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Cumulative pregnancy rates and selective drop-out of patients in in-vitro fertilization treatment

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The validity of the cumulative pregnancy rate (CPR) calculated by life-table approach, obtained in a transport in-vitro fertilization (IVF) programme, was tested by the determination of possible influence of selective drop-out of patients with a poor treatment prognosis. A cohort of 1211 patients who had a first IVF cycle was followed, and the CPR after three IVF cycles was assessed. First cycles of patients who discontinued treatment after failed IVF, and of those who did not achieve a pregnancy but proceeded to a subsequent cycle, were compared for fertilization rate and for occurrence of prognosticators of poor treatment outcome: oocyte yield $\leqslant 2$, and replacement of <2 embryos. The CPR after three cycles was 54.9%. No differences were found in the first and second cycles of patients who continued treatment and those who dropped out. Selective drop-out of patients with a poor treatment prognosis was not found. Therefore, although calculations of CPR using life-table analysis generally overestimate the real probability of pregnancy after successive IVF cycles, the calculated CPR after three IVF cycles gives a reliable indication of the chance of occurrence of a pregnancy for the population studied.

Key words: cumulative/drop-out/IVF/selective

Introduction

Patients should be provided with adequate information about their chances of pregnancy in the programme they are about to join before they start in-vitro fertilization (IVF) treatment. The estimation of the likelihood of pregnancy for couples is often based on the pregnancy rate per cycle obtained in a programme. However, several methods can be used to express pregnancy rates (PR) in IVF programmes. The definition of clinical or ongoing pregnancy can differ, and PR can be calculated per started cycle, per oocyte retrieval, or per embryo transfer. When informing patients about success rates, a possible reduction in PR in successive cycles should be considered. This phenomenon has been reported by several authors (Herschlag *et al.*, 1991; Tan *et al.*, 1992), and is explained as the result of heterogeneity of the patient population in terms of fecundity rate. For a randomly chosen patient each unsuccessful cycle constitutes evidence in favour of lower fertility potential.

The success rate in an IVF programme can also be expressed as a cumulative pregnancy rate (CPR). When CPR is used, the danger exists that unrealistic high success rates are found. Not all patients continue IVF treatment until pregnancy or for a fixed number of attempts. Therefore, when CPR calculated with the life-table approach is used, assumptions are made about the probability of occurrence of a pregnancy for those who discontinue treatment. Most authors who report CPR assume that patients who leave an IVF programme had the same probability of a pregnancy as those who continued (Guzick *et al.*, 1986; Tan *et al.*, 1992). For example, Guzick *et al.* (1986) reported a CPR of 100% after nine IVF cycles in the subgroup with tubal infertility in their population, while out of the 394 patients entering the study in this subgroup only 105 achieved a pregnancy. It is likely that those who stopped treatment because of poor results in a preceding IVF attempt in terms of oocyte yield, fertilization rate, or number of embryos available for replacement, would have had a lower chance of pregnancy than those who continued. For this reason Stolwijk *et al.* (1996) advised that the reason for cessation should be considered when calculating the CPR.

Using the life-table approach CPR were calculated for the transport IVF programme at the Zuiderziekenhuis, Rotterdam, The Netherlands, in a retrospective cohort study. To test the validity of the rates obtained, the first and second IVF cycles of patients who left the programme without a pregnancy (drop-outs) were compared with those of patients who continued for occurrence of prognosticators of poor treatment outcome in the preceding failed IVF cycle.

Materials and methods

Patients who had their first IVF attempt during the period January 1989–June 1994 were included in the study. This programme has been described previously (Roest *et al.*, 1995) and details of patient age, inclusion criteria, diagnosis etc. are given (Roest *et al.*, 1995). A first IVF attempt was defined as: treatment until the occurrence of the first pregnancy after fresh embryo transfer or after replacement of cryopreserved embryos. The consecutive IVF cycles of these patients, until the occurrence of a clinical pregnancy, with a maximum of three cycles, were used to calculate the CPR after three IVF cycles. The patients who did not obtain a clinical pregnancy in the first or second cycle were divided into two groups: those who left the programme (drop-outs), and those who proceeded to a next attempt. These two groups were compared for age, and the preceding IVF cycles were compared for fertilization rate, and for occurrence of prognosticators of poor treatment outcome: oocyte yield $\leqslant 2$, and replacement of <2 embryos, indicative of a failed (no embryo

Table I. Results of the first three in-vitro fertilization (IVF) cycles

Attempt no.	Patients (*n*)	Pregnancies[a] (*n*)	PR (%)[b]	CPR (%)[c]	CI	Drop-outs (*n*)
1	1211	324 (14)	26.8	26.8	24.0–29.2	263
2	624	151 (7)	24.2	44.4	40.4–48.4	193
3	280	53 (2)	18.9	54.9	50.9–58.9	

CI = confidence interval (%) of CPR.
PR = pregnancy rate.
CPR = cumulative pregnancy rate.
[a]Values in parentheses are the number of pregnancies obtained after cryopreservation–thaw cycles.
[b]Pregnancy rate; % clinical pregnancies per oocyte retrieval.
[c]Cumulative pregnancy rate: calculated using the life-table approach, assuming that those who dropped out would have the same probability of obtaining a pregnancy as those who continued.

Table II. Characteristics of first in-vitro fertilization (IVF) cycles of drop-outs versus those who continued

	Drop-outs	Continued	*P*-value
Number of patients	263	624	
Age (years)	32.4 ± 4.6	32.3 ± 4.4	NS
Fertilization rate (%)	43	45	NS
Oocytes ⩽ 2 (%)	11.4	12.8	NS
ET < 2 (%)	37.3	34.2	NS

NS = no statistically significant difference.
ET = number of embryos transferred.

Table III. Characteristics of second in-vitro fertilization (IVF) cycles of drop-outs versus those who continued

	Drop-outs	Continued	*P*-value
Number of patients	193	280	
Age (years)	32.4 ± 4.3	32.7 ± 4.4	NS
Fertilization rate (%)	46	45	NS
Oocytes ⩽ 2 (%)	10.8	10.8	NS
ET < 2 (%)	39.5	35.9	NS

NS = no statistically significant difference.
ET = number of embryos transferred.

transfer), or impaired (only one embryo transferred) IVF attempt.

A clinical pregnancy was defined by a positive urinary test 18 days after oocyte retrieval combined with the finding of a gestational sac 2 weeks later. Subsequent IVF cycles of women who achieved pregnancy but experienced an early pregnancy loss were not included in the analysis. The results of cryopreservation–thaw cycles were included in this analysis. Cumulative conception rates were calculated by the life-table approach. For statistical analysis χ^2 test or Student's *t*-test were used where appropriate. $P < 0.05$ was taken as level of significance. Probabilities of conception for consecutive cycles were not compared in this study. For an analysis of consecutive cycles, follow-up information of patients who abandon the programme should be available.

Results

During the study period 1211 patients entered the transport IVF programme. The results of this cohort are shown in Table I. The results of the comparison of the first IVF cycles of drop-outs and those who continued for age, fertilization rate and occurrence of prognosticators of poor treatment outcome are shown in Table II. The characteristics of the second IVF cycle of drop-outs and those who continued are shown in Table III. As shown in Tables II and III, the characteristics of IVF attempts of patients who continued and those who dropped out did not differ.

Discussion

When patients are informed about their chances of pregnancy in IVF treatment the shortcomings of the different methods used to express the success rates of IVF programmes should be kept in mind. When the success rate in an IVF programme is expressed as PR per IVF cycle, a possible reduction in PR in successive cycles should be considered. Hershlag *et al.* (1991) reported that the probability of achieving a pregnancy declines as the number of unsuccessful cycles increases. Using a mathematical model, Hershlag *et al.* (1991) estimated that 37% of couples will not conceive with IVF therapy despite multiple attempts. These authors therefore questioned the justification of continuing IVF treatment beyond some threshold number of cycles. In contrast, Guzick *et al.* (1986) found that persistence in IVF can lead to a successful pregnancy for a large proportion of couples. The authors reported an approximately constant pregnancy rate of about 15% over repeated cycles. The predicted CPR after nine and 12 cycles were 75 and 84% respectively, and consequently, a 98% cure rate was predicted if a multitude of cycles was pursued. These contradictions in reported results of different programmes may be explained as the result of selection bias. In the first place, different selection criteria will lead to different patient populations at intake. Secondly, some programmes may encourage patients to discontinue treatment after poor performance in the previous IVF cycle, whereas other programmes might encourage these patients to proceed to a subsequent attempt. Haan *et al.* (1991) used pretreatment patient characteristics to make a comparison of the prognosis for success between 'continuers' and 'quitters', and found no over-representation of patients with a poor prognosis in the group of drop-outs. However, disappointing results in terms of low oocyte yield (⩽2), low fertilization rate, and replacement of a suboptimal number (<2) of embryos in a previous IVF cycle might be more indicative of poor treatment prognosis than pretreatment characteristics (Roest *et al.*, 1996). Selective patient drop-out and, consequently, selection bias, can be expected when the occurrence of these prognosticators of poor

treatment outcome is more frequent in patients who discontinue treatment after failed IVF.

In The Netherlands the first three IVF attempts are paid for by health insurances. Therefore, for patients eligible for IVF treatment in our population, the CPR after three IVF cycles is the most useful information before the treatment is started. In this study the CPR after three cycles was calculated using the life-table approach. The disadvantage of using life-table analysis is that the real probability of pregnancy after successive cycles is overestimated. With this approach it is assumed that those who stop treatment early had the same chance of pregnancy compared with those who continued. On the other hand, assuming that the women who stop IVF treatment early will never be pregnant will obviously lead to an underestimation of the CPR. We used the method most generally used in IVF programmes, assuming the same chances for drop-outs and those who continued. To test the validity of this approach we compared previous cycles of those who continued or dropped out after failed first and second IVF attempts. These groups were compared for frequency of prognosticators of poor treatment outcome. No statistically significant differences were found between the two groups.

In conclusion, selective drop-out of patients with a poor treatment prognosis was not found in the population studied. Therefore, the CPR of 54.9% found in this study gives a reliable indication of the chance of occurrence of a pregnancy after three IVF cycles.

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