 (93.9)	384 (91.2)	
Fresh-embryo cycles initiated — no.	45,906	49,584	55,002	61,650	65,751	74,957	80,864	
Fresh-embryo transfers performed — no.	35,849	39,981	44,387	49,837	52,958	60,299	65,363	
Embryos transferred per cycle — mean no.								
<35 yr	4.0	3.9	3.7	3.4	3.0	2.9	2.8	
35–37 yr	NA	NA	3.8	3.6	3.3	3.2	3.1	
38–40 yr	NA	NA	3.9	3.7	3.5	3.5	3.4	
>40 yr	NA	NA	4.0	3.9	3.7	3.7	3.7	
All women	4.0±0.10 (3.8–4.2)	4.0±0.10 (3.8–4.2)	3.8±0.09 (3.6–4.0)	3.6±0.08 (3.4–3.7)	3.2±0.08 (3.1–3.4)	3.2±0.07 (3.0–3.3)	3.1±0.07 (3.0–3.2)	<0.001
Pregnancies — % of initiated cycles								
<35 yr	29.7	33.4	35.7	37.2	37.3	37.6	40.6	
35–37 yr	NA	NA	31.3	31.9	31.6	32.2	34.4	
38–40 yr	NA	NA	22.8	24.2	24.4	24.6	26.2	
>40 yr	NA	NA	13.2	13.4	13.6	13.5	14.4	
All women	24.4±0.20 (24.0–24.8)	27.3±0.20 (26.9–27.7)	29.5±0.19 (29.1–29.9)	30.5±0.19 (30.1–30.9)	30.6±0.18 (30.2–31.0)	30.7±0.17 (30.4–31.1)	32.8±0.17 (32.5–33.2)	<0.001
Live births — % of initiated cycles								
<35 yr	25.3	28.7	30.7	32.0	32.2	32.8	35.2	
35–37 yr	NA	NA	25.5	26.0	26.2	26.7	28.4	
38–40 yr	NA	NA	17.1	17.9	18.5	18.5	19.6	
>40 yr	NA	NA	7.6	8.2	8.2	7.7	8.4	
All women	19.6±0.42 (18.8–20.4)	22.6±0.40 (21.8–23.4)	24.0±0.18 (23.6–24.3)	24.9±0.17 (24.6–25.3)	25.2±0.17 (24.9–25.6)	25.4±0.16 (25.1–25.7)	27.0±0.16 (26.7–27.3)	<0.001
Singletons — % of pregnancies								
<35 yr	NA	NA	55.6	56.9	58.0	59.6	58.8	
35–37 yr	NA	NA	62.3	63.1	62.8	64.2	63.6	
38–40 yr	NA	NA	71.4	71.0	70.7	71.8	71.1	
>40 yr	NA	NA	81.9	82.0	85.4	82.5	83.0	
All women	NA	NA	61.3±0.38 (60.6–62.1)	61.9±0.35 (61.2–62.6)	62.6±0.34 (61.9–63.3)	63.9±0.32 (63.3–64.5)	63.3±0.30 (62.7–63.9)	0.34
Twins — % of pregnancies								
<35 yr	NA	NA	30.7	30.6	32.6	31.9	33.1	
35–37 yr	NA	NA	26.4	26.6	28.6	27.7	28.6	
38–40 yr	NA	NA	21.8	22.2	22.7	22.2	22.7	
>40 yr	NA	NA	15.3	13.9	12.2	14.6	14.5	
All women	NA	NA	27.3±0.35 (26.6–28.0)	27.4±0.33 (26.8–28.1)	29.0±0.32 (28.4–29.6)	28.4±0.30 (27.8–29.0)	29.3±0.28 (28.8–29.9)	0.29

Three or more fetuses — % of pregnancies								
<35 yr	NA	NA	13.7	12.5	9.4	8.5	8.1	
35–37 yr	NA	NA	11.3	10.3	8.6	8.1	7.8	
38–40 yr	NA	NA	6.8	6.8	6.6	6.0	6.2	
>40 yr	NA	NA	2.8	4.1	2.5	2.9	2.5	
All women	NA	NA	11.4±0.25 (10.9–11.9)	10.6±0.22 (10.2–11.1)	8.4±0.20 (8.0–8.8)	7.7±0.18 (7.4–8.0)	7.4±0.16 (7.1–7.7)	0.003

* Plus–minus values are means ±SE, with 95 percent confidence intervals shown in parentheses. NA denotes not available. Age-specific data from 1995 and 1996 were not available.
† Age-adjusted P values were calculated by tests for trend from 1995 to 2001. Because 1995 and 1996 age-specific data were not available, tests for trend with respect to the number of fetuses per pregnancy are restricted to 1997 to 2001.

relation between the establishment of embryo-transfer guidelines and changes in practice patterns, the trends in outcome are clear and consistent. The dramatic drop in the national rate of triplet and higher-order multiple births is probably due to the decline in the rate of such pregnancies attributable to assisted reproductive technology procedures, since more than one third (38.7 percent in 1996 and 43.3 percent in 1997) of such pregnancies in the United States are attributable to assisted reproductive technology.[25] Alternatively, it is possible that the decline in the national rate of triplet and higher-order births could be due in part to a substantial increase in the number of women undergoing multifetal pregnancy reduction after 1998.[26] The CDC data, however, do not include information on pregnancy reductions, and data are lacking on the use of this procedure at the national level.

Although the rate of twin pregnancies resulting from assisted reproductive technology procedures remained steady during the period from 1997 to 2001, the national rate of twin births continued to increase. This is not surprising, since the absolute number of twins conceived through assisted reproductive technology (along with the number of cycles initiated annually) has been increasing. Furthermore, twins born as a result of assisted reproductive technology account for only a small percentage of all twins born in the United States (11.4 percent in 1998)[22,27] and therefore account for only a limited portion of the increase in the national rate.

Our study, in which we used population-based data, validates the findings of prior studies[9-13] indicating that a decrease in the number of embryos transferred per cycle is associated with a decrease in the rate of high-order multiple pregnancies but not in the overall pregnancy rate. The guidelines set forth by the ASRM in 1998 were based on this premise, and it is clear that national practice patterns are moving steadily in this positive direction.

It is certainly possible that other factors besides the ASRM national guidelines influenced and helped to improve patterns of embryo-transfer practice. For example, some of the published studies[9-13] that led to the establishment of the guidelines may have directly affected practice patterns. If so, such an effect would help explain the moderate decrease in the mean number of embryos transferred per cycle beginning in 1997. Another possibility is that improvements in assisted reproductive technology since 1998 (including improved embryo-culture techniques and increased use of blastocyst trans-

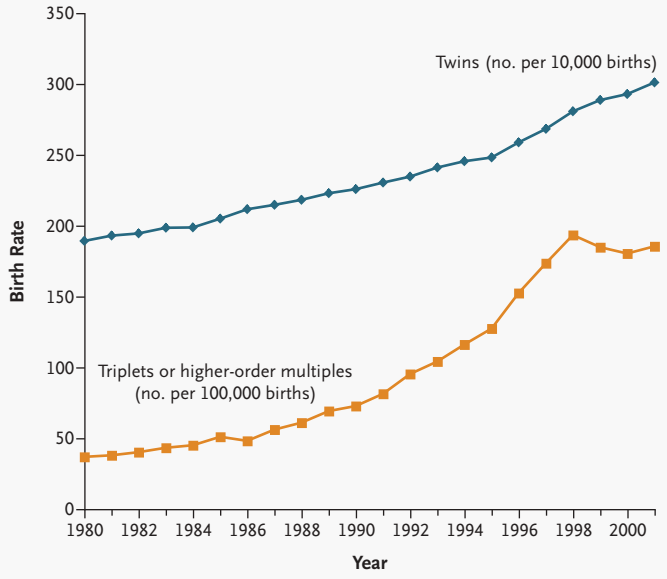

Figure 1. Trends in the United States from 1980 to 2001 in the Numbers of Twin Births and Triplet or Higher-Order Multiple Births, Relative to the Total Number of Live Births.

Standard errors for the rate of twin births are less than 0.9. Standard errors for the rate of triplet or higher-order multiple births are less than 2.3. Adapted from Jain and Hornstein,[4] with the permission of the publishers.

fers) may have led to increased rates of implantation and hence reductions in the number of embryos transferred. It is also possible that the advent of the embryo-transfer guidelines provided an impetus for clinicians to perform more blastocyst transfers, since only one or two blastocysts are usually transferred per cycle. However, the ASRM guidelines make no specific recommendations regarding blastocyst transfers. Furthermore, the transfer of blastocysts has been taking place in the United States since at least 1996[28,29]; data on its use at the national level are not available.

Another possible explanation for the improving trends is that, over time, increasing numbers of patients may have obtained insurance coverage for their infertility treatment. In a previous study, based on a review of national SART data from the CDC, we reported that the number of fresh embryos transferred per cycle and the rate of high-order pregnancies were lower in states that mandated insurance coverage for assisted reproductive technology,[1] although the relation between insurance coverage and outcomes of assisted reproductive technology procedures remains controversial.[30] Although there were no new state mandates requiring insurance companies to cover assisted reproductive procedures between 1995 and 2001, we could not control for the fact that individual insurance companies may have voluntarily expanded their policies to cover these procedures.

The lack of improvement in the rate of twin pregnancies resulting from the use of assisted reproductive technology is of concern. Even in Europe, where many fertility centers are restricted by law to the transfer of no more than two or three embryos per cycle, the incidence of twin pregnancies varies between 20 percent and 35 percent.[31] In an effort designed specifically to decrease the rate of twin gestations, fertility centers in Finland, Sweden, and Belgium have shown that the use of elective single-embryo transfers in selected patients reduces the rate of twin pregnancy without affecting overall pregnancy rates.[32,33] On the basis of their success, the European Society for Human Reproduction and Embryology in 2001 recommended elective single-embryo transfers for women less than 34 years of age who have a "top-quality embryo."[33] Furthermore, Belgium recently amended its national embryo-transfer policy to allow the transfer of only one embryo in women less than 36 years of age (on the first attempt). Sweden is trying a different approach, in that its national health care plan will cover an unlimited number of in vitro fertilization cycles in which a single embryo is transferred, but only up to four cycles if more than one embryo is transferred.[34] It is too early, however, to gauge the public health implications of these recommendations and policy changes.

Overall, our findings indicate that, in the United States, patterns in the practice of assisted reproductive technology and the associated outcomes are steadily improving. There is a consistent trend toward the transfer of fewer embryos per cycle, with an associated reduction in the rate of high-order multiple gestations, while the overall pregnancy rate remains steady. On the basis of these trends, it is reasonable and prudent to continue professional self-regulation rather than enact new legislation. Ongoing monitoring of trends is warranted to guide future changes in policy.

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