Journal of Assisted Reproduction and Genetics, Vol. 22, Nos. 11/12, December 2005 (© 2005)
DOI: 10.1007/s10815-005-6655-y

Assisted Reproduction

Likelihood of natural conception following treatment by IVF[1]

D. J. Cahill,[2,4] J. Meadowcroft,[3] V. A. Akande,[2] and E. Corrigan[3]

Submitted April 14, 2005; accepted June 17, 2005

***Purpose*:** To predict the ongoing likelihood of natural conception, when a couple has ceased to try to conceive by assisted conception.
***Methods*:** A postal questionnaire survey obtained information on further attempts to conceive and have a baby, either without treatment or by treatment elsewhere.
***Results*:** From a response rate of 44%, there were 116 couples who fulfilled the study criteria. The data presented are based on this group. The overall likelihood of conception was 18%. Cumulative results were analysed up to 3 years following treatment. Univariate analysis showed that likelihood of conception was affected by infertility diagnosis ($p = 0.024$), woman's age (>38 years; $p < 0.005$) (negatively) and duration of infertility (<3 years; $p < 0.005$) (positively), while primary infertility did not. Effects of diagnosis and infertility duration were confirmed by multivariable analysis, controlling for age and primary infertility. These latter variables had no independent effect.
***Conclusion*:** The likelihood of natural conception following IVF treatment was determined by duration of infertility and diagnosis; tubal disease in particular was associated with a very poor likelihood of natural conception.

KEY WORDS: Assisted conception; diagnostic classification; failure to conceive; fertility; likelihood of natural conception.

INTRODUCTION

Patients who attend infertility or assisted conception clinics often ask about their chances of conceiving naturally when they have completed treatment and wonder what their next step might be. Several studies have examined the likelihood of conception in spontaneous cycles either before, awaiting (1) or following assisted conception treatment (2–5). Published data on untreated couples are detailed and provide precise diagnostic and prognostic information. While adding to our knowledge, studies following treatment fail to provide a time reference (3), account for dropouts (2) or consider the diagnostic classification of the couple (4,5). Many couples complete treatment without having fulfilled their desire of having a child. What hope do they have of ever conceiving? This paper explores some of the factors that determine the likelihood of natural conception in the years following IVF treatment.

PATIENTS AND METHODS

Couples who had treatment at the University of Bristol's Centre for Reproductive Medicine were eligible for the study. These were the criteria for inclusion or exclusion—couples were not approached if any of the following personal criteria were met: a stated desire for no further contact; a

[1] This paper has been previously presented in part at the 57th Annual Meeting of ASRM, October 20–25th, 2001.
[2] University of Bristol Centre for Reproductive Medicine, Academic Unit of Obstetrics and Gynaecology, Clinical Sciences at South Bristol, St. Michael's Hospital, Bristol BS2 8EG, United Kingdom.
[3] University of Bristol Centre for Reproductive Medicine, 4 Priory Road, Clifton, Bristol BS8 1TH, United Kingdom.
[4] To whom correspondence should be addressed; e-mail: d.j.cahill@bris.ac.uk.

non-UK address; known divorce; known death of either partner; ongoing or previous legal proceedings had occurred between the couple and the Centre; current patients of the Centre. On clinical grounds, couples were excluded if the woman had bilateral tubal occlusion (confirmed by laparoscopy) or the man had azoospermia.

Approval for the study was obtained from the local Ethics Review Committee. Follow up began at least 3 years after last contact with the Centre. All eligible couples were sent a questionnaire by post. They were asked the following questions: whether further attempts at pregnancy were sought; if so, whether naturally or by treatment (whether by assisted conception or otherwise); the outcome of any pregnancy that occurred; how soon any pregnancy occurred; they were also asked about changes in their domestic circumstances such as divorce or separation. For non-responders, a second questionnaire was sent by post and at least one telephone call if possible. Analysis was undertaken to provide data on the differences between responders and non-responders in age, duration of infertility, whether they had ever been pregnant and whether they had conceived as a result of IVF treatment while patients of the clinic.

The case notes of couples in the study were examined for details on the year of first contact with the Centre, the duration of infertility at the time of referral, the age of the woman at the time of cessation of treatment, whether infertility was primary or secondary, the major diagnostic category of the couple (using previously published criteria) (6) and what treatment the couple had at the Centre and its outcome.

The diagnostic categories used were tubal damage, sperm dysfunction, endometriosis, unexplained and other (being ovulatory disorders mostly). When more than one cause of infertility was present, couples were classified by their major (most severe) infertility category. For this, we used a previously published classification system for ranking and these were the categories used (in order of severity from most severe): sperm dysfunction, tubal damage, endometriosis, unexplained infertility, ovulatory dysfunction (6).

Where appropriate, analysis of data was undertaken by the χ^2 test for comparison of proportions, by Mann–Whitney *U*-test for comparison of non-parametric numerical data, by univariate analysis for all available variables (using life table analysis), and by multivariate analysis to control for variables that had an effect on the likelihood of conception (using Cox's Proportional Hazard). The data for age and duration of infertility were analysed as categoric data for the univariate analysis, but as continuous variables for the multivariate analysis for more precise estimations of probability. Because of the effect of further treatment on the likelihood of conception, couples who had treatment elsewhere were excluded from the analysis. However, couples who went on to adopt children were not excluded from the analysis.

RESULTS

From January 1987 to April 1991, 628 couples were referred to the Centre for Reproductive Medicine. We began the follow-up period in August 1995 initially by postal questionnaires and later by telephone until December 1997 allowing for a total possible follow-up period of at least 4 and up to 10 years. We subsequently validated and analysed the data to present the information in this paper.

Of 628 couples, 475 couples fulfilled the eligibility criteria and were sent a questionnaire (see Fig. 1). The postal service returned 121 as being undeliverable. This provided 354 potential total respondents. In spite of a second postal reminder and at least one attempt by telephone, no replies were received from 195 couples. Of the remainder, 5 declined participation and 154 (44%) returned their questionnaire. Response to the questionnaire was not affected by median age of the woman (34 years for respondents versus 35 years for non-respondents, $p = 0.4$), median duration of infertility (4 years for respondents versus 4 years for non-respondents, $p = 0.7$),

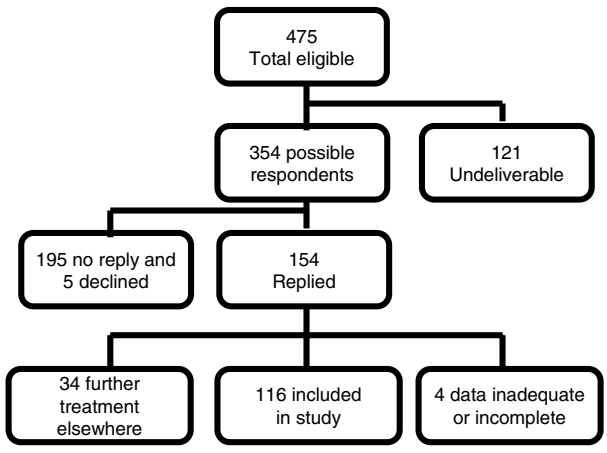

Fig. 1. Flow chart showing eligible couples studied as well as reasons for exclusion.

whether they had been ever pregnant or not (46% versus 38%, $\chi^2 = 2.409, p = 0.117$) and whether they had become pregnant from IVF while at the Centre or not (51% versus 40%, $\chi^2 = 1.308$, $p = 0.253$). Of the couples who responded, 22 couples adopted a child or children and 9 couples underwent a divorce, with 2 of them remarrying. One couple who adopted a child subsequently had a spontaneous (successful) pregnancy 7 years later. This couple and other adopting couples were included in the analysis.

Of the 154 couples, 34 had further assisted conception treatment elsewhere and were excluded from the analysis. Incomplete case records in four respondents precluded their inclusion in the analysis, leaving 116 couples in the study. Of the 116 couples who had no further treatment, 40 women conceived at least once (after a median 7 months from cessation of treatment; range 1–84 months) and 37 carried at least one baby to term. Of those who conceived spontaneously, 48% did so within 6 months, 57% by a year, 72% by 2 years and 78% by 3 years.

For respondents, the overall probably of conception in 3 years was 19% (95% CI 13–24%) (29/154). Allowing for the non-responders, over 3 years, the minimum cumulative conception rate would be 8.2% (29/354) (95% CI 5.5–10.9%). For respondents, the mean duration of infertility before IVF was 5.2 years (SD 3.5 years; range 1–20 years; 4% less than 2 years infertility) and the mean age was 34.5 years (SD 5.4 years; range: 24–44 years).

Figure 2 provides an illustration of the likelihood of conception over 3 years of follow up, according to the major infertility category noted when the couple was referred. Tubal damage was associated with the least likelihood of natural conception. Numeric data for conception rates are provided in Table I, analysed by diagnostic category, age, duration and whether the couple had primary or secondary infertility when they presented. Differences in the likelihood of conception are apparent for the diagnostic category of the couple, the woman's age and the duration of infertility at the time of initial treatment. Multivariate analyses for these data are given in Table II. From the univariate analysis (Table I), the apparent differences seen are confirmed for duration of infertility and diagnostic category only.

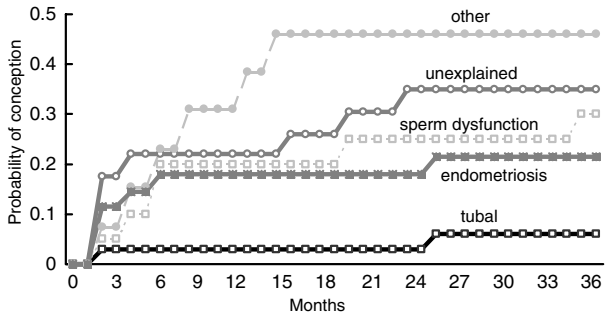

Fig. 2. Cumulative conception rates without treatment analysed by diagnosis in couples who had completed IVF treatment at least 36 months previously.

DISCUSSION

These data are from infertile couples, following assisted conception treatment, who were followed up to calculate the likelihood of spontaneous conception, accounting for the woman's age and the couple's diagnosis and duration of infertility. Other publications (1–5, 7–9) have examined treatment-independent pregnancy rates, for instance, while waiting for assisted conception or following treatment but without specific reference to diagnostic category, age or duration of infertility.

When a couple have been trying to conceive for a long time, no matter what the diagnosis is, the likelihood of getting pregnant is very small (10). This was not the case in these patients who already had a mean duration of infertility of over 5 years. Lower rates of spontaneous pregnancies have been reported (e.g. 9%) (11) and in that study, couples had already achieved a pregnancy following IVF, and data on diagnostic categories or previous duration of infertility were not supplied. Higher rates of spontaneous pregnancies have been reported (27%) (8) but these were in couples in primary care, whereas similar rates to our study were found in a population in a tertiary care setting (20%) (12), suggesting that our data are closer to that expected in such a patient population. Were our patients referred for IVF too soon? Would they have conceived spontaneously, if left untreated? We do not think so. Most of these couples had prolonged durations of subfertility prior to treatment; the mean duration of infertility before IVF was 5.2 years and only 4% had less than 2 years infertility before having IVF. While the numbers of respondents was low compared to some published studies, this is partly explained by the long interval between treatment and the study contact. Furthermore, the respondents to the study did not differ from the non-respondents in several parameters evaluated. We consider therefore that these data are representative of the population.

Table I. Univariate Analysis of the Probability of Natural Conception Within 3 Years of IVF Treatment Using Life Table Analysis

	Number (116)	Pregnancies	Pregnancy rate (%)	Significance
Age (years when treatment finished)				
≤38	91	27	29.7	$p = 0.0039$
>38	25	1	4.0	
Duration of infertility prior to IVF (years)[a]				
<3	20	10	50.0	$p = 0.0035$
≥3	91	18	20.0	
Type of infertility[a]				
Primary	69	17	24.6	$p = 0.99$
Secondary	42	11	26.2	
Diagnostic category				
Unexplained	23	8	34.8	$p = 0.024$
Tubal	32	2	6.3	
Endometriosis	28	6	21.4	
Sperm dysfunction	20	6	30.0	
Other	13	6	46.2	

Note. Comparisons made using Wilcoxon statistic.
[a]Five couples without data on duration or type of infertility.

The effect of diagnostic category and duration of infertility on the likelihood of conception has been published previously. Our data confirm those findings which were that the lowest pregnancy rates were observed in couples with sperm dysfunction or with tubal damage (6). Our study also confirms the published effects of both the woman's age (13–15) and the couple's duration of infertility on the likelihood of conception (16).

Univariate analysis identified that diagnosis, the woman's age being over 38 years and duration of infertility were likely independent contributors to the likelihood of natural conception. No effect was seen whether the infertility was primary or secondary. Multivariate analysis identified that having tubal damage or sperm dysfunction as the major cause for subfertility and the couple's duration of infertility were factors that contributed significantly (and negatively) to the likelihood of any couple conceiving subsequently. The woman's age is a strong predictor but not significant in this population.

The rates of marital separation and divorce are probably falsely lowered by the poor response. Couples who have separated are more likely to have moved from their previous address and even if they have not, are probably less likely to reply to such a questionnaire. We do not consider that this study provides any additional data in this matter.

The likelihood of conception, once IVF treatment was completed, was high, considering these were

Table II. Multivariate Analysis of the Probability of Pregnancy Within 3 Years of IVF Treatment Using Cox Proportional Hazards Method of Analysis

	Pregnancy				
	Coefficient (B)	Standard error	Risk ratio	95% CI	Significance (p)
Age of woman[a]	−0.062	0.04	0.94	[0.86–1.02]	0.130
Duration of infertility[a]	−0.266	0.38	0.77	[0.74–0.92]	0.005
Primary infertility[b]	−0.142	0.38	0.87	[0.41–1.85]	0.712
Diagnostic category					
Other	Referent category				0.014
Unexplained	−0.013	0.60	0.99	[0.31–3.17]	0.983
Tubal	−2.031	0.71	0.13	[0.03–0.52]	0.004
Endometriosis	−0.672	0.59	0.51	[0.16–1.62]	0.255
Sperm dysfunction	−0.639	0.61	0.52	[0.16–1.73]	0.292

[a]Analysed as continuous variables.
[b]In comparison to secondary infertility.

couples with prolonged infertility. After discontinuation of treatment, couples still try elsewhere hoping for better (more successful) treatment. In addition, these data support the suggestion that many couples will ultimately conceive if they persist for long enough.

ACKNOWLEDGMENT

We are grateful to the intellectual and financial support provided for this study from the Centre for Reproductive Medicine by the late Professor Michael Hull.

REFERENCES

1. Evers JL, de Haas HW, Land JA, Dumoulin JC, Dunselman GA: Treatment-independent pregnancy rate in patients with severe reproductive disorders. Hum Reprod 1998;13(5):1206–1209
2. Alam V, Solis F, Zegers-Hochschild F, Balmaceda JP: Spontaneous pregnancy after ART cycles: Follow up of 927 cycles. *In* Abstracts of the 14th Annual Meeting of the ESHRE, Goteborg, 1998; p. 70
3. Kupka MS, Dorn C, Richter O, van der Ven HH, Krebs D: Prognostic factors for treatment-independent pregnancies in assisted reproduction. *In* Abstracts of the 15th Annual Meeting of the ESHRE, Tours, France, 1999; pp. 316–317
4. Roh SI, Awadalla SG, Friedman CI, Park JM, Chin N, Dodds WG *et al.*: In vitro fertilization and embryo transfer: Treatment-dependent versus -independent pregnancies. Fertil Steril 1987;48(6):982–986
5. Shimizu Y, Kodama H, Fukuda J, Murata M, Kumagai J, Tanaka T: Spontaneous conception after the birth of infants conceived through in vitro fertilization treatment. Fertil Steril 1999;71(1):35–39
6. Hull MG, Glazener CM, Kelly NJ, Conway DI, Foster PA, Hinton RA *et al.*: Population study of causes, treatment and outcome of infertility. BMJ 1985;291:1693–1697
7. Collins JA, Burrows EA, Willan AR: The prognosis for live birth among untreated infertile couples. Fertil Steril 1995;64(1):22–28
8. Snick HKA, Snick TS, Evers JLH, Collins JA: The spontaneous pregnancy prognosis in untreated subfertile couples: The Walcheren primary care study. Hum Reprod 1997;12(7):1582–1588
9. Vardon D, Burban C, Collomb J, Stolla V, Erny R: Spontaneous pregnancies in couples after failed or successful in vitro fertilization. J Gynecol Obstet Biol Reprod (Paris) 1995;24(8):811–815
10. Hull MG, Eddowes HA, Fahy U, Abuzeid MI, Mills MS, Cahill DJ *et al.*: Expectations of assisted conception for infertility. BMJ 1992;304(6840):1465–1469
11. Olivennes F, Kerbrat V, Rufat P, Blanchet V, Fanchin R, Frydman R: Follow-up of a cohort of 422 children aged 6 to 13 years conceived by in vitro fertilization. Fertil Steril 1997;67(2):284–289
12. Gleicher N, VanderLaan B, Pratt D, Karande V: Background pregnancy rates in an infertile population. Hum Reprod 1996;11(5):1011–1012
13. Hull MG, Fleming CF, Hughes AO, McDermott A: The age-related decline in female fecundity: A quantitative controlled study of implanting capacity and survival of individual embryos after in vitro fertilization. Fertil Steril 1996;65(4):783–790
14. Ziebe S, Loft A, Petersen JH, Andersen AG, Lindenberg S, Petersen K et al.: Embryo quality and developmental potential is compromised by age. Acta Obstet Gynecol Scand 2001;80(2):169–174
15. Akande VA, Fleming CF, Hunt LP, Keay SD, Jenkins JM: Biological versus chronological ageing of oocytes, distinguishable by raised FSH levels in relation to the success of IVF treatment. Hum Reprod 2002;17(8):2003–2008
16. Glazener CMA, Ford WCL. Predicting conception. Hum Fertil 2002;5(suppl 1):S3–S8