ORIGINAL ARTICLE

Cumulative Birth Rates with Linked Assisted Reproductive Technology Cycles

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ABSTRACT

BACKGROUND

Live-birth rates after treatment with assisted reproductive technology have traditionally been reported on a per-cycle basis. For women receiving continued treatment, cumulative success rates are a more important measure.

METHODS

We linked data from cycles of assisted reproductive technology in the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database for the period from 2004 through 2009 to individual women in order to estimate cumulative live-birth rates. Conservative estimates assumed that women who did not return for treatment would not have a live birth; optimal estimates assumed that these women would have live-birth rates similar to those for women continuing treatment.

RESULTS

The data were from 246,740 women, with 471,208 cycles and 140,859 live births. Live-birth rates declined with increasing maternal age and increasing cycle number with autologous, but not donor, oocytes. By the third cycle, the conservative and optimal estimates of live-birth rates with autologous oocytes had declined from 63.3% and 74.6%, respectively, for women younger than 31 years of age to 18.6% and 27.8% for those 41 or 42 years of age and to 6.6% and 11.3% for those 43 years of age or older. When donor oocytes were used, the rates were higher than 60% and 80%, respectively, for all ages. Rates were higher with blastocyst embryos (day of transfer, 5 or 6) than with cleavage embryos (day of transfer, 2 or 3). At the third cycle, the conservative and optimal estimates of cumulative live-birth rates were, respectively, 42.7% and 65.3% for transfer of cleavage embryos and 52.4% and 80.7% for transfer of blastocyst embryos when fresh autologous oocytes were used.

CONCLUSIONS

Our results indicate that live-birth rates approaching natural fecundity can be achieved by means of assisted reproductive technology when there are favorable patient and embryo characteristics. Live-birth rates among older women are lower than those among younger women when autologous oocytes are used but are similar to the rates among young women when donor oocytes are used. (Funded by the National Institutes of Health and the Society for Assisted Reproductive Technology.)

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N Engl J Med 2012;366:2483-91.

Live-birth rates after treatment with assisted reproductive technology (the ex vivo manipulation of sperm and oocytes to achieve a pregnancy) have traditionally been reported on a per-cycle basis.[1-3] Although this measure is easily calculated and is commonly used by national registries of assisted reproductive technology around the world, it has limited usefulness in estimating cumulative success rates with continued treatment.

Previous studies of cumulative live-birth rates with assisted reproductive technology evaluated linked cycles for women with residency or treatment in Massachusetts.[4,5] This study expands on these analyses by using national data to quantify cumulative live-birth rates as a function of the method of treatment, including the use of autologous versus donor oocytes.

Methods

Study Data and Oversight

The Society for Assisted Reproductive Technology (SART) Clinic Outcome Reporting System (CORS) database contains comprehensive data from more than 90% of all clinics providing assisted reproductive technology in the United States. Data were collected and verified by SART and reported to the Centers for Disease Control and Prevention (CDC) in compliance with the Fertility Clinic Success Rate and Certification Act of 1992 (Public Law 102-493). SART makes deidentified clinical data available for research purposes to persons or entities who have agreed to comply with SART research guidelines. Patients undergoing assisted reproductive technology at SART-associated clinics sign clinical consent forms that include permission to use their deidentified data for research. The study was approved by the institutional review boards at Dartmouth and at Michigan State University, which approved the use of deidentified data provided by SART. The data are submitted by individual clinics and vouched for by the practice director of each clinic. Approximately 10% of the clinics are audited each year by the CDC and SART to validate the accuracy of the reported data.

Linking Cycles to Individual Women

Women whose initial treatment cycle was reported to the SART CORS database between January 1, 2004, and December 31, 2008, were included. All cycles for these women that were reported through December 2009 were extracted from the database. The details of the methods used to link cycles to individual women are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

We excluded from these analyses women whose initial treatment was in 2009 (owing to lack of follow-up), women with a prior cycle of assisted reproductive technology, and women whose first cycle involved the use of a thawed embryo (which indicated previous treatment with assisted reproductive technology). Cycles were excluded from analyses if they had been designated as research, embryo-banking, or gestational-carrier (surrogate) cycles; in such cases, all subsequent cycles for that woman were also excluded. Cycles for an individual woman were censored after a live birth. Few women underwent more than seven cycles; therefore, only data from the first seven cycles for any individual woman were used.

Cycle Count

We assigned two sets of cycle counts. The first assignment sequentially numbered all the cycles for a woman, regardless of which treatment was given. The second assignment renumbered the cycles according to the type of treatment. In the case of a woman whose first, second, and fourth cycles involved the use of fresh oocytes and whose third and fifth cycles involved the use of thawed embryos, for example, the first, second, and fourth cycles would be renumbered as 1, 2, and 3, respectively, for the analysis of fresh oocytes, and the third and fifth cycles would be renumbered as 1 and 2, respectively, for the analysis of thawed embryos. Renumbering was used only when the analysis was restricted to a specific treatment, and it was assumed that the success rate for the treatment was independent of any other treatments previously given.

Live-Birth Rates

Data on live births were limited to births with a gestation of at least 22 weeks and a birth weight of at least 300 g. Three types of live-birth rates were calculated: the conditional live-birth rate at a specific cycle; a conservative estimate of the cumulative live-birth rate, which was based on

the assumption that none of the women who did not return for a subsequent cycle would have had a live birth; and an optimal estimate of the cumulative live-birth rate, which was based on the assumption that women who did not return for a subsequent cycle would have had the same live-birth rates as those who did return.

STATISTICAL ANALYSIS

The live-birth rates and their standard errors were estimated as follows. The conditional live-birth rate at a specific cycle was the probability of a live birth at that cycle and was equal to the number of live births, divided by the number of women who received treatment with assisted reproductive technology at that cycle. The conservative estimate of the cumulative live-birth rate was calculated as the number of live births up to and including a specific cycle, divided by the number of women who ever received that treatment. The standard errors for both these live-birth rates were computed with the use of the binomial distribution. The optimal estimate of the cumulative live-birth rate was based on the product-limit estimate; the standard error was computed with the use of Greenwood's approximation[6] (for details, see the Supplementary Appendix). The product limit and its error were the Kaplan–Meier estimates when all cycles were included in the analysis; in these cases, the patterns of cumulative live-birth rates were compared with the use of the log-rank test.

Since the assigned diagnosis may have changed during the course of treatment, the analysis according to diagnosis was limited to women who had a single diagnosis at the time of their last cycle. All cycles were classified according to the final diagnosis.

The primary results are presented graphically. Additional figures and the live-birth estimates and their standard errors are provided in the Supplementary Appendix. Estimates were omitted when the denominator was less than 100. Since most of the standard errors for the first three cycles were less than 1.0% (see the Supplementary Appendix), pairs of conditions with a difference greater than 5% differed by at least 3 SE, and therefore a test that they were equal would be highly significant. The data were analyzed with the use of SAS software, version 9.2 (SAS Institute), and Excel (Microsoft).

Table 1. Linked National Data on Outcomes of Assisted Reproductive Technology, 2004–2009.*

Data	Women	Cycles
	no.	
Original data set	386,549	783,952
Exclusions		
Initial cycle during 2009	60,842	87,216
Previous treatment with assisted reproductive technology	71,471	148,006
Cycles after first live birth	—	50,752
Designated for research†	1,626	4,338
Designated for embryo banking†	3,098	12,819
Designated for gestational carrier†	2,772	6,252
Cycle no. >7	—	3,361
Data set used for analysis	246,740	471,208

* Data are from the Society for Assisted Reproductive Technology Clinic Outcome Reporting System database.
† A cycle with this designation and all subsequent cycles from the same woman were excluded.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

The final data set for analysis included 246,740 women, with 471,208 cycles and 140,859 live births (Table 1). Live birth occurred in 30% of the cycles, and 57% of the women had a live birth. Characteristics of the study population are shown in Table 2. About 47% of the women were younger than 35 years of age, and 15% were older than 40 years of age.

LIVE-BIRTH RATES ACCORDING TO YEAR

Figures 1A and 1B show the optimal and conservative estimates of the live-birth rate per woman according to the year of first treatment. To determine the effect of length of follow-up, we also included a truncated set of data from women who had their first treatment in 2008, and we limited that data set to cycles that occurred in 2008 (i.e., with 0 to 12 months of follow-up). The optimal cumulative estimate (Fig. 1A) was not affected by the length of follow-up. However, the conservative estimate (Fig. 1B) was biased downward by the short follow-up period; the bias was small when there was a minimum of 12 months of follow-up. This bias was caused by counting the future cycles of women who did not return for a subsequent

Table 2. Baseline Demographic and Clinical Characteristics of the Study Population.*

Characteristic	Women (N = 246,740)	
Age		
Mean (yr)	35.5±5.1	
≥30 yr (%)	20.3	
31–34 yr (%)	26.5	
35–37 yr (%)	21.2	
38–40 yr (%)	17.4	
41–42 yr (%)	7.8	
≥43 yr (%)	6.9	
Race or ethnic group (%)†		
White	48.4	
Asian	6.4	
Hispanic	5.0	
Black	4.7	
Other or mixed	1.0	
Unknown	34.6	
	At First Cycle	At Last Cycle
Infertility diagnosis (%)‡		
Male factor	35.3	35.5
Endometriosis	11.9	12.0
Ovulation disorder or PCOS	14.0	14.1
Diminished ovarian reserve	21.0	24.1
Tubal factor	18.5	18.4
Uterine factor	4.4	4.6
Other	14.3	14.6
Unknown	12.4	11.4

* Plus–minus values are means ±SD. PCOS denotes the polycystic ovarian syndrome.
† Race or ethnic group was self-reported.
‡ Multiple diagnoses were possible, and the diagnoses may have changed over time; therefore, the totals are greater than 100%.

treatment as unsuccessful (i.e., assuming that they never had a live birth); a shorter follow-up period reduced the likelihood of observing a repeat treatment that may have resulted in a live birth. Approximately 25% of the women without a live birth at the first cycle did not return for a second cycle (Fig. 1C). In subsequent cycles, approximately 33% of women without a live birth did not return.

LIVE-BIRTH RATES WITH AUTOLOGOUS OOCYTES

In the analysis of cycles with autologous oocytes, we found a progressive decline in both the optimal and conservative estimates of the cumulative live-birth rate with increasing maternal age (P<0.001) and increasing cycle number (P<0.001) (Fig. 2A and 2B). At the third cycle, the conservative and optimal live-birth rates with autologous oocytes declined from 63.3% and 74.6%, respectively, for women younger than 31 years of age to 18.6% and 27.8% for those 41 or 42 years of age and to 6.6% and 11.3% for those 43 years of age or older. When donor oocytes were used, the rates were higher than 60% and 80% for all ages.

LIVE-BIRTH RATES ACCORDING TO DIAGNOSIS

When cycles with only autologous oocytes were analyzed, diagnoses of diminished ovarian reserve and uterine-factor infertility were associated with lower live-birth rates than were other diagnoses (Fig. 2D). Women with diagnoses of diminished ovarian reserve and uterine-factor infertility were significantly older than women with other diagnoses (mean age, 40 and 37 years, respectively, vs. 33 to 35 years for those with other specific diagnoses). Women with a diagnosis of diminished ovarian reserve were the most likely to be treated with donor oocytes; 29.1% of these women were treated with donor oocytes in the first cycle, increasing to 43.1% in the fifth cycle. When the analysis was restricted to women younger than 40 years of age, the live-birth rate among those with a diagnosis of diminished ovarian reserve was about 50% lower than among those with other diagnoses, and among women with a diagnosis of uterine-factor infertility, the live-birth rate was 25% lower (data not shown).

LIVE-BIRTH RATES ACCORDING TO TREATMENT

Figure 3 shows optimal estimates of live-birth rates as a function of the method of treatment, according to the original cycle numbering. The optimal estimates of live-birth rates after renumbering of the cycles to account for treatment changes between cycles, as well as the conservative estimates both with the original cycle numbering and after renumbering, are provided in the Supplementary Appendix.

We assessed live-birth rates in relation to oocyte source (autologous vs. donor) and embryo state (fresh vs. thawed). Figure 3A shows the optimal estimates of live-birth rates for the four possible combinations of these variables according to the original cycle numbering; thawed embryos could not be used in the first cycle. Fresh donor oocytes were associated with the highest

success rates. When cycles were renumbered (i.e., according to whether it was the first, second, or third time a given treatment was used), the cycles with fresh autologous oocytes and those with thawed autologous oocytes had similar success rates (see panels D and E in Fig. 3a in the Supplementary Appendix).

Additional subgroup analyses were restricted to cycles with fresh oocytes. Live-birth rates were significantly higher in cycles for which simultaneous cryopreservation was reported than in those for which it was not (Fig. 3B). Figure 3C shows the optimal estimates of live-birth rates categorized according to the number of embryos transferred (one, two, or three); for both autologous and frozen oocytes, the success rates were highest when two embryos were transferred. When autologous oocytes were used, the conservative and optimal estimates of cumulative live-birth rates at the third cycle with two embryos transferred were 49.1% and 76.7%, respectively, as compared with 21.9% and 42.7% when one embryo was transferred. Transfers performed at the blastocyst stage (day 5 or 6) were associated with higher success rates than those performed at the cleavage stage (day 2 or 3) (Fig. 3D). The respective conservative and optimal estimates of cumulative live-birth rates at the third cycle were 42.7% and 65.3% for transfer of cleavage embryos versus 52.4% and 80.7% for transfer of blastocyst embryos, when fresh autologous oocytes were used.

We estimated the live-birth rates for the first and second attempts (i.e., with renumbered cycles) when fresh embryos were transferred on day 5 or 6 with simultaneous cryopreservation. At the first attempt, the rates were 49.3% with an autologous oocyte and 59.4% with a donor oocyte when one embryo was transferred, and 55.8% and 65.9%, respectively, when two embryos were transferred. The optimal estimates of cumulative live-birth rates from two attempts (i.e., two renumbered cycles) were 71.7% (autologous) and 82.6% (donor) with one embryo transferred, and 77.4% and 85.9%, respectively, with two embryos transferred.

DISCUSSION

This study of nationwide U.S. data on cumulative live-birth rates per woman extends our prior studies of cumulative live-birth rates with assisted reproductive technology.[4,5] The overall success rates

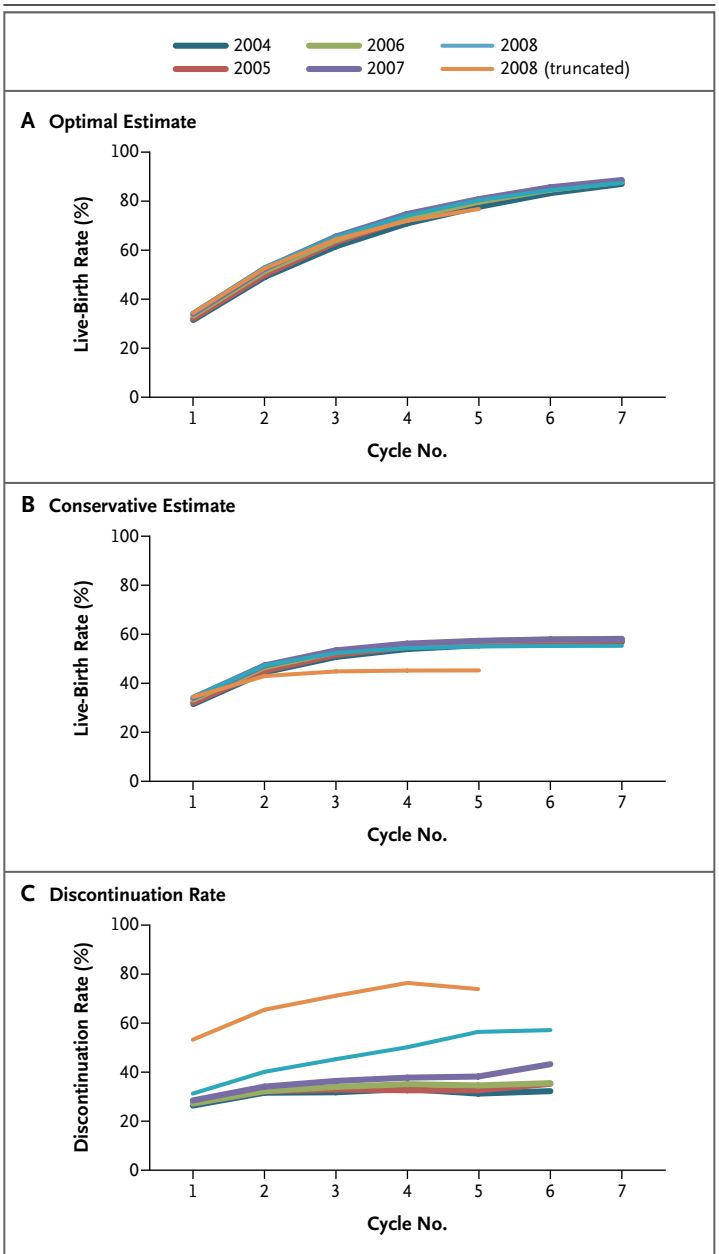

Figure 1. Cumulative Live-Birth Rates, According to Initial Treatment Year, 2004–2008.

Panel A shows the optimal estimate of the cumulative live-birth rate, which assumed that the live-birth rate among women who did not return for further treatment would be the same as the rate among those who continued treatment. Panel B shows the conservative estimate of the cumulative live-birth rate, which assumed that women who did not return for further treatment would never have a live birth. Panel C shows the discontinuation rate, expressed as the percentage of women without a live birth who did not return for a subsequent cycle of treatment. The data from 2008 (truncated) show the results for women whose initial treatment was in 2008, with cycles truncated to those occurring during 2008.

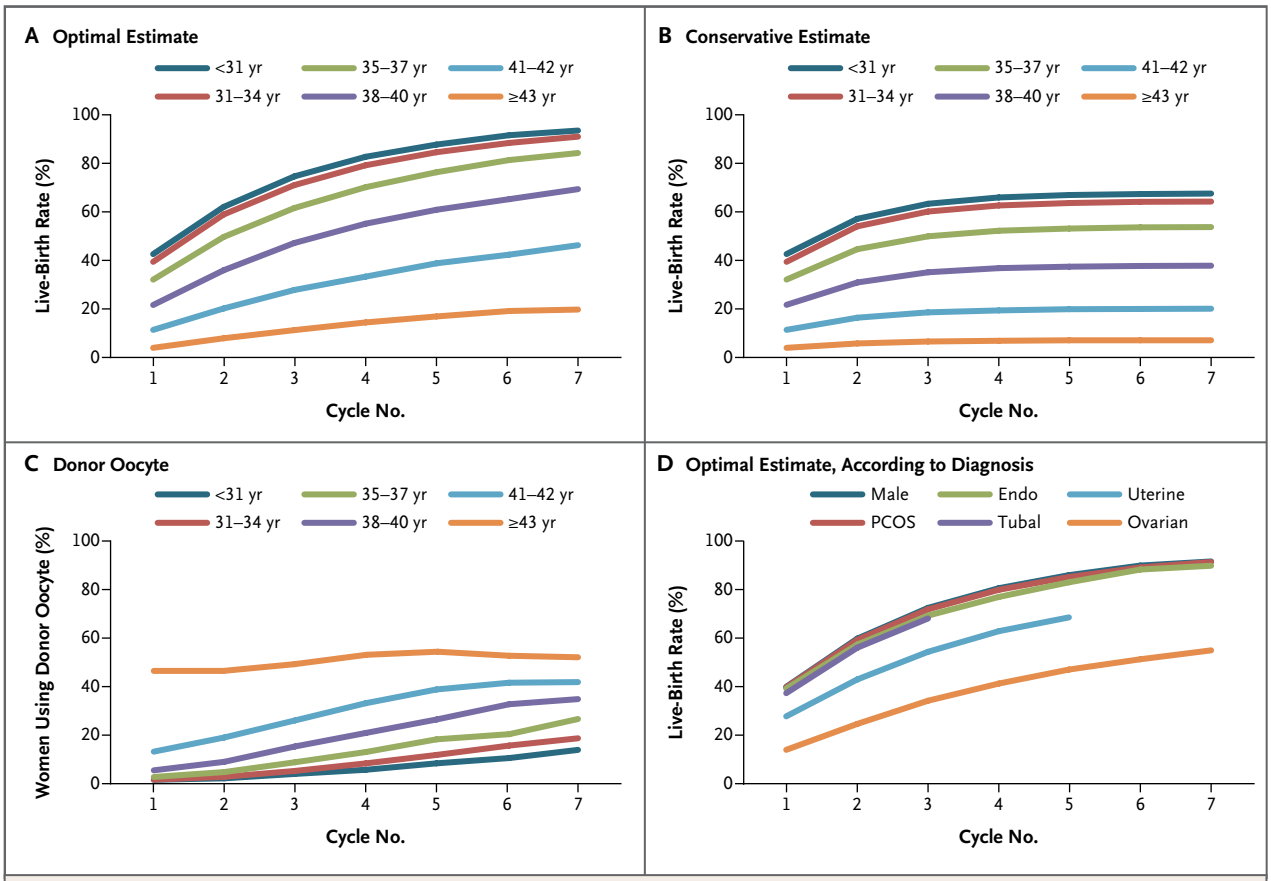

Figure 2. Cumulative Live-Birth Rates in Cycles with Only Autologous Oocytes, According to Maternal Age and Infertility Diagnosis, with Original Cycle Numbering.

Panel A shows the optimal estimates of cumulative live-birth rates, Panel B the conservative estimates, and Panel C the percentage of cycles in which a donor oocyte was used, according to maternal age group at the first cycle. Panel D shows the optimal estimates of cumulative live-birth rates, according to diagnosis. Endo denotes endometriosis, Male male-factor infertility, Ovarian diminished ovarian reserve, PCOS the polycystic ovarian syndrome (including ovulation disorders), Tubal tubal-factor infertility, and Uterine uterine-factor infertility.

reported here are similar to those reported with the use of the SART CORS data from Massachusetts, but the present study adds estimates of rates according to different assumptions about birth rates among women who did not return for further treatment,[4,5] and the considerably larger size of the current study allowed for analyses of subsets that were based on status with respect to simultaneous use of cryopreservation, number of embryos transferred, and day of transfer.

Our analyses took into account maternal age, diagnosis, response to treatment, and treatment method. Cycles with donor oocytes were consistently associated with higher live-birth rates than those with autologous oocytes. Live-birth rates declined with maternal age when autologous oocytes were used but not when donor oocytes were used. Cycles with simultaneous cryopreservation of supernumerary embryos, an imperfect proxy measure of embryo quality, yielded better results than those without cryopreservation.[7] Transferring the embryo at the blastocyst stage was associated with higher live-birth rates than transfer at an earlier stage; this may be an indirect measure of embryo quality or favorable patient characteristics.

The estimated natural fecundity rate of the general population is about 20% per month, and estimated rates of conceiving naturally are 45%, 65%, and 85% after 3, 6, and 12 months, respectively. Our optimal estimates — representing the likelihood of a live birth when there are no barriers to treatment continuation — support the hypothesis

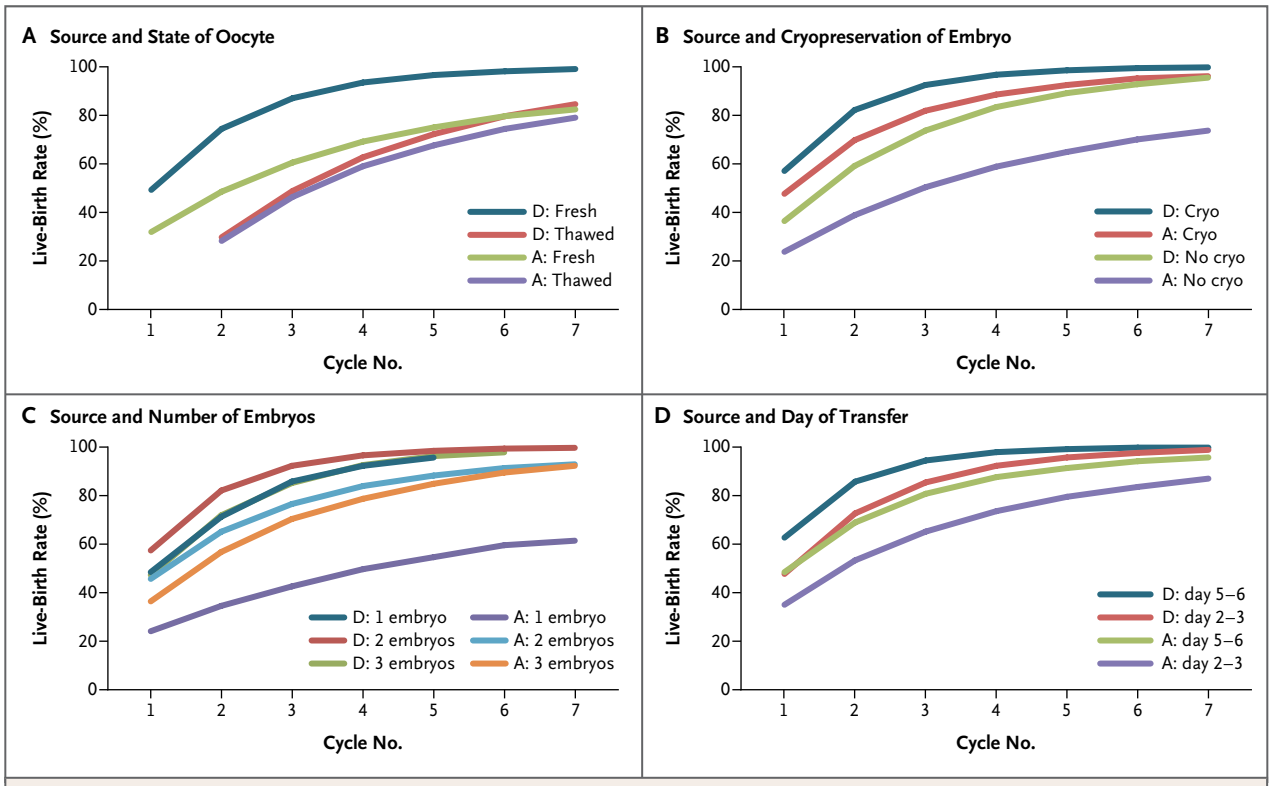

Figure 3. Optimal Estimates of Cumulative Live-Birth Rates, According to Treatment Method, with Original Cycle Numbering.

Panel A shows the rates according to source (donor [D] vs. autologous [A]) and state of the oocyte (fresh vs. thawed). Panel B shows the rates associated with cycles with fresh oocytes, according to source and status with respect to simultaneous cryopreservation of embryos (cryopreservation [Cryo] vs. no cryopreservation [No cryo]). Panel C shows the rates according to source and the number of embryos transferred (1, 2, or 3). Panel D shows the rates according to source and day of transfer of the embryo (day 2 or 3 vs. day 5 or 6).

that similar rates can be achieved by means of assisted reproductive technology, in the context of favorable patient characteristics (e.g., uterine environment), embryo quality, and treatment method; for example, our data suggest that the cumulative live-birth rates from two attempts can be greater than 70%. However, it should be recognized that our more conservative estimates represent the overall likelihood of success if the barriers that cause treatment termination, such as discontinuation for financial or social reasons, are similar to those for women included in our database.

Previous studies in the United States and Europe have cited stress, lack of treatment success, and finances as the major reasons for discontinuation of treatment.[8-10] Even when treatment is covered by insurance, discontinuation rates are high, ranging from 17%[10] to 65%.[11-14] In our study, the discontinuation rate was 25% after an unsuccessful first cycle and 33% after subsequent cycles. However, our results suggest a substantive potential benefit of additional cycles of treatment in many cases, unless physiologically contraindicated.

Our optimal estimates are similar to those from a small study conducted in Israel,[15] where there was no cost to the parents for treatment and no limit on the number of cycles. In that study, the cumulative live-birth rate among women younger than 35 years of age was 54.5% for up to three cycles and 85.1% for up to eight cycles.[15] In a Dutch study, 90% of the pregnancies achieved with the use of assisted reproductive technology were conceived within the first three cycles.[16]

A recent randomized, controlled trial in which embryos were randomly assigned to be transferred fresh versus thawed showed no significant difference in the implantation or pregnancy rate.[17] This finding is similar to our results for autologous oocytes; however, for cycles that used donor oocytes, the live-birth rate was higher for fresh embryos than for thawed embryos.

We found that live-birth rates were lowest among women whose infertility was attributed to diminished ovarian reserve or uterine factors, even after stratifying the analysis according to oocyte source and restricting the sample to women younger than 40 years of age. In pregnancies conceived by means of assisted reproductive technology, uterine-factor infertility is also associated with adverse obstetrical outcomes, even with adjustment for age, which supports the principle that the uterine environment affects pregnancy outcomes.[18]

It is standard practice to transfer the "better" embryos (according to morphologic measures) and to freeze those that are second tier. This may indicate a selection bias that existed when additional embryos were cryopreserved during the same cycle. In a prior analysis of the Massachusetts data, the use of cryopreservation in the first cycle of linked cycles was associated with increased cumulative success rates.[5]

Although the highest live-birth rates for both autologous and donor oocytes were achieved when two embryos were transferred, this also increased the possibility of a multiple birth.[19] The transfer of more embryos to obtain higher live-birth rates needs to be balanced against the increased risk of a multiple gestation and associated risks when more than one embryo is transferred.

Currently, many U.S. states have laws requiring insurance coverage for infertility treatment, although benefits vary widely. When it is specified, the number of treatment cycles is typically limited to two or three. Our findings show that when autologous oocytes are used, the success rates continue to rise beyond these limits, which has implications for insurance coverage. Also, our results may help providers and women decide when it is appropriate to change to donor oocytes.

There are several limitations of this study. First, because of the nature of the database, these outcomes do not account for naturally conceived pregnancies, which have been reported to occur in 9 to 28% of women who discontinue treatment with assisted reproductive technology.[15,16,20] Second, body-mass index was not considered in these analyses, since it was not included in the SART CORS database until 2007, but it is known to affect success rates.[21,22] Third, we evaluated oocyte state and oocyte source separately. In clinical practice, a patient might have successive cycles with fresh and thawed oocytes, and the oocyte source might change from autologous to donor. Our analyses did not estimate success rates over a complete (and often complicated) course of treatment.

The cumulative success rates derived from the present analyses can be used in the counseling of patients at the start of treatment; the conditional rates presented in the Supplementary Appendix can be used when making decisions about treatment continuation, if one or more cycles have been unsuccessful. The observation that success rates associated with the use of fresh donor oocytes did not decline with increasing maternal age or increasing cycle number supports consideration of their use in cases in which success with autologous oocytes is expected to be limited.

The views expressed in this article are those of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Supported by the National Cancer Institute, National Institutes of Health (grant R01 CA151973), and the Society for Assisted Reproductive Technology (SART).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank all the members of SART for providing clinical information to the SART Clinic Outcome Reporting System database for use by patients and researchers.

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