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Comparison of the cumulative probability of pregnancy after in vitro fertilization-embryo transfer by infertility factor and age*

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Objective: To compare the cumulative probability of pregnancy after multiple IVF cycles by age and cause of infertility.

Design: A prospective study was done in which patients were followed from the time they registered for their first IVF cycle until they achieved a clinical pregnancy, withdrew from treatment, or study was terminated.

Patients, Setting, Treatments: Infertile women undergoing IVF-ET at the Cooper Institute for In Vitro Fertilization were enrolled in this study if the luteal phase leuprolide acetate (LA) and hMG controlled ovarian hyperstimulation (COH) regimen was used.

Main Outcome Measures: Clinical pregnancy, as determined by a positive β-hCG level and ultrasonographic confirmation of a gestational sac, and delivery rates based on number of women with live births were compared by infertility factor and age.

Results: The 3-month cumulative probability of pregnancy based on life table analysis was 33% in women with tubal factor who were ≤35 years of age, 25% in women with tubal factor who were >35 years of age, 30% for women with multiple factors who were ≤35 years of age, and 14% for women with multiple factors who were >35 years of age. The rate for the older women with multiple factors was significantly lower than that for the other groups. The delivery rates were lower for the women with multiple factors than for women under 35 with tubal factor only.

Conclusions: There is a significant effect of age and infertility factor on pregnancy and delivery rates. Physicians should consider these factors in evaluating their patients' prospects for success in IVF-ET. Fertil Steril 1994;61:257–61

Key Words: IVF, cumulative pregnancy rate, life table analysis, infertility, age

Couples presented with the option of undergoing IVF-ET for infertility often are interested in knowing not only the pregnancy rate (PR) per cycle, but the probability of pregnancy that can be expected after a specified number of IVF cycles. This information would enable the infertile couple, as well as the physician, to make an informed decision as to the benefit of continued IVF-ET cycles.

Evaluations of the IVF success after multiple cycles in six centers in the United States, United Kingdom, Australia, France, and Holland (1–6) have been performed using life table analysis. Pregnancy rates were 13% to 28% in the first cycle, 35% to 51% after three cycles, and 54% to 66% after six cycles. These studies conclude that there is little or no reduction in the chance of pregnancy in successive cycles for as many cycles as there have been sufficient data to study reliably. However, review of the patient characteristics of the populations used

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in each of these studies has shown that the couples studied varied in age, infertility factor, time undergoing treatment, type of controlled ovarian hyperstimulation (COH) used, and eligibility criteria for treatment at the center. All these variables must be taken into account when interpreting the results of each study to identify the patients for whom these results apply.

The objective of this study was to evaluate the cumulative probability of pregnancy and delivery after a series of IVF-ET cycles performed in one IVF center using the luteal phase leuprolide acetate (LA)-hMG COH regimen. Patients were classified by diagnosis and age; life table analysis was used in an attempt to evaluate the cumulative probability of pregnancy for each subgroup of patients. The goal of the study was either to corroborate the majority of previous studies showing a good prognosis for each new cycle or possibly to identify certain subgroups that demonstrate decreasing PRs with successive cycles.

MATERIALS AND METHODS

Data from all IVF cycles initiated in our IVF center from 1987 to 1992 were prospectively collected and stored in a computer database. Patients selected for inclusion in this study underwent cycles using a long LA and hMG COH regimen (7). The COH regimen was modified as previously described (8).

Patients were followed until a clinical pregnancy was achieved or they withdrew from the program. A clinical pregnancy was defined as one in which there was a positive β-hCG level together with identification of a gestational sac by ultrasound. Delivery rates were computed based on the number of women who delivered at least one live baby. Cycles that reached the stage of oocyte retrieval were included in the analysis.

Patients were first classified by single infertility factor or multiple infertility factors. The patients in the single infertility group were further classified into tubal factor only, endometriosis and/or pelvic adhesions, male factor, unexplained infertility, or other (including ovulatory dysfunction, uterine defects, or exposure to diethylstilbestrol). Within infertility groups, the patients were further subdivided by age at first IVF cycle, those $\leq$ 35 years of age and those $>$ 35 years of age.

Life table analysis was used to estimate the cumulative probability of pregnancy and delivery after multiple cycles of IVF. Pregnancy curves were compared by infertility factor and age group. The log rank test was used to evaluate differences in the pregnancy curves among the four groups. Based on the available sample size, the study had power of 0.8 to detect a 15% difference in PRs between the groups at the 0.10 significance level.

RESULTS

There were a total of 859 patients who underwent 1,500 cycles of IVF through the retrieval stage using the LA-COH regimen. There were 151 couples with multiple factors and 708 with single factors: 347 tubal, 74 endometriosis and/or pelvic adhesions, 112 male factors, 94 unexplained infertility, and 81 other factors. Because the groups had to be further classified by age at first cycle, there were insufficient sample sizes in the endometriosis, male, unexplained, and other groups to report on those results at this time. Further analysis was restricted to patients with either tubal factor only (239 were $\leq$35 years, 108 were $>$35 years) or those with multiple factors (101 were $\leq$35 years, 50 were $>$35 years).

The PRs by infertility factor and age are summarized in the life table presented in Table 1. Life table analysis showed that the 3-month cumulative probability of pregnancy for each of these groups was 33% for women with tubal factor who were $\leq$35 years of age, 25% for women with tubal factor who were $>$35 years of age, 25% for women with multiple

Table 1 Comparison of Cumulative Pregnancy Rates by Age and Infertility Diagnosis Using Life Table Analysis*

	Diagnosis age			
	Tubal ≤35 y	Tubal >35 y	Multiple ≤35 y	Multiple >35 y†
Cycle 1				
No. in cycle	239	108	101	50
No. of pregnancies	43	13	10	5
Pregnancy rate per cycle (%)	18	12	10	10
Cumulative probability of pregnancy (%)	18	12	10	10
Cycle 2				
No. in cycle	89	42	48	24
No. of pregnancies	10	4	6	1
Pregnancy rate per cycle (%)	11	10	13	4
Cumulative probability of pregnancy (%)	27	20	21	14
Cycle 3				
No. in cycle	36	17	17	13
No. of pregnancies	3	1	2	0
Pregnancy rate per cycle (%)	8	6	12	0
Cumulative probability of pregnancy (%)	33	25	30	14

* $P < 0.10$, log rank test comparing the four life tables.
† $P < 0.10$, log rank test comparing women >35 y with multiple factors to the other groups.

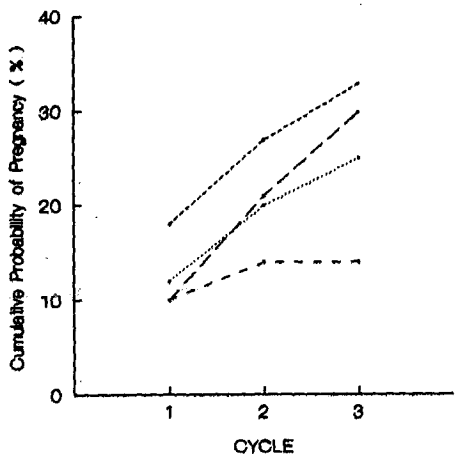

Figure 1 Cumulative pregnancy curves for all patients using life table analysis. ------, patients with tubal factor who are ≤35 years, · · · · · ·, patients with tubal factor who are >35 years; — — —, women with multiple factors who are ≤35 years; – – – –, indicates patients with multiple factors who are >35 years.

factors who were ≤35 years of age, and 14% for women with multiple factors who were >35 years of age.

Comparison of these PRs using the log rank test showed a significant difference between the four groups ($P < 0.10$). Further comparison showed that the couples with multiple factors in which the female was >35 years old had the lowest 3-month cumulative probability of success.

Although the PR in the tubal groups was lower for the older women, it did not reach statistical significance when compared with the younger women with tubal disease. Thus, there is a significant interaction effect between infertility factor and age. This interaction effect is illustrated in Figure 1.

The cumulative probability of delivering at least one live baby after IVF-ET is summarized in Table 2. These rates represent the proportion of women who deliver babies irrespective of the number of gestations. The highest rate was 30% and was attained by women ≤ 35 years with tubal factor only. The rate was significantly higher ($P < 0.10$) than the 20% rate attained by women ≤ 35 years with multiple factors and the 12% rate for women > 35 years with multiple factors. There were six sets of twins born to women in group 1 (tubal, ≤35 years), five sets of twins born to women in group 2 (tubal, >35 years), and five sets of twins and one set of triplets born to women in group 3 (multiple, ≤35 years); there were no multiple births in group 4 (multiple, >35 years).

DISCUSSION

As the national interest in controlling health care costs grows, the need for objective evaluation of expensive therapies becomes more imperative. This is applicable particularly to IVF-ET. As more insurance companies consider limiting the number of IVF cycles covered under policies and consider imposing a lifetime limit on infertility treatment, it becomes critical that both the patient and physician have some objective means for evaluating the success of continuing a specific treatment for each patient.

The methods used to date for evaluating IVF success have included the computation of PRs per cycle, life table analysis to estimate the cumulative probability of pregnancy after multiple IVF cycles, and mathematical modeling to estimate the "cure" rate. The results from these studies have been contradictory. Although the earliest study using life table analysis concluded that the PR per IVF cycle remains constant over multiple attempts and predicted a 98% cure rate if multiple cycles were pursued (1), Hershlag et al. (9) demonstrated marked reduction in cycle fecundity in successive cycles and explains this in terms of the heterogeneity of fecundity rates in the patient population. Using a mathematical model, they estimate that there are as many as 37% of couples who will never be "cured" and will not conceive with IVF therapy.

Some of the differences in results may be due to differences in the populations studied. Age and

Table 2 Comparison of Cumulative Live Birth Rates by Age and Infertility Diagnosis Using Life Table Analysis*

	Tubal ≤35 y	Tubal >35 y	Multiple ≤35 y†	Multiple >35 y†
Cycle 1				
No. in cycle	239	108	101	50
No. with live birth	40	11	7	4
Live birth rate per cycle (%)	17	10	7	8
Cumulative probability of live birth (%)	17	10	7	8
Cycle 2				
No. in cycle	89	42	48	24
No. with live birth	7	4	4	1
Live birth rate per cycle (%)	8	10	8	4
Cumulative probability of live birth (%)	23	19	15	12
Cycle 3				
No. in cycle	36	17	17	13
No. with live birth	3	1	1	0
Live birth rate cycle (%)	8	6	6	0
Cumulative probability of live birth (%)	30	24	20	12

* $P < 0.10$, log rank test comparing the four life tables.
† $P < 0.10$, log rank test comparing this group to women ≤ 35 years with tubal factor only.

cause of infertility also have been found to correlate with IVF success. Most studies that have demonstrated constant PR per cycle in IVF were done on women who were <40 years. Tan et al. (6) limited the study to women < 35 years because they had shown a marked reduction in success rate with women between the age of 35 and 39 years and a further reduction in women > 40 years. A significant negative correlation between age and IVF outcome was also shown by Padilla and Garcia (10). Similarly, reduced rates have been demonstrated for couples with male factor (1).

Most of the studies using life table analysis that have described a steady PR over multiple IVF cycles and recommend continued use of IVF by their patients may be misleading because results on cycles past six are based on small sample sizes. Most of the pregnancies observed in the other studies occurred in the first four cycles (93.4%, Guzick et al. [1]; 93.9%, Kovacs et al. [4]; 98.1%, Tan et al. [6]; and 87.7%, Haan et al. [11]).

In trying to explain the differences found by the studies, some discussions have centered on differences in the statistical methodology used to analyze the data to explain the differences found by the studies (9, 12). Besides the limitations inherent in each of these methodologies, interpretation of results has been hampered by the nonstandardization of terms used in the IVF literature. Standard definitions of pregnancy and cycle have not been adapted by all researchers. Pregnancy has been defined by use of β-hCG levels (4), ultrasound evidence of a gestational sac (6), or fetal viability as detected by heartbeat (11). Some rates have been reported for live births (12). Rates have been reported per IVF attempt (6), per oocyte retrieval (1, 4, 11), and per ET (11, 13).

Explicit descriptions of the patient population sampled in each study have not been given. Some centers have strict screening procedures for eligibility for entry into the IVF study. These selection criteria may influence the success rate of their patients. Thus, reports from centers with patients who are <35 years of age only present a much more optimistic view of the continued success of patients using IVF.

Studies that have reported results for specific causes of infertility have sometimes failed to state a clear definition of the cause and parameters used. Male factor has been found to correlate with reduced success, but the semen parameters used to define male factor are not always stated and uniform throughout the literature.

The time frame covered in each study has varied over a number of years in which the personnel, equipment, and general advances in IVF have increased greatly. As the technology of IVF has improved, the PRs have increased, with a dramatic improvement since 1990 (12, 14). In our center, the cumulative probability of pregnancy after three cycles for all patients with tubal and multiple factors has increased from 27% before 1991 to 33% after 1991.

In addition, there has been no standard definition used for the treatment, "IVF cycle," that is being evaluated. Some studies (1, 6) have included all cycles in which oocyte aspiration has been attempted irrespective of the stimulation protocol used; our study evaluated cycles in which the same protocol has been used throughout; and still others (10) have based their conclusions on programs that customize each IVF cycle to the patient's response on the previous cycle. It is thus difficult to differentiate whether success on a later cycle is due to the fact that the patients underwent multiple cycles or to the change in the protocol and thus a new "treatment" that has worked.

If multiple cycles of IVF only maintain their success rate if modifications are made each cycle, then the patient has to be informed of need for modifications and the physician has justification for expanding facilities and financing the cost of training, equipment, and personnel needed to maintain multiple protocols in one center.

Our results show that there is an interaction effect of age and infertility factor on the cumulative probability of pregnancy after three cycles of IVF. Older women with multiple factors have only a 14% probability of achieving a pregnancy after three cycles compared with a 30% probability for younger women with multiple factors and a 25% probability for older women with tubal factors. Thus, we can conclude that the cumulative probability of pregnancy after IVF is not uniform for all couples. Older couples with multiple factors need to be advised of other possible stimulations, donor options in IVF, or other therapies. Women with multiple factors also have a lower probability of delivering a live baby. Further study of patients with other factors are needed to identify other couples with reduced chances of success in multiple cycles of IVF.

In our study, the long LA-hMG was the protocol evaluated. Patients using other stimulations were excluded. Further studies to compare the success of these protocols with that found with the long LA-

hMG COH are ongoing. Also, the PRs for patients who have switched protocols are being evaluated.

We recommend that more studies be done to evaluate a series of recent IVF programs in which standard definitions of all parameters and treatments are used. Cumulative PRs must be classified by specific diagnostic categories, age, and treatment modality to enable the physician to evaluate more accurately the probability of success for patients with specific characteristics. Delivery rates should be reported in all studies to further substantiate the patient's prognosis for taking home an infant.

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