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Success rate with repeated cycles of in vitro fertilization–embryo transfer

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Objective: To analyze data from a large multicenter study to determine whether pregnancy and delivery rates decrease with repeated IVF-ET cycles.

Design: Multicenter retrospective study.

Setting: Participating centers from the Society of Assisted Reproductive Technology.

Patient(s): Fifty-four centers contributed 4,043 cycles of oocyte retrieval for uterine transfer.

Intervention(s): Oocyte retrieval for uterine transfer.

Main Outcome Measure(s): Pregnancy and delivery rates, analyzed according to age, program success rate, and whether the program was doing assisted hatching.

Result(s): Pregnancy and delivery rates for cycles 1, 2, 3, 4, and >4 were 33.7% and 27.0%, 33.9% and 27.4%, 28.9% and 23.4%, 25.9% and 16.1%, and 21.0% and 15.4%, respectively. The pregnancy rate decreased significantly for >4 cycle; delivery rate decreased significantly for cycles 4 and >4. Assisted hatching was strongly related to better odds of pregnancy (OR, 1.50) and delivery (OR, 1.44) in women under age 40, and for pregnancy (1.64) in women age 40–42 years.

Conclusion(s): Success rates do not decrease markedly with repeated IVF attempts, and the decrease did not change with program success rate, suggesting the IVF population is not markedly heterogeneous. Uncontrolled studies of new treatments for cycle repeaters cannot assume that success rate is poor without a treatment change. (Fertil Steril® 1998;69:1005–9. ©1998 by American Society for Reproductive Medicine.)

Key Words: In vitro fertilization, embryo transfer, pregnancy rate, delivery rate

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It is essential in counseling couples who have failed one or more cycles of assisted reproductive technology (ART) to be able to provide a reasonably precise estimate of the negative impact, if any, of previous treatment failure(s). This information is also important for third-party payors to calculate cost per success specific to cycle rank and for the purpose of policy decisions regarding insurance coverage.

Publications to date have included small to large data sets, reports from different countries, and data from either a single center or from multicenter studies. The latter have the advantage of avoiding inaccurate success rates because of small numbers, particularly at higher cycle ranks, and to average out any unusual selection of patients for initial or repeat cycles or aspects of management peculiar to a single center. Published studies often have tabulated pregnancies rather than deliveries, which does not assess any impact of cycle rank on miscarriage. Data usually spans a number of years, magnifying the confounding variable of rapidly improving success rates, which would tend to reduce any true decline with cycle rank. Finally, available data do not clearly include cycles performed at other centers, which could influence the validity of conclusions on the impact of cycle rank.

The present study was designed to obtain a large data set from multiple participating centers from the American Society for Reproductive Medicine (ASRM)/Society for Assisted Reproductive Technology (SART) registry for a single year (1994). A request was sent to all members asking them to participate if they believed that they had accurate data on all previous ART attempts, regardless of where these cycles had been performed. This required a separate submission of data on cycles according to whether previous ART attempts had

TABLE 1

Clinical pregnancy and delivery rates by cycle rank.

Cycle rank*	No. of pregnancies/ no. of retrievals (%)†	No. of deliveries/ no. of retrievals (%)‡
1	814/2,414 (33.7)	652/2,414 (27.0)
2	321/948 (33.9)	260/948 (27.4)
3	114/394 (28.9)	92/394 (23.4)
4	37/143 (25.9)	23/143 (16.1)
>4	30/143 (21.0)	22/143 (15.4)

Note: NS = not significant.

* No relationship to age or program success rates.

† P = NS for cycle 1–4 comparisons, $P < 0.01$ for cycle 1 versus cycle >4.

‡ P = NS for cycle 1–3 comparisons, $P < 0.01$ for cycle 1 versus cycle 4 and cycle 1 versus cycle >4.

TABLE 2

Effect of age on pregnancy and delivery rates.

Age group (y)	No. of pregnancies/ no. of retrievals (%)	No. of deliveries/no. of retrievals (%)
<40	1,209/3,468 (34.9)	980/3,468 (28.3)
40–42	95/447 (21.3)	63/447 (14.1)
>42	13/127 (10.2)	6/127 (4.7)

been made, because the standard SART registry did not contain this information. By obtaining a large data set from multiple centers, with all previous ART cycles identified, from a single year and with clinical pregnancy and delivery as outcome variables, we hoped to eliminate as many of the above criticisms as possible and to provide North American data that have not been available previously.

MATERIALS AND METHODS

Fifty-four member programs participated, providing a total of 4,043 oocyte retrievals. The index cycle was an oocyte retrieval for the purpose of uterine ET. A previous cycle was defined as an oocyte retrieval for the purpose of uterine or tubal transfer of gametes or embryos. Outcomes were clinical pregnancies and deliveries as defined by the SART/ASRM registry (1). If all embryos were frozen, outcomes from the first frozen ET cycle were assessed. Data were analyzed according to patient age, whether the program was performing assisted hatching in 1994, and the program's success rate in 1994. Oocyte donation and cycles requiring assisted fertilization by micromanipulation were not included.

Submitted data were rigorously examined for inconsistencies and returned to the submitting program for correction if necessary (e.g., if pregnancy rates [PRs] in women >40 indicated that oocyte donation was inadvertently included).

Data were analyzed with the use of a SAS program (SAS Institute, Inc., Cary, NC). The χ^2 test was used for categorical comparisons, and Pearson's correlation coefficient was used to determine correlations. Stepwise multiple logistic regression analysis was used to determine those predictor variables best correlated with cycle outcome.

RESULTS

Table 1 shows the clinical pregnancy and delivery rates for cycle ranks 1–4. Cycles with more than four previous retrievals were combined because of insufficient numbers at each cycle rank. Results were unchanged for a second cycle and then underwent a steady modest decline. For pregnancy only five or more was significantly lower than the initial cycle ($P < 0.01$). For delivery, both cycle rank 4 and 5 or more were significantly reduced ($P < 0.01$). The decline of cycle outcome showed no relationship to age or program success rate.

Table 2 shows the effect of age on IVF success. The delivery rate for women aged 40–42 was one half of that for women under age 40. The delivery rate for women age 43 or older was one third that of women aged 40–42 and one sixth that of women under age 40.

Assisted hatching was strongly related to improved pregnancy and delivery rates (odds ratio [OR], 1.5 and 1.44, respectively) for patients under 40 years of age ($P < 0.0001$). Although assisted hatching also was associated with improved PRs for patients 40–42 (OR, 1.64, $P = 0.042$), the OR for delivery (1.27) did not achieve statistical significance. We were unable to detect any change in either PRs or delivery rates related to assisted hatching in patients >42 years of age ($P > 0.1$).

DISCUSSION

Table 3 shows the results from previous studies (2–9) that have numerical data, tabulated for repeat cycles and contrasted to the present results. With one exception (study 3), results are remarkably consistent despite varying outcome measures and design, showing a modest reduction of successful outcome with increasing previous cycle failures. Note that study 3 (4) had the lowest number of pregnancies at cycle ranks three or more; a small number of additional pregnancies would have had a marked effect on their resulting conclusions. Another study that did not yield numerical results also showed a modest decline with increasing cycle rank, which was not statistically significant (10).

Multicenter studies not only yield large numbers, which reduce the possibility of erroneous conclusions because of small numbers, but also average out any unusual selection of patients in a particular center or unusual selection for repeat cycles or management of repeat cycles peculiar to a partic-

TABLE 3

Reported IVF outcomes according to cycle rank from previous publications compared with the present study.

Study (reference)	Cycle rank 1	2	3	4	>4
1. Guzick et al. (2) (no. of pregnancies/no. of retrievals) (%)	53/394 (13.5)	25/183 (13.7)	15/85 (17.6)	6/44 (13.6)	8/49 (16.3)
2. Padilla and Garcia (3) (no. of pregnancies/no. of transfers) (%)	119/486 (25)	66/229 (29)	32/114 (28)	20/60 (33)	14/41 (34)
3. Hershlag et al. (4) (no. of pregnancies/no. of "cycles") (%)	75/571 (13)	36/338 (11)	12/173 (7)	4/93 (4)	2/82 (2)
4. Haan et al. (5) (no. of ongoing pregnancies/no. of "started cycles") (%)	141/1,158 (12.2)	89/845 (10.5)	56/548 (10.2)	21/281 (7.5)	16/270 (5.9)
5. Tan et al. (6) (no. of births/no. of "treatment cycles") (%)	290/2,735 (10.6)	131/1,267 (10.3)	50/547 (9.1)	22/238 (9.2)	11/171 (6.4)
6. Fivnat (7) (no. of pregnancies/no. of retrievals) (%)	4,689/25,666 (18.3)	2,563/15,021 (17.1)	1,523/8,576 (17.8)	816/4,846 (16.8)	1,006/6,209 (16.2)
7. Yovel et al. (8) (no. of births/no. of cycles) (%)	NA	NA	NA	26/169 (15.4)	27/257 (10.5)
8. Templeton et al. (9) (no. of births/no. of retrievals) (%)	2,918*/18,239 (16.0)	1,169*/8,123 (14.4)	467*/3,706 (12.6)	86*/864 (10.0)	101*/1,084 (9.3)
9. Present study (no. of births/no. of retrievals) (%)	652/2,414 (27.0)	260/948 (27.4)	92/394 (23.4)	23/143 (16.1)	22/143 (15.4)
Studies 4,6,8,9 (%)	8,400/47,477 (17.7)	4,081/24,937 (16.4)	2,138/13,224 (16.2)	946/6,134 (15.4)	1,145/7,706 (14.8)
% of cycle 1	100	92.7	91.5	87.0	83.6

Note: NA = not applicable.
* Actual numbers calculated from percentages.

ular center. Single center reports also suffer from the likelihood of selective reporting because results may have been observed to be particularly good or poor, whereas other centers without unusual findings would have been less likely to submit their results.

When results from this study and the three other large multicenter studies (5, 7, 9) are combined (Table 3), delivery rates expressed as a percentage of the first cycle were 93%, 92%, 87%, and 84% for the second, third, fourth, and greater than four cycle ranks.

Factors other than the fertility potential of remaining couples could influence success with repeat cycles. Couples with a lower prognosis could elect to stop therapy or could be actively discouraged or even refused further treatment. Land et al. recently examined this effect (11). Although based on a relatively small number of pregnancies, the decline at cycle 3 was 24% compared with no decline in uncorrected rates in their program. In contrast, Haan et al. examined this same issue for their program and concluded that the prognosis was the same for couples who did or did not return for repeat cycles (12). In our experience the latter is more representative of the clinical practice of IVF, but a significant impact on results cannot be excluded and could overestimate the prognosis for poorer prognosis couples. Nevertheless, this does not invalidate these results as being representative of actual practice.

In contrast with the above negative selection factor, several investigators have mentioned the improved prognosis that is often achieved by modifying clinical management (e.g., for stimulation, hCG timing, semen preparation, and transfer method based on experience obtained in the previous cycle). This factor would tend to be maximal for cycle 2 and may explain the lack of decline we observed.

In this study, previous cycles were included from other programs. Because patients who have failed previously may seek out programs with higher success rates, participating programs could achieve better results than with comparable patients failing to conceive in their own program. However, as pointed out below, results were not influenced by program success rates.

Women having repeat cycles are older than those having their first cycle. In the French National registry, when results were corrected for age, there was no longer any significant decline with cycle rank (7).

The more heterogeneous the fertility potential of the couples starting treatment, the more marked the decline of success would be with repeat cycles, because the more fertile women would be removed from the population having repeat cycles (4). The modest decline in success would indicate that the IVF population is not markedly heterogeneous.

Clearly, small subsets of patients such as those with markedly reduced uterine blood flow (13) or a hydrosalpinx (14) have been identified to have a lower prognosis, but these results would indicate that the IVF population is fairly homogeneous and therefore that improved results will depend more on systematic improvements applied to all patients (e.g., better culture media or conditions) and less on modified treatment for poor prognosis subsets. Likewise, uncontrolled studies of new treatments for couples having repeated failure cannot be supported by an assumption that the success rate is poor without a treatment change.

We found that programs that were performing assisted hatching had significantly higher success rates than programs that were not performing assisted hatching. This could result in part from a positive effect of assisted hatching, but because of study design, it could also result from better programs having adopted assisted hatching relatively early in its development. Our finding that assisted hatching did not alter the decline with cycle rank does not conflict with studies showing that assisted hatching improves outcome with previous failed IVF (15, 16), because assisted hatching was not used only for cycle failure in this study. The lack of a significant effect of assisted hatching in women over age 43 and for delivery at age 40–42 may have resulted from inadequate sample size.

A surprising finding of the present study that has not been examined previously was that the decline was not greater in programs with higher success rates. This again would suggest that the patient population is not markedly heterogeneous. Also, because the better programs were using assisted hatching, one source of heterogeneity (patients with reduced prognosis without assisted hatching) may have been removed with the use of this ancillary technique.

In summary, when combining the results of this study with three other large multicenter trials, there is only a modest decline of success with repeated IVF cycle attempts, part of which results from the older age of cycle repeaters. These results suggest that any selection of patients with a better prognosis for repeat cycles may be counterbalanced by modifying the treatment of repeaters, that the IVF population is not markedly heterogeneous, and that better overall results will be obtained by general improvements of programs with lower results and by systematic improvements in IVF techniques.

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