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A more realistic approach to the cumulative pregnancy rate after in-vitro fertilization

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As most studies overestimate the cumulative pregnancy rate, a method is proposed to estimate a more realistic cumulative pregnancy rate by taking into account the reasons for an early cessation of treatment with in-vitro fertilization (IVF). Three methods for calculating cumulative pregnancy rates were compared. The first method assumed that those who stopped treatment had no chance at all of pregnancy. The second method, the one used most often, assumed the same probability of pregnancy for those who stopped as for those who continued. The third method assumed that only those who stopped treatment, because of a medical indication, had no chance at all of pregnancy and that the others who stopped had the same probability of pregnancy as those who continued treatment. Data were used from 616 women treated at the University Hospital Nijmegen, Nijmegen, The Netherlands. The cumulative pregnancy rates after five initiated IVF cycles for the three calculation methods were in the ranges 37–51% for the positive pregnancy test result, 33–55% for a clinical pregnancy and 30–56% for an ongoing pregnancy. As expected, the first method underestimated the cumulative pregnancy rate and the second overestimated it. The third method produced the most realistic cumulative pregnancy rates.

Key words: epidemiology/in-vitro fertilization/pregnancy rate/statistics

Introduction

Information about the probability of pregnancy after successive treatments with in-vitro fertilization (IVF) is important for candidate patients and for the physicians who are counselling them. Several authors have reported cumulative pregnancy rates and recognized the importance of the variation in patient populations and treatment, including age, type of infertility and ovulation stimulation regimen, on the cumulative pregnancy rates (Guzick *et al.*, 1986; Tan *et al.*, 1992, 1994a,b; Simon *et al.*, 1993; Check *et al.*, 1994). Far less attention has been paid to the impact on cumulative pregnancy

rates of the reason for the early cessation of IVF treatment (Page, 1989; Te Velde *et al.*, 1992; De Mouzon *et al.*, 1993).

As it is neither ethical nor practical to force patients to continue IVF treatments until pregnancy or for a fixed number of treatments (e.g. at least five), the real cumulative pregnancy rate after five IVF cycles for a specific population cannot be calculated. Therefore, to estimate the cumulative pregnancy rate, assumptions are necessary about the probability of the occurrence of pregnancy for those who discontinue treatment without achieving pregnancy. Most studies assume implicitly that all the patients who stop treatment early have the same probability of pregnancy as those who continue (Guzick *et al.*, 1986; Hull *et al.*, 1992; Tan *et al.*, 1992, 1994a,b; Simon *et al.*, 1993; Check *et al.*, 1994). Haan *et al.* (1991) noted the importance of selective early cessation but compared the cumulative rate based on the assumption that the pregnancy rate of the first IVF treatment held good for the following IVF treatments with the cumulative rate based on the assumption that the same chance of pregnancy could be applied to women who stopped treatment early compared with those who continued treatment. Both of these methods will overestimate the real probability of pregnancy after successive IVF treatments. The other extreme, i.e. assuming that the women who stop IVF treatment early will never become pregnant, will obviously underestimate the cumulative pregnancy rate. The examples below show how large the bias can be.

Recently Tan *et al.* (1994a) presented a cumulative live birth rate of 68.6% after five IVF treatments in women who had previously achieved an IVF live birth. A life-table analysis was used because it takes into account the experience of the entire cohort by using all the treatment cycles. However, this method implicitly assumes that the women who stopped IVF treatment early (in this case before the fifth treatment) had the same probability of having a live birth as those who continued treatment. Using the number of women per IVF treatment and the cumulative live birth rates, the calculated numbers of live births following each of the five IVF treatments were 21 in 105 women after the first treatment, six in 48 after the second, one in 30 after the third, one in 14 after the fourth and four in eight after the fifth. If we assume that none of the women who stop treatment early will ever achieve a live birth, the cumulative live birth rate would be 31%. The actual rate would be higher of course, but certainly not as high as the 68.6% presented by Tan *et al.* (1994a).

In the same manner, Guzick *et al.* (1986) calculated the cumulative rates for clinical pregnancy in treatments where oocyte retrieval was performed, excluding couples in whom the male partner had poor semen characteristics. They reported a cumulative pregnancy rate after six cycles of

Table I. Cumulative pregnancy rates for successive in-vitro fertilization (IVF) treatments calculated on the basis of three assumptions

IVF treatment	No. of women who became pregnant	No. of women who stopped treatment ^a	No. of women at risk ^b			Cumulative pregnancy rate (%)		
			AI ^{c,f}	AII ^{d,g}	AIII ^{e,h}	AI	AII	AIII
Positive pregnancy test result								
1	131	120	616	616	616	21.3	21.3	21.3
2	56	102	485	365	407	30.4	33.3	32.1
3	34	133	429	207	307	35.9	44.3	39.6
4	5	31	395	40	179	36.7	51.3	41.3
5	0	—	390	4	158	36.7	51.3	41.3
Clinical pregnancy								
1	112	123	616	616	616	18.2	18.2	18.2
2	56	105	504	381	423	27.3	30.2	29.0
3	33	140	448	220	320	32.6	40.7	36.3
4	4	37	415	47	186	33.3	45.7	37.7
5	1	—	411	6	160	33.4	54.8	38.1
Ongoing pregnancy								
1	94	127	616	616	616	15.3	15.3	15.3
2	49	109	522	395	437	23.2	25.8	24.8
3	33	148	473	237	337	28.6	36.1	32.1
4	3	42	440	56	195	29.1	39.5	33.2
5	3	—	437	11	165	29.5	56.0	34.4

^aWomen who stopped after this treatment without becoming pregnant.

^bNumber of women who did not become pregnant in the previous IVF treatment(s).

^cAssumption I (AI): women who stopped treatment had no chance of becoming pregnant.

^dAssumption II (AII): women who stopped treatment had the same probability of pregnancy as those who continued.

^eAssumption III (AIII): women who stopped treatment because of a medical indication had no chance of becoming pregnant, while those who stopped treatment for other reasons had the same probability of pregnancy as those who continued.

^fWomen included who stopped treatment after the foregoing IVF treatment(s) without becoming pregnant.

^gWomen excluded who stopped treatment after the foregoing IVF treatment(s) without becoming pregnant.

^hWomen who stopped treatment because of a medical indication included; women who stopped treatment for other reasons excluded (in comparison with those at risk in the case of assumption II, for IVF treatment 2, +42; for treatment 3, +100; for treatment 4, +139; and for treatment 5, +154).

59.6%. Furthermore, they predicted the cumulative pregnancy rates after nine and 12 cycles to be 75 and 84% respectively. As all these calculations implicitly assumed the probability of pregnancy for those who stopped treatment early to be the same as for those who continued treatment, these rates are overestimated. Here, the assumption that those who stopped treatment early would not become pregnant leads to a cumulative pregnancy rate of 27% after six cycles. The actual rate would be between 27 and 59.6%, analogous to the first example.

More precise estimates of the cumulative pregnancy rates can be made if the reason for the early cessation of treatment is known. If, for instance, women stop treatment for financial or emotional reasons, they can be expected to have a higher probability of achieving a pregnancy than those who stop treatment because of poor IVF results such as low fertilization rates and poor embryo quality. To illustrate the importance of the assumption underlying the estimation of the cumulative pregnancy rates, here cumulative pregnancy rates have been calculated for patients of the University Hospital Nijmegen, The Netherlands during 1988–1993. Estimations of the cumulative pregnancy rates, assuming a difference in the probability of pregnancy for specific reasons for the discontinuation of treatment, were compared with those based on more extreme assumptions.

Materials and methods

At the University Hospital Nijmegen, The Netherlands, 872 women were treated for the first time with IVF between August 1, 1988 and

January 1, 1993. In this study only women were included who were treated with human menopausal gonadotrophin in combination with a long protocol of gonadotrophin-releasing hormone agonist, with or without oral contraceptives during the preceding menstrual cycle, and who did not use donor spermatozoa ($n = 616$). Only the results of the first five initiated IVF treatments were analysed (whether or not oocyte aspiration and embryo transfer were performed). Three definitions of pregnancy were used: (i) positive pregnancy test result, measured 16 days after embryo transfer; (ii) clinical pregnancy — a positive pregnancy test result and ultrasonographic evidence of at least one gestational sac 4 weeks after embryo transfer; and (iii) ongoing pregnancy — a pregnancy continuing for >12 weeks after embryo transfer. To calculate the cumulative rates for each of these types of pregnancy, only the data up to the first pregnancy in question were included in the analysis. To be clear, data were also included if women did not achieve pregnancy during the first five treatments.

Three assumptions were used to deal with the effect of the early cessation of IVF treatment (i.e. before a woman became pregnant): assumption I, women who stopped treatment had no chance of becoming pregnant; assumption II, women who stopped treatment had the same probability of becoming pregnant as those who continued; and assumption III, only the women who stopped treatment because of a medical indication had no chance of becoming pregnant, while the women who stopped treatment for other reasons had the same probability of pregnancy as those who continued treatment. A medical indication for stopping further IVF treatment was assumed to include: (i) a previous treatment with a fertilization rate of <10%, despite the presence of more than three large follicles (≥ 15 mm) on the day of human chorionic gonadotrophin (HCG) administration and the performance of oocyte aspiration, or (ii) three or less large follicles during two previous treatments.

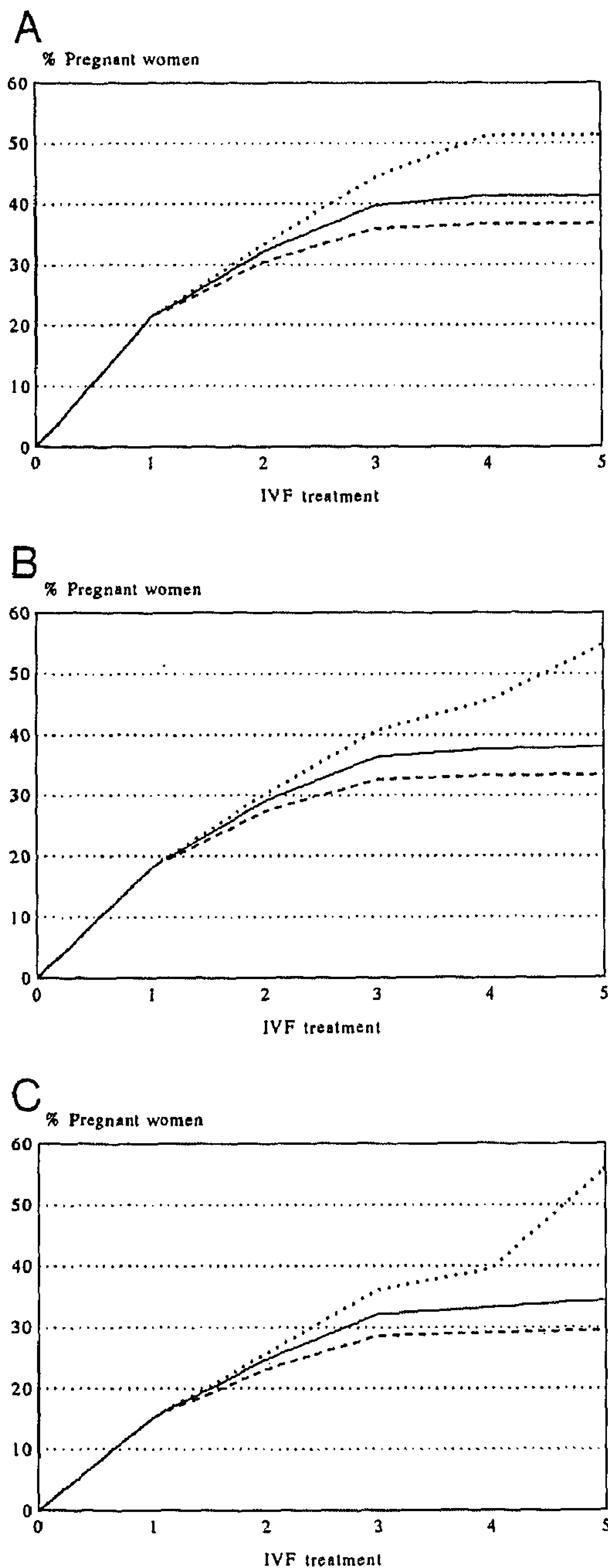


Figure 1. Cumulative rates for a positive pregnancy test result (A), clinical pregnancy (B) and ongoing pregnancy (C) for successive in-vitro fertilization (IVF) treatments calculated on the basis of three assumptions: (---) assumption I, women who stopped treatment had no chance of becoming pregnant; (.....) assumption II, women who stopped treatment had the same probability of pregnancy as those who continued; and (—) assumption III, women who stopped treatment because of a medical indication had no chance of becoming pregnant, while those who stopped for other reasons had the same probability of pregnancy as those who continued treatment.

The cumulative pregnancy rate after x initiated treatments was calculated as follows (Kalbfleisch and Prentice, 1980): $[1 - \Pi(1 - \text{number of pregnant women in treatment } x / \text{number of women at risk in treatment } x)] \times 100\%$. In this formula, Π indicates the product of the terms specified within the parentheses for each of the x treatments.

Results

The numbers of women who achieved pregnancy per IVF treatment and who stopped after each treatment without becoming pregnant are shown in Table I. Note that the number of women who stopped treatment after a specific IVF cycle was the highest for the calculation of ongoing pregnancy, then for clinical pregnancy, and the lowest for the positive pregnancy test result. This was because all women who stopped treatment before achieving an ongoing pregnancy were also included in the numbers of those not achieving a positive pregnancy test result or a clinical pregnancy. The reverse situation did not apply. After the first IVF treatment, 42 women were advised to stop further treatment because of a medical indication; the corresponding figures were 58, 39 and 15 after the second, third and fourth treatments respectively.

The results of the calculations of the cumulative rates for a positive pregnancy test result, clinical pregnancy and ongoing pregnancy based on each of the three assumptions are shown in Figure 1A–C and Table I. As expected, the cumulative pregnancy rates were the lowest with assumption I, highest with assumption II and intermediate with assumption III (Table I). The cumulative pregnancy rates after five successive IVF treatments ranged from 37 to 51% for a positive pregnancy test result, from 33 to 55% for a clinical pregnancy and from 30 to 56% for an ongoing pregnancy. The cumulative pregnancy rates calculated by taking into account the reason for early cessation were 41% for a positive pregnancy test result, 38% for a clinical pregnancy and 34% for an ongoing pregnancy.

Discussion

In most of the studies that present cumulative pregnancy rates, the implicit assumption is that the women who stop IVF treatment before the occurrence of pregnancy have the same probability of becoming pregnant as those who continue. The consequence is an overestimation of the cumulative pregnancy rates, especially at higher IVF treatment numbers where many women stop further treatment. More realistic cumulative pregnancy rates can be estimated by incorporating the reason for the early cessation of the IVF treatment in the assumption. Cumulative pregnancy rates based on the third assumption, which takes into account a medical indication for the cessation of IVF treatment, will be the most reliable. However, as the probability of pregnancy in those with a medical indication for stopping treatment is assumed to be zero, it is reasonable to expect the cumulative pregnancy rate to be slightly underestimated. In particular, at higher treatment numbers this assumption will result in a slight underestimation, as women who received a medical indication for stopping further treatment only after the third or fourth cycle had reasonable results in at least one treatment cycle.

The deviations in the cumulative pregnancy rates found when using the different assumptions are highly dependent on the number of women who discontinued treatment before the occurrence of pregnancy. The overestimation of the real cumulative pregnancy rate by a life-table analysis (which uses the assumption that those who stop treatment have the same probability of becoming pregnant as those who continue) will

be particularly large in clinics with a high percentage of patients for whom the IVF procedure is mainly performed for diagnostic purposes before a final decision is made to continue IVF treatment, e.g. in cases of severe male infertility, unexplained infertility problems or a high level of follicle stimulating hormone in young women. In those cases, the method for the calculation of the cumulative pregnancy rate by taking into account whether or not one stopped treatment because of a medical indication (assumption III) is highly recommended.

In a recent study, Alsalili *et al.* (1995) calculated cumulative pregnancy rates by using a life-table analysis. They discussed the importance of the underlying assumption that the probability of pregnancy is the same for those who continue and those who discontinue treatment. They state that: 'The two factors, prognostic information...' (which is used to decide whether or not to continue treatment) '... and successive cycle reduction in fertility, work in opposite directions on the assumption that pregnancy rates are constant for treated and non-treated individuals. Acknowledging its limitations, life-table analysis remains the conventional method for assessing IVF success and comparing results from different IVF centres.' Their argument for the two factors working in opposite directions is, however, incorrect. This can be explained by considering that those who stop treatment because of poor prior results (i.e. prognostic information) would have had a lower probability of pregnancy than those women who continued treatment, even if it is assumed that those who continued treatment would have a lower chance of pregnancy than in their previous cycle (i.e. successive cycle reduction). It seems that the authors confused the assumption made in life-table analysis: the probability of pregnancy for those who continue and those who discontinue treatment is not assumed to be the same at every cycle but in fact it applies to a specific cycle. Thus, the overestimation when using life-table analysis remains.

One result that might seem strange is that the estimated cumulative pregnancy rate after five treatments was higher for ongoing pregnancy than for clinical pregnancy and lowest for a positive pregnancy test result when using assumption II (i.e. women who stopped treatment had the same probability of pregnancy as those who continued), as shown in Table I. However, this can be explained by looking at the denominator, i.e. the number of women at risk. All women who had not yet achieved a pregnancy but had stopped treatment are excluded from the denominator. As for the calculation of cumulative rates per type of pregnancy, women should only be included if they did not achieve that particular kind of pregnancy; notice that the numbers of women included at the fifth cycle are not the same for the three definitions of pregnancy. From Table I it can be inferred that only 11 women received a fifth IVF treatment because they had not achieved an ongoing pregnancy in the previous four cycles. Only six of them had not achieved a clinical pregnancy and four did not even have a positive pregnancy test result. As three and two of the women who were excluded from the calculation of the cumulative rate for a positive pregnancy test and a clinical pregnancy after the fifth cycle, respectively, achieved ongoing pregnancy during

the fifth cycle, the cumulative pregnancy rate after the fifth cycle was higher for an ongoing pregnancy than for a clinical pregnancy or a positive pregnancy test result.

Comparison of the cumulative pregnancy rates between clinics and between types of assisted reproductive techniques can be very misleading. Reasons for this are not only the use of different definitions of pregnancy and the kind of assumption used to calculate the cumulative pregnancy rates, but also differences in the characteristics of the populations (e.g. age, type of infertility, reproductive history), the characteristics of treatments (e.g. type of ovulation stimulation protocol, experience of the IVF clinic) and the number of and reason for couples discontinuing treatment before the occurrence of pregnancy. Caution is thus required when calculating, interpreting and comparing cumulative pregnancy rates. The figures presented here are only valid for the IVF clinic in Nijmegen, The Netherlands, between 1988 and 1993.

Multivariable prognostic models are necessary to take into account the influence of patient and treatment characteristics. In these models, the reason for cessation, i.e. a medical indication or another reason, should also be considered when calculating the cumulative pregnancy rate for specific patients. Only in that case can the cumulative pregnancy rate give reliable information for the candidate IVF patients.

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