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Cumulative pregnancy rate following in-vitro fertilization: the significance of age and infertility aetiology

J.Dor[1,3], D.S.Seidman[1], I.Ben-Shlomo[1], D.Levran[1], Z.Ben-Rafael[2], and S.Mashiach[1]

[1]Department of Obstetrics and Gynaecology, The Chaim Sheba Medical Centre, Tel Hashomer and Sackler School of Medicine, Tel Aviv University, Tel Aviv and [2]Department of Obstetrics and Gynaecology, Golda Medical Centre, Petach Tikva, Israel

[3]To whom correspondence should be addressed at: IVF Unit, Department of Obstetrics and Gynaecology, The Chaim Sheba Medical Centre, Tel Hashomer 52621, Israel

During the years 1984–1992, 951 couples completed 2252 in-vitro fertilization (IVF) treatment cycles at the In-Vitro Fertilization Unit of The Chaim Sheba Medical Centre. This study was conducted to evaluate the success of IVF using the cumulative pregnancy rate (CPR), with special emphasis on the optimal number of treatment cycles, the age of the patients and female infertility factors. It was found that the CPR showed a constant rise during the six initial IVF treatments (56% CPR), and plateaued in the subsequent three cycles (63% CPR). Various female infertility factors did not influence this rate. Women ≥40 years of age have a significantly lower CPR. Thus, it was concluded that the CPR in IVF declined after the sixth initial treatment cycle, and in women ≥40 years of age. The infertility factor did not significantly influence CPR.

Key words: cumulative pregnancy rates/fertility by age/infertility factor/IVF

Introduction

In-vitro fertilization (IVF) has become the standard treatment not only for couples who suffer from infertility due to tubal obstruction, but also for couples who have failed to conceive by way of all previous treatment modalities. The complexity of this method is inevitably associated with high physical, emotional, and financial costs. It is therefore of prime importance constantly to assess treatment outcome and, specifically, the influence of various factors on this outcome, in order to provide the most efficient treatment to defined groups of patients (Wilcox *et al.*, 1993). Several recent studies assessed the success rates of single treatment cycles rather than the pregnancy rates (PR) of the entire treatment course in the individual couples involved. In this context, cumulative pregnancy rates (CPR), often used to assess fertility treatment efficacy (Dor *et al.*, 1980; Guzick *et al.*, 1986; Hull *et al.*, 1992) can be used for a more comprehensive overview of the issue. The current study is a retrospective life-table analysis of our entire computerized data base from the years 1984 through 1992 inclusive, that assesses the effect of assorted variables on CPR in IVF treatments.

Materials and methods

Nine hundred and fifty-one infertile couples with various aetiological factors underwent 2252 consecutive treatment cycles, with a maximum of 10 treatments per couple. Patients were accepted into our IVF programme only after a minimum infertility duration of 30 months. The three protocols used for induction of follicular growth were as follows: i) CC 100 mg/day, days 5–9, followed by human menopausal gonadotrophin (HMG) (Pergonal: Teva Pharmaceutical Industries Ltd, Kfar Sava, Israel), 150 IU/day of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from day 8 of the cycle; ii) HMG, 225 IU/day from day 3 of the cycle; and iii) gonadotrophin-releasing hormone analogue (GnRHa) (D-Trip-6-LHRH microcapsules; Decapeptyl Depot 3.2 mg microcapsules: Ferring Ltd, Malmo, Sweden), which is a slow-release injection on cycle day 2 that acts over a period of 30 days, followed by HMG 150 IU/day 15 days later after verification of complete ovarian suppression. Follicular growth was monitored by daily measurements of serum oestradiol and progesterone and by performing transvaginal sonography. Human chorionic gonadotrophin (HCG; ChorigonL: Teva Pharmaceutical Industries Ltd, Israel), 10 000 IU, was administered when at least two follicles with a mean diameter of ≥18 mm and serum oestradiol concentrations of at least 1468 pmol/l were noted. Oocyte retrieval, culture, fertilization, embryo culture, and transfer were carried out as previously described (Rudak *et al.*, 1984; Dor *et al.*, 1986). For each woman all IVF treatment cycles were included until the first ongoing pregnancy was achieved. Further treatment cycles were not included in the study. The primary outcome was clinical pregnancy completed and ongoing, per treatment cycle. Ongoing pregnancy was defined as a pregnancy for which an intrauterine fetus with a pulsating heart could be demonstrated by ultrasonography.

Statistical analysis

Cumulative pregnancy rate was calculated by using the 'Proc lifetest' (SAS Institute Inc., 1991). To estimate the expected CPR we used the Kaplan Meier estimation (Kaplan and Meier, 1958) which is not based on a specific assumption with respect to the distribution of the data. Between-group differences were tested by the log rank test (Mantel and Haenszel, 1959). In order to assess homogeneity within various groups in this study, the χ^2 test was used.

Results

Clinical PR per cycle, including all treatment cycles, remained similar during the first six successive cycles, reaching a CPR of 56%. During the next three cycles the PR declined significantly from a mean of 9.3 to 2.4% per cycle, reaching a CPR of only 63% after nine treatment cycles (Table I; CPR

Table I. Life-table analysis of cumulative pregnancy rates in in-vitro fertilization (IVF) treatments resulting in clinical pregnancies

Treatment cycle	No. of patients treated	Pregnancies (*n*)	Cumulative pregnancy rate %	5–95% CI*
1	951	109	11.4	9.4–13.5
2	570	75	23.1	20.1–26.1
3	323	31	30.5	26.8–34.2
4	193	30	41.3	36.6–46.0
5	94	13	49.4	43.6–55.2
6	53	7	56.1	49.3–62.9
7	33	1	57.4	50.3–64.5
8	24	1	59.2	51.6–66.8
9	10	1	63.3	53.1–73.5
10	1	0	63.3	53.1–73.5

*CI = Confidence interval.

Table II. Life table analysis of cumulative pregnancy rates by age of the women

	IVF treatment cycle					
	1	2	3	4	5	6
Age ≤34 years						
No. of patients	478	262	135	70	27	15
Pregnancies	68	46	17	14	6	2
Cumulative pregnancy rate (%)	14	29	38	50	61	66
Age 35–39 years						
No. of patients	248	131	64	35	16	5
Pregnancies	38	17	8	6	4	2
Cumulative pregnancy rate (%)	15	26	35	46	59	75
Age ≥40 years*						
No. of patients	112	64	37	17	9	7
Pregnancies	3	4	2	0	0	2
Cumulative pregnancy rate (%)	2	8	13	13	13	38

*$P < 0.0001$ when compared with other age groups.

for IVF treatment are illustrated in Figure 1). In order to evaluate the effect of age on the CPR, women were divided into three age groups: 1) ≤34 years; 2) 35–39 years; 3) ≥40 years. Women who moved from one age group to another during their series of treatments were excluded. This led to a smaller group of patients analysed (n = 838) than in the original cohort. Table II shows a breakdown of these results by age, which indicates that women ≥40 were significantly less likely to conceive with repeated treatment cycles, compared to those aged 35–39 years and ≤34 years ($P < 0.0001$; these CPR are illustrated in Figure 2). For evaluation of the effect of female infertility factors on treatment outcome, couples with only one of the following causes of infertility were included: i) tubal disease and obstruction; ii) anovulation; iii) unexplained infertility. No male factors were involved in any of these couples. No difference in age distribution was found in the aetiology of the groups. No difference was found in the CPR among women with tubal, anovulatory or unexplained infertility (Table III; Figure 3).

Discussion

In recent years, infertility treatment by assisted reproduction has often been performed repeatedly due to a relatively low

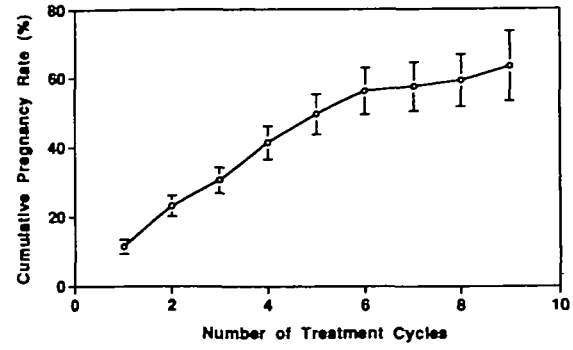

Figure 1. Overall cumulative pregnancy rate in in-vitro fertilization (IVF) treatment (with 95% confidence interval).

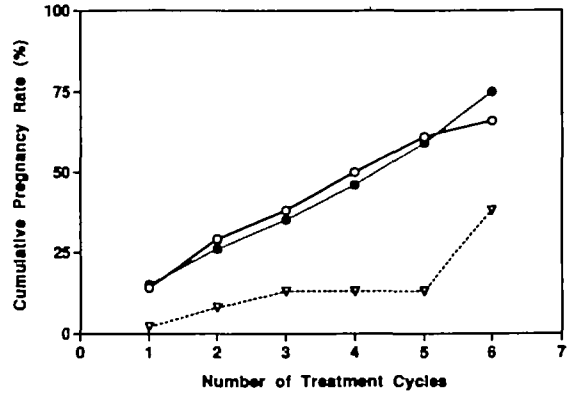

Figure 2. Cumulative pregnancy rate in in-vitro fertilization (IVF) by age of the patients. ▽ ≥ 40 years; ● ≤ 39 years; ○ ≤ 34 years,

Table III. Life-table analysis of cumulative pregnancy rates by infertility factors in in-vitro fertilization (IVF)

	IVF treatment cycles							
	1	2	3	4	5	6	7	8
Infertility factor								
Tubal								
No. patients	350	218	138	85	42	20	14	11
Pregnancies	52	36	15	13	8	1	0	0
Cumulative pregnancy rate (%)	14	28	36	46	56	58	58	58
Unexplained								
No. patients	158	92	52	30	15	11	9	6
Pregnancies	15	10	6	4	2	2	0	0
Cumulative pregnancy rate (%)	9	19	28	38	46	56	56	56
Anovulation								
No. patients	101	61	34	23	12	9	6	4
Pregnancies	7	8	2	5	2	2	1	0
Cumulative pregnancy rate (%)	6	19	23	40	50	61	67	67

success rate per cycle. It is therefore important to estimate the couple's expected PR after a defined number of treatment cycles (Hull *et al.*, 1992). The present analysis demonstrated that the CPR following IVF treatment increases constantly during the initial six cycles, and levels off thereafter. This is in agreement with Guzick *et al.* (1986), who described a

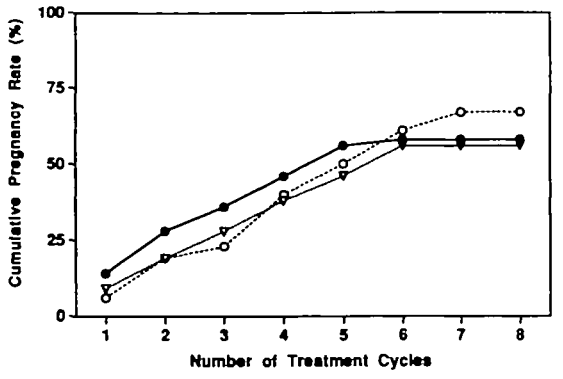

Figure 3. Cumulative pregnancy rate in in-vitro fertilization (IVF) by the cause of infertility. ● tubal disease or obstruction; ○ anovulation; ▽ unexplained infertility.

similar constant PR in each successive cycle. This study extends their observation over consecutive cycles and examines the CPR during the seven to nine IVF attempts.

The need to provide couples seeking assisted conception with reliable prognostic information is of importance in light of growing economic constraints (Wilcox *et al.*, 1993). Calculating CPR has become a widely used method for presenting couples with relevant estimates of therapy success rates (Hull *et al.*, 1992; Tan *et al.*, 1992). The use of life-table analysis for infertility study data is currently considered the preferable method because of its clarity and applicability to a variety of study designs (Doody, 1993). However, the limitations of this method must be recognized in order to avoid over-reliance on estimates produced through this method. The benefits of life-table analysis of CPR is that it does not require all patients to enter the study simultaneously, and it allows the inclusion of cycles from patients who drop out of the study and those lost to follow-up (Doody, 1993). Results based on cumulative data are therefore superior to estimates calculated per cycle, as they prevent a bias towards couples who are less successful at becoming pregnant with IVF–embryo transfer. The latter will inevitably be over-represented in pooled data, since they undergo more cycles before achieving pregnancy, or discontinuing treatment (Wilcox *et al.*, 1993). Furthermore, the evaluation of cumulative results provides patient characteristics, such as age or infertility aetiology, and treatment regimens, a better opportunity to manifest their effect through repeated cycles (Walters, 1994). The limitations of the life-table analysis include the repetition of the same information along the time-scale, since early differences may be carried over to subsequent cycles (Walters, 1994). Another well recognized limitation is that patients undergoing repeated cycles are not necessarily a random subgroup of the initial group. Patients may leave the IVF programme due to financial reasons, or because they fared poorly in their first cycles (Tan *et al.*, 1992). Financial constraints are unlikely to influence conception rate per cycle. However, the decline in the proportion of less fertile couples included in repeated cycles may actually provide couples requiring multiple treatment cycles with more reasonable expectations. Other factors that may influence success rates in repeated cycles include changes in management, such as an increase in the number of embryos transferred, which may improve the chances of pregnancy. Various biological factors, as yet poorly understood, may decrease the probability of pregnancy in successive IVF–embryo transfer cycles, including the development of anti-ovarian antibodies in women receiving repeated ovarian stimulation and punctures (Barbarino-Monnier *et al.*, 1991). Additional objections to life-table analysis include the possibility that infertility patients may be more likely to return to their physician's attention if they become pregnant (Doody, 1993). This return of pregnant drop-out patients could result in a bias towards reporting more pregnancies. Doody (1993) stressed the need for active follow-up of all subjects within each study time-interval, an approach which he called the 'fertility table method', as this would minimize the suggested bias. To a large extent, these guidelines have been followed in our IVF patient population, where only treatment cycles were considered in the pregnancy outcome calculation. This is also why we refrain from comparing the result of treatment cycles with cumulative spontaneous PR (Dor *et al.*, 1980). Furthermore, it has been suggested that cumulative studies should be avoided 'until (if ever) the technique becomes freely available on demand' (Walters, 1994). In this regard, our data may have special merit as the National Health Insurance Policy in Israel provides financial support for at least eight IVF–embryo transfer cycles. IVF is widely available in Israel, with more than 20 IVF programmes serving a population of 5 million.

Our observation that CPR is not influenced by the aetiology of the women's infertility concurs with earlier findings by Guzick *et al.* (1986) and is also supported by a recent study by Tan *et al.* (1992). These observations validate the status of assisted reproductive treatment as an efficient treatment for female infertility in couples with various aetiologies who fail to conceive with other treatment modalities.

The analysis of CPR with respect to age confirms the dramatic decline of PR in IVF in women ≥40 years, compared to young patients. This is substantially different from results of studies on fecundability (Federation CECOS *et al.*, 1982) and egg donation treatments (Levran *et al.*, 1992), which have shown that conception rates begin to decline at 30–33 years of age, due to both oocyte and endometrial ageing. Our findings suggest that women ≥40 years of age may benefit from the option of egg donation if they fail to conceive after several IVF treatments (Navot *et al.*, 1991). A recent study by Scott *et al.* (1995) using similar statistical methods found a similar fall in CPR after the age of 40 years in a general infertile population. They suggested that the combined use of maternal age and ovarian reserve screening may provide a better assessment of long-term prognoses for conception.

In conclusion, the calculation of CPR in IVF shows that success rate levels off after the sixth treatment cycle, and that women ≥40 years are less likely to conceive than are younger women.

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