Smoking and In Vitro Fertilization: A Meta-Analysis

WILFRIED FEICHTINGER,^{1,3} KATHARINA PAPALAMBROU,¹ MICHAELA POEHL,¹
URSULA KRISCHKE,¹ and KURT NEUMANN²

Submitted: August 12, 1997

Accepted: August 19, 1997

Purpose: Including our own data and seven relevant publications from the literature, this meta-analysis aimed to establish the influence of the status of female smokers on the clinical pregnancy rate after the first attempt at in vitro fertilization-embryo transfer (IVF-ET).

Methods: We started to collect information about our own patient's smoking habits in January 1996 to evaluate prospectively the influence on IVF success. Information regarding 799 patients (607 nonsmokers and 192 smokers) was obtained. Additionally we retrieved seven relevant publications from the unabridged MEDLINE 1982-1996. They were recalculated to first cycles, because from a biometrical point of view, only the results of the first IVF cycle are really well comparable, as the number of necessary IVF cycles always correlates with the number of pregnancies. These data were compared in the nonparametric sign test according to Dixon-Mood and calculated as relative success ratios, defined as the quotient of the probability of IVF-ET success of nonsmokers divided by that of smokers for each publication.

Results: This meta-analysis, based on a total of 2314 first IVF-ET treatments, showed that almost twice as many IVF-ET cycles were needed for smokers as for nonsmokers to become pregnant. For the success quotient, we obtained a ratio of 1.79, with an associated 95% confidence interval of from 1.24 to 2.59. The total analysis shows, with a P value of less than 0.01, significantly higher pregnancy rates (21%) in nonsmokers compared to smokers (14%).

Conclusions: Based on the analyzed data there exists—from a statistical point of view—a significant negative effect on the chances of success for smokers to become pregnant compared to nonsmokers.

KEY WORDS: smoking; in vitro fertilization; embryo transfer; meta-analysis.

INTRODUCTION

The effects of cigarette smoking on pregnancy and fetal outcome, and recently on fertility, have been frequently investigated and reported. A reduction in fertility was shown by Jick *et al.* (1) and later confirmed by Baird and Wilcox (2), Stillmann *et al.*, (3) and Laurent *et al.* (4). MacMahon *et al.* (5) described lower estrogens in smokers compared with nonsmokers. Furthermore, smoking leads to earlier menopause (1), increased risk of ectopic pregnancy (6), and impairment of semen parameters (3). Several studies have hence attempted to establish whether smoking habits could influence in vitro fertilization (IVF) and embryo transfer (ET).

With the inclusion of our own data, it was the aim of this meta-analysis to assess the influence of the status of smokers on the pregnancy rate after IVF-ET.

METHODS

Our data were derived from the institute's IVF data bank, where we started to collect information about the patients' smoking habits in January 1996 to evaluate prospectively their influence on IVF success. Information about 799 patients (607 nonsmokers and 192 smokers) was obtained. After analyzing the Excel-Smoker data bank, it was established that this data bank was arranged on the basis of IVF cycles. From a biometrical point of view, only the results of the first IVF cycle are really well comparable, as the number of necessary IVF cycles always correlates with the number of pregnancies (when a patient wants to become pregnant, sometimes several IVF attempts are necessary; then, from a statistical point of view, the smoker status and the IVF result are always confounded). Therefore the smoker data bank was evaluated on the basis of first cycles, which contained the outcomes of 541 patients in their first IVF cycle (399

¹ Institut für Sterilitätsbetreuung, 1130 Wien, Trauttmansdorffgasse 3A, Austria.

² Datenverarbeitung, Mathematik/Statistik-Beratung, 1070 Wien, Mariahilferstrasse 88a, Austria.

³ To whom correspondence should be addressed.

nonsmokers and 142 smokers) and was used in the meta-analysis.

Additional data were obtained from the following publications, which were retrieved under the search formulation "Smoking" and "Vitro and Fertilization" from the unabridged MEDLINE 1982–December 1996 (Aries Systems Corp., USA):

- (A) Trapp *et al.* (7),
- (B) Sterzik *et al.* (8),
- (C) Harrison *et al.* (9),
- (D) Hughes *et al.* (10),
- (E) Pattinson *et al.* (11),
- (F) Elenbogen *et al.* (12), and
- (G) Hughes *et al.* (13).

Publications offering pure cycle information without results with regard to "clinical pregnancy rates per patient" (14–16) were omitted. All the remaining references (A–G) were recalculated to first cycles according to possibility and the experiences from our own data bank.

Statistics

The strategy of analysis was explorative. All stated error probabilities were two-sided and referred to the individual test.

The statistic software is a proprietary development and was written in IBM APL2. This software was tested according to the rules of the European Organization for Quality, Section for Quality in the Pharmaceutical Industry, "Principles of Computer Use in a Regulated Pharmaceutical Industry" (1989).

RESULTS

The total analysis shows, with a *P* value less than 0.01, significantly higher pregnancy rates (21%) in nonsmokers compared to smokers (14%) (Table I and Fig. 1). A statistically significant influence of the smoker status on the IVF-ET pregnancy rate is found in publications C and E (*P* < 0.05). Our material showed, in view of the absolute success rate, the highest pregnancy rates of all: 31% at the first cycle. This was with a *P* value less than 0.001, significantly higher than the pooled pregnancy rates of 16% for all other publications without taking the smoker status into consideration.

Basically the eight pregnancy rates of references A–H could be interpreted as stochastically independent tests. We always find a higher success rate with non-

Table I. Results of IVF Outcomes of First Treatment Cycles in Nonsmokers Versus Smokers Based on Seven References (A–G) and Our Own Data (H)^a

	Nonsmokers	Smokers	<i>P</i>
(A) Trapp <i>et al.</i> (7)			
Pregnant	12	3	
Not pregnant	64	35	
Total	76	38	
%	16	8	n.s.
(B) Sterzik <i>et al.</i> (8)			
Pregnant	15	23	
Not pregnant	53	80	
Total	68	103	
%	22	22	n.s.
(C) Harrison <i>et al.</i> (9)			
Pregnant	119	9	
Not pregnant	423	99	
Total	542	108	
%	22	8	<0.05
(D) Hughes <i>et al.</i> (10) ^b			
Pregnant	16	4	
Not pregnant	147	55	
Total	163	59	
%	10	7	n.s.
(E) Pattinson <i>et al.</i> (11)			
Pregnant	40	11	
Not pregnant	196	113	
Total	236	124	
%	17	9	<0.05
(F) Elenbogen <i>et al.</i> (12)			
Pregnant	4	1	
Not pregnant	17	19	
Total	21	20	
%	19	5	n.s.
(G) Hughes <i>et al.</i> (13) ^b			
Pregnant	16	8	
Not pregnant	103	88	
Total	119	96	
%	13	8	n.s.
(H) Feichtinger <i>et al.</i>			
Pregnant	126	40	
Not pregnant	273	102	
Total	399	142	
%	32	28	n.s.
Total, A–H			
Pregnant	348	99	
Not pregnant	1276	591	
Total	1624	690	
%	21	14	<0.01

^a These data were used for meta-analysis.

^b Correction of data according to the same method as in H.

smokers compared to smokers, except in reference B, regarding the pregnancy rates of B as identical. Comparing these data in the nonparametric sign test according to Dixon–Mood, the nonsmokers have a seven times higher pregnancy rate and, in no case, a worse rate; thus, we derive with this model a statistically significant difference of *P* being less than 0.05. The relative success ratios are indicated in Fig. 2 and are defined as the quotients of the probability of IVF-

Fig. 1. Meta-analysis: Smoking and IVF. Results of IVF outcomes of first treatment cycles in nonsmokers versus smokers based on seven references (A–G) and our own data (H). A–H (total) summarize the total result ($n = 2314$).

ET success of nonsmokers divided by that of smokers for each publication. This success quotient thus shows how many IVF-ET cycles a smoker compared to a nonsmoker has to undergo to become pregnant. For this value, we obtain—after log-transformation of the raw data and back transformation—a success ratio of 1.79, with an associated 95% confidence interval of from 1.24 to 2.59 (Fig. 2). Because this interval does not cover the number 1, the result can be interpreted as meaning that smoking reduces the chance of becoming pregnant by a factor close to 2 and that this effect has to be regarded as statistically significant.

DISCUSSION

Among other parameters in IVF such as age, body weight, baseline follicle stimulating hormone (FSH)

levels, thickness and ultrasonic appearance of the endometrium, and uterine and ovarian perfusion, smoking has to be considered as an interfering factor. It may influence ovarian stimulation and oocyte and embryo quality, as well as implantation.

Rhodanate (thiocyanate), a marker for smoke exposure, was measured in serum and follicular fluid of IVF patients, and high concentrations were found (7). Cotinine, a marker for nicotine exposure, was detected in the follicular fluid of smoking women (17, 18). Cadmium, a heavy metal in cigarette tobacco, was also found in follicles of smokers (19), but none of these reports demonstrated a direct negative effect on oocyte or embryo quality. On the other hand, it has been shown that smoking has an influence on hormone levels, e.g., estradiol-17 β serum levels were significantly decreased in women who smoked, compared with the

Fig. 2. Meta-analysis: smoking and IVF ($n = 2314$). Relative success rates (ratios with 95% confidence limits).

results obtained from nonsmokers and passive smokers (8). It was stated that smoking adversely affects ovulation induction parameters and alters the follicular fluid hormonal milieu (20). Smokers produced fewer oocytes (9), and we found significantly lower embryo scores (21), and also altered hormone parameters, when further analyzing our smokers' data (Feichtinger *et al.*, in preparation).

There is also evidence that smokers who became pregnant showed a markedly increased rate of miscarriage (9, 14), but it was impossible to include this important question in our meta-analysis, due to the limited number of publications mentioning miscarriage rates.

However, our statistical meta-analysis now demonstrates from a total of 2314 first IVF cycles, that smokers would need approximately twice as many attempts to get pregnant compared to nonsmokers, i.e., a significant negative effect on IVF pregnancy rates. The basic data of this meta-analysis, of course, do not prevalently fulfill the criteria of prospective randomized placebo-controlled study designs in parallel groups. Furthermore, the number of cases in the evaluated publications partly differ significantly; uniform IVF-ET therapies and selection cannot be assumed. In view of the methodical weakness mentioned above, a certain caution in the final medical interpretation seems advisable regarding the accuracy of the results obtained. Regarding the degree of representativeness of this meta-analysis, this weakness has to be interpreted as a reversed positivism of a relatively high degree of representativeness, which is also based on the high number of cases.

In conclusion, these findings suggest that infertile women should be advised to quit or reduce smoking, particularly before treatment with IVF-ET. We agree with Rowlands *et al.* (16) that it has yet to be investigated how quickly the benefit of stopping may be gained.

REFERENCES

1. Jick H, Porter J, Morrison AS: Relation between smoking and age of natural menopause. *Lancet* 1977;1:1354-1355
2. Baird DD, Wilcox AJ: Cigarette smoking associated with delayed conception. *JAMA* 1985;253:2979-2983
3. Stillman RJ, Rosenberg MJ, Sachs BP: Smoking and reproduction. *Fertil Steril* 1986;46:545-566
4. Laurent SL, Thompson SJ, Addy C, Garrison CZ, Moore EE: An epidemiologic study of smoking and primary infertility in women. *Fertil Steril* 1992;57:565-572
5. MacMahon B, Trichopoulos D, Cole P, James B: Cigarette smoking and urinary estrogens. *N Engl J Med* 1982;307:1062-1065
6. Campbell OM, Gray RH: Smoking and ectopic pregnancy. A multinational case control study. *In Smoking and Reproductive Health*, MJ Rosenberg (ed). Littleton, MA, PSG, 1986
7. Trapp M, Kemeter P, Feichtinger W: Smoking and in-vitro fertilization. *Hum Reprod* 1986;6:357-358
8. Sterzik K, Strehler E, De Santo M, Trumpp N, Abt M, Rosenbusch B: Influence of smoking on fertility in women attending an in-vitro fertilization program. *Fertil Steril* 1996;4:810-814
9. Harrison K, Breen T, Hennessey J: The effect of patient smoking habit on the outcome of IVF and GIFT treatment. *Aust NZ J Obstet Gynaecol* 1990;30:340-343
10. Hughes EG, Young LE, Ward SM: Cigarette smoking and outcomes of in-vitro-fertilization and embryo transfer. A prospective cohort study. *Hum Reprod* 1992;7:358-361
11. Pattinson HA, Taylor PJ, Pattinson MH: The effect of cigarette smoking on ovarian function and early pregnancy outcome of in-vitro fertilization treatment. *Fertil Steril* 1991;55:780-783
12. Elenbogen A, Lipitz S, Mashiach S, Dor J, Levran D, Ben-Rafael Z: The effect of smoking on the outcome of in-vitro fertilization-embryo transfer. *Hum Reprod* 1991;6:242-244
13. Hughes EG, Yeo J, Claman P, Young Lai EV, Sagle MA, Daya S, Collins JA: Cigarette smoking and the outcomes of in-vitro fertilization. Measurement of effect size and levels of action. *Fertil Steril* 1994;62:807-814
14. Maximovich A, Beyler SA: Cigarette smoking at time of in-vitro fertilization cycle initiation has negative effect on in vitro fertilization-embryo transfer success rate. *J Assist Reprod Genet* 1995;12:75-77
15. Rosevar SK, Holt PW, Lee TD, Ford WC, Wardle PG, Hull MG: Smoking and decreased fertilization rates in-vitro. *Lancet* 1992;340:1195-1196
16. Rowlands DJ, McDermott A, Hull MG: Smoking and decreased fertilization rates in-vitro. *Lancet* 1992;340:1409-1410
17. Weiss T, Eckert A: Cotinine levels in follicular fluid and serum of IVF patients: Effect on granulosa-luteal cell function *in vitro*. *Human Reprod* 1989;4:482-485
18. Zenses MT, Reed TE, Wang P, Klein J: Cotinine, a major metabolite of nicotine, is detectable in follicular fluid of passive smokers in in vitro fertilization therapy. *Fertil Steril* 1996;66:614-619
19. Zenses MT, Krishnan S, Krishnan B, Zhang H, Casper RF: Cadmium accumulation in follicular fluid of women in in-vitro fertilization-embryo transfer is higher in smokers. *Fertil Steril* 1995;64:599-603
20. Van Voorhis BJ, Syrop CH, Hammitt DG: Effects of smoking on ovulation induction for assisted reproductive techniques. *Fertil Steril* 1992;58:981-985
21. Steer CV, Mills CL, Tan SL: The cumulative embryo score: A predictive embryo scoring technique to select the optimal number of embryos to transfer in an in-vitro fertilization and embryo transfer programme. *Hum Reprod* 1992;7:117-119