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Effects of subfertility cause, smoking and body weight on the success rate of IVF

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BACKGROUND: We investigated the separate and combined effects of smoking and body mass index (BMI) on the success rate of IVF for couples with different causes of subfertility. METHODS: The success rate of IVF was examined in 8457 women. Detailed information on reproduction and lifestyle factors was combined with medical record data on IVF treatment. All IVF clinics in The Netherlands participated in this study. The main outcome measures were live birth rate per first cycle of IVF differentiated for the major predictive factors. RESULTS: For male subfertility the delivery rate per cycle was significantly lower than unexplained subfertility, OR of 0.70 (95% CI 0.57–0.86); for tubal pathology, the delivery rate was slightly lower, OR = 0.86 (95% CI 0.70–1.01). Smoking was associated with a significantly lower delivery rate was slightly lower; for OR = 0.72 (95% CI 0.61–0.84) and a significantly higher abortion rate compared to non-smoking delivery rates of 21.4% and 16.4%, respectively ($P = 0.02$). Women with a BMI of ≥27 kg/m^2 had a significantly lower delivery rate, with an OR of 0.67 (95% CI 0.48–0.94), compared with normal weight women (BMI ≥20 and <27 kg/m^2). CONCLUSIONS: Both smoking and overweight unfavourably affect the live birth rate after IVF. The devastating impact of smoking on the live birth rate in IVF treatment is comparable with an increase in female age of >10 years from age 20 to 30 years. Subfertile couples may improve the outcome of IVF treatment by lifestyle changes.

Key words: body mass index/IVF/live birth rate/smoking/subfertility diagnosis

Introduction

The improving success rates of IVF, initially developed as a technique to assist reproduction in women with bilateral tubal obstruction (Steptoe and Edwards, 1978), have extended its use to other subfertility diagnoses. For women with severe bilateral tubal occlusion, evidence for the effectiveness of IVF has been available for years (Corabian and Hailey, 1999). Recently a randomized controlled trial, although small, suggested the efficacy of IVF for subfertility causes other than tubal pathology (Hughes *et al.*, 2004). Other studies on the success rate of IVF by cause of subfertility have shown inconsistent results (Alsalili *et al.*, 1995; Tan *et al.*, 1996). However, in the largest study on IVF effectiveness (Templeton *et al.*, 1996), carried out in the UK between 1991 and 1994 and including 36 961 cycles, no significant differences were observed in live birth rate comparing tubal pathology, endometriosis, unexplained subfertility and cervical and uterine subfertility. The prognostic model developed by Templeton *et al.* did not give additional predictive information for the majority of IVF patients in The Netherlands in the study by Smeenk *et al.* (2000). Lifestyle factors were not included in these studies.

The main goal of the present analyses was to explore possible predictive factors such as duration of subfertility, and female age, for subfertile couples with different causes of subfertility. As there is evidence of an overall detrimental effect of female smoking on natural and assisted fecundity in the literature (Hughes and Brennan, 1996; Feightinger *et al.*, 1997; Augood *et al.*., 1998; Hassan and Killick, 2004) and indication for an unfavourable effect of extremes of body mass index (BMI) on the outcome of fertility treatment (Norman and Clark, 1998; Wang *et al.*, 2000, 2002; Nichols *et al.*, 2003), we also studied smoking and BMI as possible prognostic factors. Like the Templeton model we distinguished the major causes of subfertility, and added male subfertility and lifestyle factors. We executed this study with data from a large Dutch nationwide retrospective cohort study (the so called 'OMEGA study') including 19 840 women who underwent IVF treatment between 1983 and 1995.

Materials and methods

Patients

The study population, study procedures and data collection methods have been described elsewhere (Klip *et al.*, 2001, 2003; De Boer *et al.*, 2003). In short, the OMEGA study, initiated in 1995 to examine the late effects of hormone stimulation in IVF-treated women, comprised 19 840 women treated with IVF in a nationwide cohort study. Women with subfertility of ≥1 year duration were included if they had completed at least one IVF treatment cycle between January 1, 1983, the start of IVF treatment in The Netherlands, and January 1, 1995. A 23 page questionnaire was sent to 19 242 women between January 1997 and January 2000 to obtain information on gynaecological disorders before and after subfertility treatment, reproductive risk factors for hormone-related cancers and several other lifestyle factors. Figure 1 gives a graphical presentation of the study population. As there was no national registry of IVF treatments, data from both the patient records and pregnancy follow-up were collected by trained research assistants, who abstracted data from the medical files on gynaecological history, subfertility diagnosis, fertility hormones used prior to IVF treatment, and detailed information about each subsequent IVF treatment, the number of retrieved oocytes, occurrence of complications and whether or not the treatment resulted in a pregnancy. Additional information on pregnancy outcome, reproductive and lifestyle factors were obtained through the mailed questionnaire.

For the present analyses, all ICSI attempts were excluded because of the small number. Unstimulated cycles, other IVF-related treatments such as zygote intra-Fallopian transfer, gamete intra-Fallopian transfer, gamete and embryo donation and frozen embryo transfers were also excluded from the study (in total 1568 cycles).

In The Netherlands, three IVF cycles were covered by health cost insurances in the period under study, leading to a low drop-out rate in the first three cycles. Eighty-seven per cent of the women

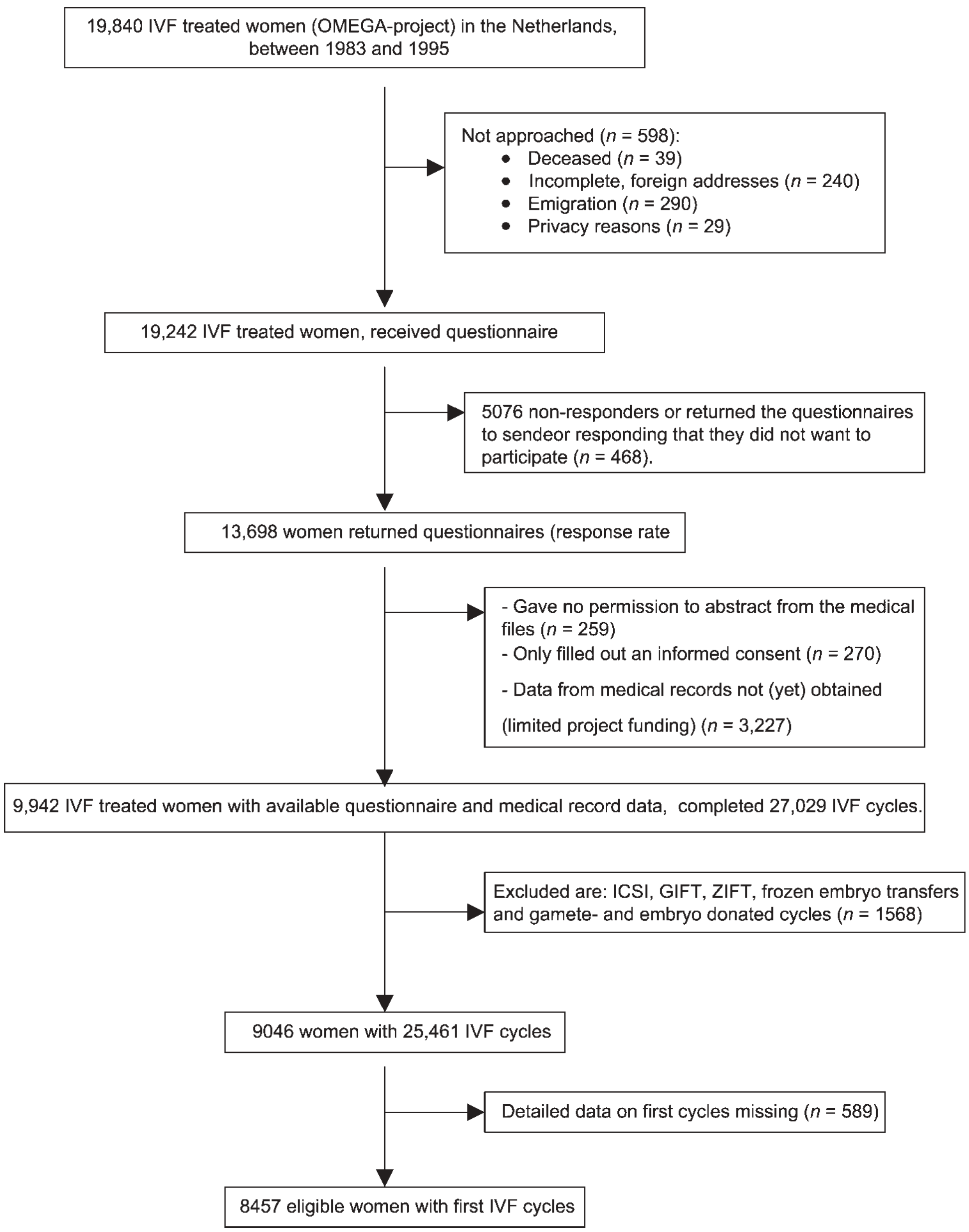

Figure 1. Description of the recruitment of eligible women and cycles. GIFT = gamete intra-Fallopian transfer; ZIFT = zygote intra-Fallopian transfer.

completed at least three cycles, or became pregnant in the first two cycles. As continuation of IVF depends on predictors of success observed in the first cycle, such as number of oocytes, fertilization rate and embryo morphology (Stolwijk *et al.*, 1996), we restricted all analyses to the first attempt, leaving 8457 first cycles for analysis.

Definition of variables

Subfertility diagnosis was based on medical record information and divided into four categories: tubal pathology, male subfertility, unexplained subfertility and other known subfertility causes, mainly women with polycystic ovarian syndrome (PCOS) or endometriosis. Each woman was only categorized once, the one assumed to contribute most to the subfertility. For 831 first cycles there was no cause of subfertility known and these were therefore not analysed in detail. Duration of subfertility was determined by the period between the start of the involuntary childlessness, as reported by the woman, and the date of first IVF attempt. Primary subfertility was defined as having no pregnancy before the IVF treatment. Education level was divided into low (those without completed vocational training), middle (with vocational training) and high (with high vocational training or academic degrees). Women were defined as smokers when they smoked more than one cigarette a day for ≥1 year at the time of the first oocyte retrieval. Underweight was defined as having a BMI $<20\,kg/m^2$, normal weight as a BMI of $20-27\,kg/m^2$ and overweight as a BMI $\geq 27\,kg/m^2$, as there were not enough women with a BMI $\geq 30\,kg/m^2$ for analysis. The BMI was calculated with the women's weight at the time of first visit to the gynaecologist for her fertility problem. The woman's age at the IVF attempt was computed by subtracting the date of birth from the IVF attempt date. IVF attempts obtained from the medical records were linked with live births as reported by the women on the questionnaire. Conception dates were calculated by subtracting the reported duration of pregnancy from the delivery date, as reported by the women. If an IVF attempt had started within 4 weeks of the estimated conception date, the pregnancy was considered to be the result of the IVF attempt, unless the medical record stated that a spontaneous pregnancy followed the IVF attempt. The implantation rate was defined as the number of live born children per embryo transferred. The live birth rate was the delivery rate with at least one live born child per cycle. Total fertilization failure (TFF) was defined when none of the oocytes was fertilized after IVF. An abortion was defined as a pregnancy loss between 6 and 16 weeks of amenorrhoea. The following complications were registered: ovarian hyperstimulation syndrome (OHSS) leading to hospitalization, other medical problems resulting in admission and ectopic pregnancies.

Table I. Characteristics of women in the OMEGA cohort at first IVF cycle

	All women in first cycle[a]	Tubal pathology	Male subfertility	Unexplained subfertility	Other known subfertility causes[b]
No. of first cycles	8457	3008 (35.6)	2179 (25.8)	1828 (21.6)	611 (7.2)
Age (years)					
Average (SD)	32.8 (3.9)	32.8 (4.0)	32.4 (3.9)	33.3 (3.7)	32.5 (3.9)
20–24	187 (2.2)	80 (2.7)	48 (2.2)	22 (1.2)	19 (3.1)
25–29	1833 (21.7)	653 (21.7)	553 (25.4)	326 (17.8)	135 (22.1)
30–34	3915 (46.3)	1361 (45.3)	1014 (46.5)	862 (47.2)	290 (47.5)
35–39	2262 (26.7)	821 (27.3)	520 (23.9)	556 (30.4)	151 (24.7)
≥40	235 (2.8)	86 (2.9)	40 (1.8)	59 (3.2)	14 (2.3)
Unknown	25 (0.3)	7 (0.2)	4 (0.2)	3 (0.2)	2 (0.3)
Duration of subfertility (years)					
Mean (SD)	5.35 (3.0)	5.11 (3.3)	5.34 (2.9)	5.60 (2.7)	5.83 (3.2)
Median (IQR)	4.65 (3.3)	4.33 (3.7)	4.64 (3.1)	4.89 (2.8)	5.08 (3.6)
Unknown	1286 (15.2)	434 (14.4)	245 (11.2)	140 (7.7)	50 (8.2)
Subfertility					
Primary	4009 (47.4)	1090 (36.2)	1246 (57.2)	1044 (57.1)	366 (59.9)
Secondary	1944 (23.0)	974 (32.4)	305 (14.0)	460 (25.2)	90 (14.7)
Unknown	2504 (29.6)	944 (31.4)	628 (28.8)	324 (17.7)	155 (25.4)
Level of education[c]					
Low	2323 (27.5)	862 (28.7)	567 (26.0)	478 (26.1)	194 (31.8)
Middle	4085 (48.3)	1421 (47.2)	1095 (50.3)	888 (48.6)	255 (41.7)
High	1865 (22.1)	651 (21.6)	475 (21.8)	423 (23.1)	152 (24.9)
Unknown	184 (2.2)	74 (2.5)	42 (1.9)	39 (2.1)	10 (1.6)
Smoking at 1st IVF					
Yes	3617 (42.8)	1536 (51.1)	841 (38.6)	673 (36.8)	229 (37.5)
No	4706 (55.6)	1423 (47.3)	1306 (59.9)	1127(61.7)	371 (60.7)
Unknown	134 (1.6)	49 (1.6)	32 (1.5)	28 (1.5)	11 (1.8)
BMI (kg/m^2) at 1st IVF					
Average (SD)	22.27 (3.3)	22.36 (3.3)	22.25 (3.1)	22.04 (3.1)	22.46 (3.6)
<20	1752 (20.7)	607 (20.2)	433 (19.9)	409 (22.4)	134 (21.9)
20–25	5132 (60.7)	1818 (60.4)	1357 (62.3)	1127 (61.7)	351 (57.4)
25–27	602 (7.1)	228 (7.6)	144 (6.6)	110 (6.0)	52 (8.5)
>27	619 (7.3)	231 (7.7)	153 (7.0)	117 (6.4)	46 (7.5)
Unknown	352 (4.2)	124 (4.1)	92 (4.2)	65 (3.6)	28 (4.6)

Values in parentheses are percentages unless otherwise specified.
[a]Including those with unknown subfertility cause.
[b]Including: polycystic ovary syndrome 16.5%, other ovarian problems 28.8%, endometriosis 34.4%, other causes 21.3%.
[c]low = not completed vocational training; middle = with vocational training; high = high vocational training and academic training.
IQR = interquartile range.
SD = standard deviation.

Statistical analyses

The statistical program SAS: The SAS system for window 8.2, SAS Institute Inc. Cary NC, USA, was used for statistical analyses. Univariate frequencies and means were calculated to describe the women and their first IVF cycles. The results are given in Tables I and II. All analyses were done first on all women, including those with unknown cause of subfertility, and then by cause of subfertility.

Contingency tables were used to calculate live birth rates per cycle, live birth rate per oocyte retrieval and live birth rate per embryo transfer as well as the implantation rate for categories according to the cause of subfertility, age, smoking, period of IVF and BMI (Tables III and IV). This value was then averaged across cycles.

Multivariate logistic regression was done to study the independent and combined effects of potential determinants on the live birth rate. We included cause of subfertility, smoking, BMI (continuous and in three categories) and period of IVF in the model, together with factors that have previously been reported in the literature to predict the success rate of IVF. These factors were: primary versus secondary subfertility, age at treatment (continuous and in two categories) and duration of subfertility. We corrected for period of IVF by adding a factor indicating whether the IVF was before or after January 1, 1990. In univariate analyses, we found higher pregnancy rates after 1990 than before that date; however, differences in live birth rates over time were small. The results for the other variables included in the model did not change according to whether we included age and BMI as categorical or continuous variables. We included the results for the categorical variables in Table V and added the estimates for the continuous variables per unit change to the text. The resulting regression estimates were transformed to present odds ratios (OR) for those in a category as compared with the reference category, with all other factors equal.

Results

Population

The study population consisted of 8457 women who underwent their first cycle of IVF. The characteristics of the women are presented in Table I. Education was comparable to the Dutch population of women of childbearing age in the period studied and the different education levels were equally represented in all subfertility categories. There was no difference in duration of subfertility before the first treatment between the major subgroups we analysed. Of all women, 43% smoked during the first IVF attempt. Fifty-one per cent of the women with tubal pathology smoked at the time of the first attempt, which was significantly more than in the other diagnostic groups. No significant differences in the distribution of extreme over- or underweight women between diagnostic categories were observed. Women with tubal pathology were significantly more secondary subfertile.

Cycles

The characteristics of the first IVF cycles of our population are described in Table II. The outcome of the first cycles in women with a main diagnosis of tubal pathology (3008 cycles), male subfertility (2179 cycles) and unexplained subfertility (1828 cycles) were analysed, using various outcome measures. Cycles with other known causes of subfertility (611) were also examined. The proportion of first cycles with TFF was 27.1% in the male subfertility group. This was significantly higher than for unexplained subfertility and tubal pathology, (10.6 and 7.3% respectively). The abortion rate was significantly lower in the male subfertility group compared to both other indication categories. The overall proportion of first cycles with complications after IVF treatment (excluding TFF) was 4.9%. Ectopic pregnancies occurred significantly more often in the group with tubal pathology, compared to the other groups. The percentage of cycles with OHSS leading to hospitalization was significantly higher in the 'other known' indication group (including PCOS) compared to the main indication categories.

Table II. Characteristics and various outcome measures of first IVF cycles of women in the OMEGA cohort

	All subfertility	Tubal pathology	Male subfertility	Unexplained subfertility	Other known causes
No. of cycles (% of all first cycles)	8457	3008 (35.6)	2179 (25.8)	1828 (21.6)	611 (7.2)
With oocyte retrievals	7529 (89.0)	2636 (87.6)	1995 (91.6)	1644 (89.9)	530 (86.7)
Median no. of oocytes (IQR) (25–75)	8 (5–12)	8 (4–12)	8 (5–13)	8 (5–12)	8 (5–13)
With embryo transfers	6286 (74.3)	2388 (79.4)	1389 (63.7)	1437 (78.6)	469 (76.8)
Median no. of embryos (IQR) (25–75)	2 (1–3)	3 (2–3)	63.7 2 (0–3)	2 (2–3)	2 (2–3)
No. of pregnancies[a]	1664 (19.7)	580 (19.3)	369 (16.9)	418 (22.9)	140 (22.9)
No. of abortions[b,c]	313 (18.8)	118 (20.3)	57 (15.5)	84 (20.1)	30 (21.4)
Deliveries[a]	1282 (15.2)	439 (14.6)	296 (13.6)	326 (17.8)	103 (17.0)
No. of singletons[d]	915 (71.4)	312 (71.1)	205 (69.3)	228 (69.9)	79 (76.7)
No. of twins[d]	310 (24.2)	101 (23.0)	81 (27.4)	84 (25.8)	21 (20.4)
No. of triplets or more[d]	57 (4.4)	26 (5.9)	10 (3.4)	14 (4.3)	3 (2.9)
Complications					
TFF	1164 (13.8)	221 (7.3)	590 (27.1)	194 (10.6)	57 (9.3)
OHSS	206 (2.4)	58 (1.9)	58 (2.7)	49 (2.7)	25 (4.1)
Other	154 (1.8)	77 (2.6)	24 (1.1)	33 (1.8)	15 (2.5)
Ectopic pregnancies[c]	56 (3.4)	35 (6.0)	7 (1.9)	8 (1.9)	3 (2.1)

Values in parentheses are percentages unless otherwise specified.
[a]Percentage of cycle.
[b]Between 6 and 16 weeks of pregnancy.
[c]Percentage of pregnancies.
[d]Percentage of deliveries.
IQR = interquartile range; TFF = total fertilization failure; OHSS = ovarian hyperstimulation syndrome.

Table III. Comparison of live birth rates and implantation rates, per diagnostic category, according to age

	Age (years)	No. of deliveries	Live birth rate per first cycle[a]						Implantation rate (%)[b]
			Per cycle		Per oocyte retrieval		Per embryo transfer		
			n	%	*n*	%	*n*	%	
Tubal pathology		439	3007	14.6	2635	16.7	2387	18.4	9.3
Male subfertility		296	2178	13.6	1994	14.8	1388	21.3	11.8
Unexplained subfertility		326	1827	17.8	1643	19.8	1436	22.7	12.2
Tubal pathology	20–24	21	80	26.3	75	28.0	70	30.0	16.1
	25–29	100	653	15.3	578	17.3	522	19.2	10.6
	30–34	208	1360	15.3	1195	17.4	1089	19.1	9.7
	35–39	108	821	13.2	709	15.2	645	16.7	7.4
	40–44	2	85	2.4	71	2.8	55	3.6	1.5
Male subfertility	20–24	10	48	20.8	46	21.7	31	32.3	18.3
	25–29	79	552	14.3	518	15.3	368	21.5	13.1
	30–34	141	1014	13.9	944	14.9	646	21.8	11.9
	35–39	62	520	11.9	446	13.9	314	19.8	9.6
	40–44	4	40	10.0	37	10.8	27	14.8	5.9
Unexplained subfertility	20–24	4	22	18.2	21	19.1	17	23.5	13.7
	25–29	68	326	20.9	294	23.1	255	26.7	14.5
	30–34	165	861	19.2	779	21.2	684	24.1	13.5
	35–39	85	556	15.3	495	17.2	433	19.6	9.5
	40–44	4	58	6.9	51	7.8	45	8.9	4.8

[a]Delivery rate with at least one live born.
[b]Number of live born children per embryo transferred.

The average number of embryos per transfer was 2.2 (range 0–7, median 2). The overall live birth rate per cycle was 15.2%. The live birth rate per first cycle for the unexplained subfertile couples was higher (17.8%) in comparison with tubal pathology (14.6%) and male subfertility (13.6%). The live birth rates according to age and diagnostic categories are shown in Table III. For male subfertility there was no significant difference in the live birth rate per embryo transfer, in comparison with the unexplained subfertile couple (21.3 and 22.7%). Tubal pathology was associated with the lowest live birth rate per embryo transfer (18.4%). The overall implantation rate per cycle was 10.7%.

For the three major subfertility causes analysed, we found evidence of a clear and significant ($P < 0.0001$) trend of declining live birth rates with increasing female age (Figure 2). The overall live birth rate per cycle decreased with 2% ($P = 0.03$) for each additional year of the female age.

We compared the effects of smoking and BMI per diagnostic category in Table IV. In all subgroups according to

Table IV. Comparison of live birth rates and implantation rates per diagnostic category, stratified by smoking, and body mass index (BMI)

	Smoking	BMI (kg/m^2)	No. of deliveries	Live birth rate per first cycle[a]						Implantation rate (%)[b]
				Per cycle		Per oocyte retrieval		Per embryo transfer		
				n	%	*n*	%	*n*	%	
Tubal pathology	Yes		208	1536	13.5	1330	15.6	1199	17.3	8.4
	No		228	1422	16.0	1264	18.0	1149	19.8	10.3
Male subfertility	Yes		98	840	11.7	762	12.9	534	18.4	10.1
	No		191	1306	14.6	1203	15.9	831	23.0	12.6
Unexplained subfertility	Yes		90	673	13.4	592	15.2	520	17.3	9.1
	No		233	1126	20.7	1026	22.7	897	26.0	14.1
Tubal pathology		<20	98	607	16.1	546	18.0	494	19.8	10.0
		20–25	264	1817	14.5	1604	16.5	1461	18.1	9.2
		25–27	33	228	14.5	195	16.9	170	19.4	8.4
		≥27	29	231	12.6	191	15.2	171	17.0	9.2
Male subfertility		<20	59	433	13.6	399	14.8	282	20.9	11.6
		20–25	191	1356	14.1	1244	15.4	856	22.3	12.1
		25–27	20	144	13.9	134	14.9	100	20.0	11.4
		≥27	20	153	13.1	135	14.8	92	21.7	13.2
Unexplained subfertility		<20	72	408	17.7	369	19.5	323	22.3	11.4
		20–25	207	1127	18.4	1017	20.4	899	23.0	12.4
		25–27	23	110	20.9	94	24.5	80	28.8	17.1
		≥27	16	117	13.7	103	15.5	86	18.6	11.5

[a]Delivery rate with at least one live-born.
[b]Number of live born children per embryo transferred.

Table V. Multivariable logistic regression model of the probability of a live birth after first cycle of IVF

	Per cycle	Per oocyte retrieval	Per embryo transfer
Intercept	−1.4426	−1.2229	−0.9500
Pregnancy rate (%)[a]	19.1	22.7	27.9
Smoking			
No	1	1	1
Yes	0.72 (0.61–0.84)	0.74 (0.63–0.87)	0.73 (0.62–0.86)
Age (years)			
<35	1	1	1
≥35	0.80 (0.67–0.96)	0.83 (0.69–1.00)	0.83 (0.69–1.00)
Body mass index (kg/m^2)			
20–27	1	1	1
<20	0.99 (0.82–1.19)	0.97 (0.80–1.17)	0.97 (0.80–1.18)
≥27	0.67 (0.48–0.94)	0.72 (0.51–1.02)	0.73 (0.52–1.03)
Unexplained subfertility	1	1	1
Tubal pathology	0.86 (0.70–1.01)	0.86 (0.71–1.05)	0.81 (0.66–0.99)
Male subfertility	0.70 (0.57–0.86)	0.69 (0.56–0.85)	0.93 (0.75–1.16)
Other known factor	0.92 (0.68–1.23)	0.94 (0.70–1.27)	0.92 (0.68–1.25)
Secondary subfertility	1	1	1
Primary subfertility	0.96 (0.81–1.15)	0.96 (0.81–1.15)	0.99 (0.83–1.16)
Period of IVF			
< 1990	1	1	1
≥ 1990	1.54 (1.18–2.02)	1.36 (1.03–1.79)	1.24 (0.94–1.65)
Duration of subfertility (years)			
< 8	1	1	1
≥ 8	0.79 (0.62–1.00)	0.84 (0.66–1.08)	0.90 (0.70–1.16)

Values are odds ratios (95% confidence intervals) unless otherwise indicated.
[a]Calculated pregnancy rate.
The final model to calculate the pregnancy rate (PR) is shown below. All variables are indicators: ln (PR/(1 − PR)) = −1.4426–0.3285 smoking − 0.2231 age ≥35–0.010 BMI <20–0.4005 BMI ≥27–0.1508 tubal pathology–0.3567 male subfactor–0.0834 other factor–0.041 primary subfactor + 0.0432 treatment ≥1990 −0.236 duration subfactor ≥8 years.

subfertility diagnosis, the delivery rate for non-smoking women was significantly ($P < 0.0001$) higher than for smoking women (Figure 3). The effect of smoking was the largest for women with unexplained subfertility; smoking decreased the live birth rate by 7.3% compared with decreases of 3.0 and 2.5% for women with male subfertility and tubal pathology respectively. Overall we found no significant difference between the mean number of oocytes for non-smokers (9.6 oocytes per cycle) compared to smoking women (9.0 oocytes per cycle) (95% CI 0.35–1.0). Although the mean number of embryos replaced for smoking women was higher (2.2 embryos per transfer) compared to non-smoking women (2.14 embryos per transfer), this led to lower pregnancy rates for smoking women. The abortion rate per pregnancy was significantly higher for smoking women compared to non-smoking women, respectively 21.4 and 16.4% ($P = 0.02$). The ectopic pregnancy rate for both smoking and non-smoking women was not significantly different, respectively 3.8 and 2.9% per pregnancy ($P = 0.3$).

There was a significantly higher live birth rate per cycle in women with normal weight (BMI ≥20–25 kg/m^2) and slight overweight (BMI 25–27 kg/m^2) compared with women with evident overweight with a BMI ≥27 kg/m^2. The unfavourable effect of overweight was largest for women with unexplained subfertility. Underweight women had similar live birth rates compared to women of normal weight.

Table V shows the results of multivariate analyses of predictors of the live birth rate as a result of the first IVF cycle,

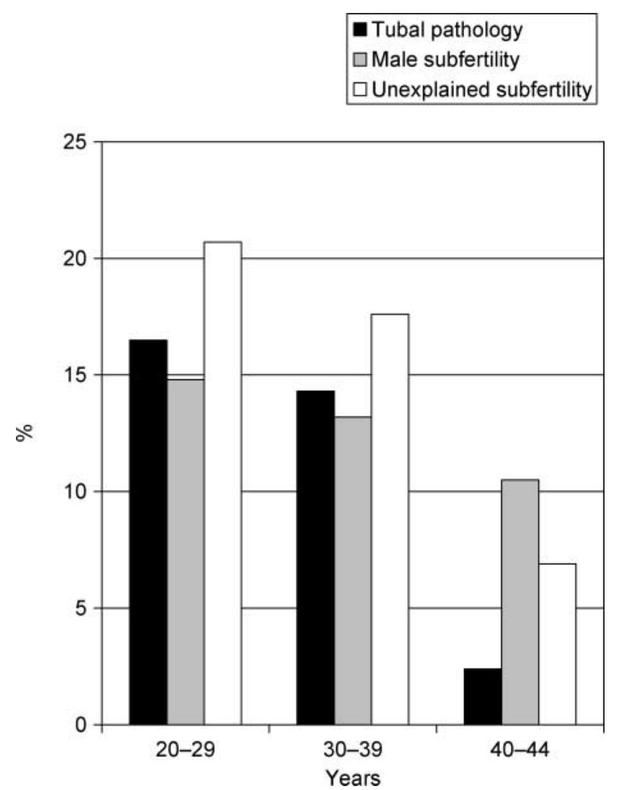

Figure 2. IVF live birth rate by cause of subfertility, for three age groups; % = proportion of first cycles resulting in a live birth. *P*-value for the age effect $P < 0.0001$.

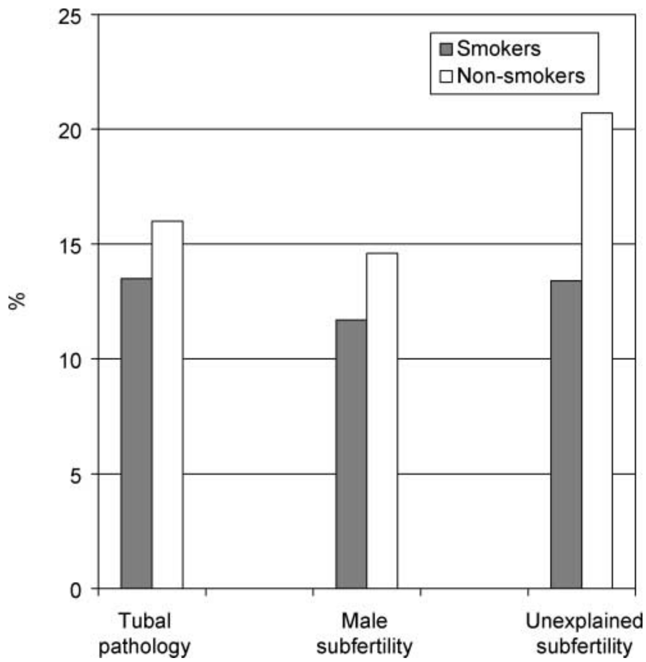

Figure 3. IVF live birth rate for smoking and non-smoking women, by cause of subfertility; % = proportion of first cycles resulting in a live birth. *P*-value for the smoking effect $P < 0.0001$.

after successful oocyte retrieval and after embryo transfer. The first row gives the intercept, and the corresponding live birth rate for those with reference values for all variables. In the other rows, OR are presented. These can be interpreted as follows: the live birth rate of smokers decreased with 28% compared with the live birth rate of non-smokers, adjusted for the following confounders: age, BMI, indication for IVF, previous pregnancies, duration of subfertility and calendar period in which IVF took place. There was only a significantly lower live birth rate per treatment cycle by cause of subfertility for couples with male subfertility. We found that the adjusted effect of smoking on the live birth rate was even stronger than an increase in female age with >10 years, from age 20 to 30 years, with an OR of 0.78 (95% CI 0.63–0.96). The strength of the association with smoking differed between the subfertility groups. As in the univariate analyses, smoking was most deleterious to the couples with unexplained subfertility, and least to those with tubal pathology (Table IV). Overweight women (BMI $>27\ kg/m^2$) had a 33% reduced chance of a live birth in their first IVF cycle. As for smoking, the association with overweight was strongest in women with unexplained subfertility. BMI and age were also both included as continuous variables. The effect estimates were similar for live birth rate per cycle, per oocyte retrieval and per embryo transfer: BMI per unit OR = 0.98 (0.95–1.00) and age per year OR = 0.98 (0.96–1.00). Women with primary subfertility had the same live birth rate as women with secondary subfertility. The duration of subfertility did not influence the live birth rate for the three major subfertility categories. Even after 8 years of subfertility, no significant decrease in live birth rate could be detected.

Discussion

In this large nationwide dataset we found that the live birth rate for male subfertility was significantly lower compared to unexplained subfertility and tubal pathology. Advancing female age had an unfavourable effect on the success rate of IVF for all subfertility causes. Smoking and overweight during IVF treatment had deteriorating effects on the live birth rates. Women who smoked had a significantly higher abortion rate than non-smoking women. Furthermore the effect of smoking was comparable to an increase in female age with 10 years, from age 20 to 30 years.

When interpreting our results, the strengths and limitations of our study must be considered. Advantages of our analyses include the large size of the study population and the availability of nearly complete information on details of IVF treatment from the medical records and outcome of all pregnancies from the women themselves. A limitation of our study is that the analyses had to be based on women who responded to the questionnaire (a 71% response rate). Women who had a live birth after IVF were possibly more likely to participate to the OMEGA project than those who remained childless. From two participating hospitals, a non-responder analysis to the questionnaire was performed. Indeed, we observed a higher response rate among women who had a live birth rate after IVF, compared to women who did not (response rates of 73 and 64% respectively). This might have resulted in a slight overestimation of live birth rates after IVF in Tables II–IV. However, assuming that non-response was not associated with lifestyle factors, the estimate of the OR is unbiased. For 3227 IVF-treated women who returned the questionnaire, data from the medical files could not yet be obtained. Since this was due to limited project funding resulting in a random sample of records not yet completed, it is highly unlikely that this has led to selection bias. Another restriction of our study is that we should take into account that the success rates in these older data might differ from the success rates today (Kremer *et al.*, 2002). One unique feature of our analyses is that we were able to study the separate and combined influences of smoking and BMI for a very large number of IVF treatments.

Most of our results correspond with the results of the study by Templeton *et al.* (1996). We found that only male subfertility was associated with a significantly lower delivery rate per cycle compared with tubal pathology and unexplained subfertility. If we considered the delivery rates per embryo transfer, i.e. after fertilization had occurred, we did not observe a difference between unexplained subfertility and male subfertility. The abortion rate was significantly lower in the male subfertile group. These results imply that the receptiveness of the women with unexplained subfertility and male subfertility was at least the same, and probably better in the male subfertile group. For tubal pathology the delivery rate was significantly lower given an embryo transfer, compared to unexplained subfertility and male subfertility. The explanation for this difference could be the negative effect of tubal pathology on the implantation processes and the embryotoxicity of hydrosalpinx fluid (Johnson *et al.*, 2002).

Individual studies comparing smoking and non-smoking women undergoing IVF treatment do not always indicate a decreased live birth rate with smoking. A meta-analysis (Augood *et al.*, 1998) showed that women who smoked had significantly lower pregnancy rates per IVF treatment compared to non-smokers. However, in none of these studies was a subdivision made according to the indication for IVF, and each of the studies reported different confounding factors and calculated OR using different statistical methods. In a review (Zenzes, 2000) on the genetic damaging effects from smoking and its components on germinal cells, evidence was found that smoking affected the quantity and quality of oocytes and that it leads to an early age of menopause. Our results show a lower live birth rate and higher abortion rate for smoking women unless they had a higher mean number of embryos transferred. This might explain the lower quality of these embryos.

We studied the effects of both smoking and age on the live birth rate and found a trend of decreasing live birth rates with increasing age, which was consistently lower for smokers. Among women with tubal pathology, the diagnostic group with significantly more smokers than in the other subfertility causes, we found that the deteriorating effect of smoking on the live birth rate per embryo transfer was not as strong as among women in the other diagnostic categories. The difference in influence of smoking on the outcome of pregnancy per indication category was not statistically significant (Breslow–Day test for homogeneity of odds ratios, $P = 0.19$).

There is a clear association of an increased BMI, risk of complications during pregnancy and a higher chance of abortion and subfertility (Norman and Clark, 1998; Wang *et al.*, 2000, 2002). After multivariable logistic regression modelling, we also found a significant effect of overweight (BMI $\geq 27\,kg/m^2$) on the live birth rate per cycle, with an OR of 0.67 (95% CI 0.48–0.94).

Besides dependency on calendar period, prognostic models for IVF depend on the success rate of the treating hospital (Haan *et al.*, 1991a; Templeton *et al.*, 1996; Kremer *et al.*, 2002), patient characteristics and the number of previous IVF cycles (Tan *et al.*, 1996; Templeton *et al.*., 1996; De Mouzon *et al.*, 1998). Publications suggest constant success rates for each of the first three cycles (Haan *et al.*, 1991b; De Vries *et al.*, 1999). Some attribute this to active censoring, which leads to withdrawal of couples with poor prognosis (Land *et al.*, 1997). In our study, continuation of IVF treatment depended on indication, due to the differences in fertilization rate. Twenty-five per cent of the couples diagnosed with male subfertility did not complete three cycles and remained childless as compared with 13% of couples with unexplained subfertility and 5% of couples with tubal pathology. For reasons of comparability we therefore restricted our analyses in the present study to the first IVF treatment cycle only.

Our historical cohort study enables us to assess the differences in success rates of IVF between the various subfertility causes. However, to study the efficacy of IVF in various diagnostic categories, a long-term clinical trial will be the best option, comparing the pregnancy rates of IVF or ICSI treatments with no treatment. A second-best option is the comparison of the spontaneous pregnancy rate in subfertile couples on the waiting list for IVF or ICSI, with the results of IVF- or ICSI-treated couples. We are expecting results from such a study in The Netherlands in the near future.

In conclusion, we observed differences in success rate between subfertility causes in favour of unexplained subfertility. Smoking had an unfavourable effect on the outcome of IVF and was comparable with an increase in female age of >10 years from age 20 to 30 years. Overweight had a strong harmful effect on the live birth rate after IVF. The effect of smoking and overweight was largest among women with unexplained subfertility. These results suggest that women, and in particular those with unexplained subfertility, may be able to improve the outcome of subfertility treatment by quitting smoking and losing weight.

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