

Smoking and female infertility: a systematic review and meta-analysis

C.Augood¹, K.Duckitt¹ and A.A.Templeton²

¹Clinical Guidelines, Royal College of Obstetricians and Gynaecologists, 27 Sussex Place, Regent's Park, London NW1 4RG, and ²Department of Obstetrics and Gynaecology, Aberdeen Maternity Hospital, Foresterhill, Aberdeen AB25 2ZN, UK

³To whom correspondence should be addressed

The high prevalence of smoking among women in their reproductive years continues to be a matter of concern. The negative effects of smoking on general health are well known, but smoking may also affect fertility. The objective of the present study was to perform a systematic review of the literature to determine whether there is an association between smoking and risk of infertility in women of reproductive age, and to assess the size of this effect. In the 12 studies used for this meta-analysis, the overall value of the odds ratio (OR) for risk of infertility in women smokers versus non-smokers was 1.60 [95% confidence interval (CI) 1.34–1.91]. Studies of subfertile women undergoing in-vitro fertilization (IVF) treatment also show a reduction in fecundity among women smokers. A meta-analysis of nine studies found an OR of 0.66 (95% CI 0.49–0.88) for pregnancies per number of IVF-treated cycles in smokers versus non-smokers. Despite the potential limitations of meta-analyses of observational studies, the evidence presented in this review is compelling because of the consistency of effect across different study designs, sample size and types of outcome. However, continued reassurance is needed that the calculated overall effect is not in fact due to confounding variables.

Key words: infertility/in-vitro fertilization/meta-analysis/smoking/systematic review

Introduction

The high prevalence of smoking among women in their reproductive years continues to be a matter of concern. Whilst in the UK smoking in adult females is in gradual decline, there is a worrying increase in the smoking prevalence among 11- to 15-year-old girls (Department of Health, 1996). Latest figures indicate that, at the age of 15, 33% of girls are regular smokers (Jowell, 1997). The negative effects of cigarette smoking on general health are well known, but smoking may also affect fertility.

Classical reviews of the literature (Weisberg, 1985; Stillman *et al.*, 1986; Fredricsson and Gilljam, 1992) have found a number of epidemiological studies addressing the effects of

female cigarette smoking on fecundity. Most suggest impaired fecundity in smokers, but controversial results have also been published. Hughes and Brennan (1996) conducted a systematic review of published studies and found a total of 13 studies suggesting consistently an association between impaired natural fecundity and female smoking.

The objective of the present study was to perform a systematic review of the literature to determine whether there is an association between cigarette smoking and risk of infertility in women of reproductive age, and to assess the size of this effect.

To assess the size of the association between smoking and infertility, the method of meta-analysis was used, in which results from individual studies become units of observation, evaluation and synthesis. Although there are potential limitations of meta-analyses of observational studies, some areas of health policy will never have evidence from randomized controlled trials. Smoking exposure and its effect on the fertility of women of reproductive age is one such example.

Materials and methods

The Medline and Embase databases from 1966 and 1974, respectively, to August 1997 were searched to identify papers on the association between cigarette smoking and female infertility. Due to the nature of the research objective, it was not expected that any randomized controlled trials would be found, but only observational studies (cohort and case-control). The search was limited to studies in which the type of exposure was active cigarette smoking by women of reproductive age. Studies in which the exposure was passive smoking, or studies in which the exposure of women to tobacco smoke had occurred before their reproductive age, were excluded. The reported end points varied among the studies. In this review the outcome measures used were either pregnancy rate, conception rate, time to pregnancy or conception delay of one year or more.

Initially, publications were selected from their title and abstract. The fields containing authors' names, institution where the study was carried out and title of paper and of journal were then removed before printing the results of the searches. Only the Medline identification number, abstract and language of article were kept. The abstracts were read in random order, chosen according to a table of random numbers. Ideally, the decision to include a paper would be made by looking only at its methods and not at its results, but this was not practically possible. Letters and classical review articles were kept as a useful source of references. The papers selected were then identified using the Medline identification number. Due to the higher cost of searching on Embase, this database was searched after scanning the results from Medline and publications were selected from their title. Bibliographies of relevant studies were handsearched.

Case-control and cohort studies were selected if sufficient data were included to construct 2×2 contingency tables for smoking

exposure and fertility status. The definition of smokers used in this analysis was those currently smoking only cigarettes. The preferred definition of non-smokers was those who had never smoked. However, data were not always presented in this way. Studies have shown that the fertility of ex-smokers resembles that of non-smokers, rather than that of current smokers (Baird and Wilcox, 1985; Howe *et al.*, 1985; Phipps *et al.*, 1987). Therefore, in the analysis, former smokers were considered together with non-smokers, rather than with current smokers.

The definition of infertility is a potential source of variation and confusion. It has an impact on research findings related to which and how many women are classified as infertile, the age at infertility classification, and the probability of future conception (Marchbanks *et al.*, 1989). For example, the prevalence of a history of infertility can range from 6.1% when a physician is making the diagnosis, to 32.6% when the diagnosis is made on unprotected intercourse for 12 months (Marchbanks *et al.*, 1989). For previous pill users, at least 15 months of unsuccessful trying might be a more appropriate working definition of infertility, rather than the 12 month interval generally accepted for this purpose (Linn *et al.*, 1982). The definition of infertility for the present review was that used in each individual study. In practice, the cut-off point is generally taken as 12 consecutive months of unprotected intercourse without conception. This clinical definition of infertility is insensitive to short-term effects (Baird *et al.*, 1986). Moreover, time-to-pregnancy data cannot be validated by medical records and it integrates effects of exposures to both parents and to the conceptus (Baird *et al.*, 1986). Time to pregnancy measures fecundability (the probability of pregnancy in each cycle). A further source of confusion is that parameters estimated from retrospectively collected data may reflect subfecundity (difficulty in achieving term birth) rather than infertility (difficulty in conceiving).

For practical reasons, the present review was based on published studies only. The main concern with unreported studies is that they may contain valid results that conflict with the evidence summarized in the meta-analysis. This is of particular concern when attempting a meta-analysis of observational studies since there is a greater tendency towards publication bias with these types of studies than there is with randomized clinical trials (Easterbrook *et al.*, 1991). However, it can be argued that because the peer review process is an important means of ensuring quality, only published data and papers should be used, as 'the investigator has indicated a willingness to stand behind them in public' (Chalmers *et al.*, 1987).

The odds ratio (OR) (95% CI) for each study and across studies was calculated using the random effects model with the Metaview statistical package (MetaView 3.01, Update Software, Oxford, UK).

Results

Twelve studies matched the inclusion criteria and were selected (Baird and Wilcox, 1985; Cramer *et al.*, 1985; Daling *et al.*, 1985; de Mouzon *et al.*, 1988; Suonio *et al.*, 1990; Laurent *et al.*, 1992; Joesoef *et al.*, 1993; Tzonou *et al.*, 1993; Joffe and Li, 1994b; Alderete *et al.*, 1995; Bolumar *et al.*, 1996; Spinelli *et al.*, 1997). Twelve other studies were excluded, nine of which could not be used because data were not presented in a way that allowed the construction of 2×2 contingency tables (Linn *et al.*, 1982; Olsen *et al.*, 1983; Harlap and Baras, 1984; Howe *et al.*, 1985; Hartz *et al.*, 1987; Phipps *et al.*, 1987; Ghazi *et al.*, 1991; Olsen, 1991; Curtis *et al.*, 1997). The study by Curtis *et al.* (1997) also had a reproductive end-point 'time to pregnancy' less than or over 6 months. Two studies (Joffe and Li, 1994a,b) presented data

from the same cohort and only the study with the most complete data was kept, and one (Li *et al.*, 1990) had an imprecise definition of both participants and exposure. Finally, another study (Tokuhata, 1968) was not used as it included childless women rather than infertile women. A brief description of these studies is presented in Tables I and II.

The tests for statistical heterogeneity were significant, especially for the case-control studies. For this reason, the random effects model in estimating overall OR was used. The OR (95% CI) of infertility in smoking relative to non-smoking women across all studies was 1.60 (1.34–1.91) (Figure 1). In cohort studies the OR for conception delay over one year in smoking versus non-smoking women was 1.42 (1.27–1.58); in case-control studies the OR of infertility versus fertility in smokers relative to non-smokers was 2.27 (1.28–4.02). These results are strongly supportive of an association between active cigarette smoking and infertility. The narrow CI and the 95% confidence limits indicate that the summary OR is a precise estimate of the effect and that the results are unlikely to have arisen by chance. In keeping with the generally weaker design of case-control studies, it is not surprising to find that they give a stronger association between smoking and infertility. Most of the studies excluded from the meta-analysis support the above conclusion. Infertility rates are higher in smokers compared with non-smokers (Li *et al.*, 1990), fecundability rates are reduced (Curtis *et al.*, 1997), time to conception is increased (Linn *et al.*, 1982; Olsen *et al.*, 1983), or smoking had no effect on fertility (Harlap and Baras, 1984; data not shown). In some studies the effects on fertility were only seen for smoking more than 20 cigarettes per day (Howe *et al.*, 1985; Hartz *et al.*, 1987), though there was a trend for all levels of smoking (Howe *et al.*, 1985; Curtis *et al.*, 1997).

In the present meta-analysis, publication bias was assessed graphically. In the funnel graph (Figure 2) the OR are plotted against the number of women exposed to smoking on which these OR were based. As expected, the larger studies lie closer to the marked 'true' value shown by the vertical line. Figure 2 would suggest that studies, however small, showing a positive association were published while few studies, of any size, showing a negative association were published.

Discussion

The purpose of this study was to perform a systematic review of the literature relating to the relationship between smoking and risk of infertility in women of reproductive age, and to assess the size of this association. At present, there is no standard method for performing meta-analyses, and even less so for meta-analyses of observational studies.

There are a number of sources of clinical heterogeneity among the studies of the present review. The definition of infertility has an impact on research findings related to which and how many women are classified as infertile, the age at infertility classification, and the probability of future conception (Marchbanks *et al.*, 1989). In practice, the cut-off point is generally taken as 12 consecutive months of unprotected intercourse without conception. The present meta-analysis includes studies in which time to pregnancy

Table I. Studies included in the meta-analysis

Study	Participants	Exposure	Reported outcome (adjusted OR, 95% CI)	Calculated outcome ('crude' OR 95% CI, random effects model)
Cohort studies				
Baird and Wilcox, 1985	678 pregnant women, <2 years to conception	Smokers: ≥ 1 cigarette/day during at least the first month of TTP	Crude RR of taking >1 year to conceive in smokers versus non-smokers 3.4. Rate ratio of smokers compared with non-smokers 0.72 (0.59,0.87); controlled for: BMI, parity, previous infertility, frequency of intercourse, OCP use, recent pregnancy or nursing, age, alcohol consumption	OR for TTP >12 months in smokers versus non-smokers 3.62 (1.58–8.26)
de Mouzon <i>et al.</i> , 1988	1887 couples followed-up prospectively until a pregnancy occurred, or 12 months. (Excluded couples with 'obvious signs of infertility' and those who had tried for over 6 months)	Smokers: smoked ≥ 1 cigarette/day at the beginning of the study	Relative fertility rates (OR) in women smokers versus non-smokers 0.86 (0.63–1.19); controlled for: smoking by husband, birth control method, previous deliveries, social class, trying to conceive before entering the study, reference year. NOT controlled for age.	OR for TTP >12 months in smokers versus non-smokers 3.62 (1.58–8.26)
Suonio <i>et al.</i> , 1990	2198 pregnant women (20th week)	Smoking before pregnancy: 0, 1–4 cigarettes/day (light smokers); >4 cigarettes/day	OR for TTP <6 months versus TTP between 6–12 months in non-smokers versus smokers 1.5 (1.3–1.8); controlled for: age, number of previous pregnancies, number of previous spontaneous abortions, number of previous legal abortions, alcohol consumption, occupation, working time, work strain, father smoking, father alcohol consumption	OR for TTP >12 months in smokers versus non-smokers 1.69 (1.29–2.20)
Laurent <i>et al.</i> , 1992	483 women with primary infertility (24 consecutive months of unprotected intercourse without conception)	Smokers: began smoking before or during the period of unprotected intercourse	OR for primary infertility 1.02 (1.01, 1.03) for every cigarette smoked. OR for primary infertility for smokers of 1–10 cigarettes/day versus non-smokers 1.17 (1.09, 1.28) OR for primary infertility in smokers of 20 cigarettes/day versus non-smokers 1.36 (1.14, 1.61)	OR for primary infertility (24 months without conception) in smokers versus non-smokers 1.37 (1.13–1.67)
Joffe and Li, 1994b	33-year-old women: data on TTP for 3132 first pregnancies	Smoking habit during the 12 months before conception	Risks for smoking before conception shown in relation to miscarriage, low birthweight, preterm labour	OR for TTP >12 months in smokers versus non-smokers 1.24 (1.05, 1.46)
Alderete <i>et al.</i> , 1995	1341 primigravidae	Smokers: ≥ 1 cigarette/day after discontinuation of contraception Light: 1–9 cigarettes/day Moderate: 10–19 cigarettes/day Heavy: ≥ 20 cigarettes/day Non-smokers: never smoked (Past smokers excluded)	Crude OR for time to conception >12 months versus ≤ 12 months for smokers, non-coffee drinkers versus non-smokers, non-coffee drinkers 0.7 (0.3–1.9) Adjusted OR presented for TTP >12 months versus ≤ 12 months relative to non-coffee drinkers non-smokers in smokers of 1–9, 10–19, ≥ 20 cigarettes/day; coffee drinkers (of 1–3 and >3 cups/day) and smokers (0, 1–9, 10–19, ≥ 20 cigarettes/day). OR adjusted for: age, race, education, marital status, income, BMI, tea, alcohol, husband smoking, OCP, abnormal reproductive conditions, immune and endocrine disorders, planned pregnancy	OR for TTP <12 months in (current) smokers versus never smokers 1.11 (0.76–1.62)
Bolumar <i>et al.</i> , 1996 (1)	Population sample of 6630 women aged 25–44; 3187 planned pregnancies	Smoking at TTP starting time: 0, 1–10, ≤ 11 cigarettes/day	OR of TTP >9.5 months versus ≤ 9.5 months for first pregnancy in smokers of 1–10 cigarettes/day versus non-smokers 1.4 (1.1–1.7). OR of TTP >9.5 months versus ≤ 9.5 months for first pregnancy in smokers of ≥ 11 cigarettes/day versus non-smokers 1.7 (1.3–2.1). OR adjusted for: education, age, coffee, OCP use, frequency of sexual intercourse	OR for TTP >9.5 months in smokers versus non-smokers 1.40 (1.17–1.67)
Bolumar <i>et al.</i> , 1996 (2)	Pregnancy sample of 4035 women (>20 weeks pregnant)	As above	OR of TTP >9.5 months versus ≤ 9.5 months for first pregnancy in smokers of 1–10 cigarettes/day versus non-smokers 1.4 (1.0–1.8). OR of TTP >9.5 months versus <9.5 months for first pregnancy in smoker of ≥ 11 cigarettes/day versus non-smokers 1.7 (1.3–2.3) > OR adjusted for: education, age, coffee, OCP use, frequency of sexual intercourse smokers	OR for TTP >9.5 months in smokers versus non-smokers 1.54 (1.32–1.80)
Spinelli <i>et al.</i> , 1997	Retrospective study of 622 women who delivered a child; planned pregnancy non-smokers	Mother smoking: yes/no	Rate ratio adjusted for 15 variables in mothers*, four variables in fathers** and one for the couple*** for TTP>12 months in mother smoking versus non-smoking 0.81 (0.67–0.98)	OR for TTP >12 months in smokers versus 1.54 (0.92–2.19)
Case-control studies				
Cramer <i>et al.</i> , 1985	1880 infertile couples (cases). 4023 women who delivered a liveborn child (matched controls)	Never smoking versus ever smoking	Risks presented for IUD use and primary tubal infertility; adjusted for: region, year of menarche, religion, education, smoking, number of sexual partners	OR of primary tubal infertility in ever smokers versus never smokers 1.10 (0.98–1.22)
Daling <i>et al.</i> , 1985	159 primary tubal infertility. Primary infertility: never conceived despite trying for ≥ 1 year. Tubal infertility: HSG or abnormality at surgery; 159 age-matched controls	Smoking: never, past, current	Risks presented for IUD use and primary tubal infertility; adjusted for: number of sexual partners, income, methods of contraception, education, occupation, religion, 'social' drug use, appendectomy, pelvic surgery, age at first intercourse, history of genital herpes or of gonorrhoea, use of douches	OR of primary tubal infertility in current smokers versus never and former smokers 3.25 (1.90–5.54)
Joesoef <i>et al.</i> , 1993	1818 women with primary infertility ('diagnosed by a physician'). 2817 primiparous controls with a planned pregnancy	Current smokers Past smokers: >100 cigarettes in lifetime in the past. Never smokers: ≤ 100 cigarettes in lifetime	RR of mean time to conceive in fertile controls current smokers versus never smokers 0.9 (0.8–1.0). OR of primary infertility for current smokers versus never-smokers 1.9 (1.5–2.3). RR and OR controlled for: alcohol, marijuana, cocaine, age, BMI, education, age at menarche, number of previous pregnancies, number of previous miscarriages, frequency of sexual intercourse	OR of primary infertility for current smokers versus never smokers 2.24 (1.89–2.64)
Tzonou <i>et al.</i> , 1993	84 women with secondary infertility (after ≥ 18 months) 168 pregnant women (matched controls)	Never smoking Past smoking Present smoking	RR for secondary infertility in ever smoked (past and present) versus never smoked 3.0 (1.3–6.8), $P = 0.01$ RR adjusted for: livebirths, miscarriage, induced abortion, ectopic pregnancy	OR of secondary infertility in present smokers versus past and never smokers 4.40 (2.13–9.07)

Rate ratios adjusted for: *working hours, shift work, use of visual display terminals, industrial occupation, noisy workplace, solvents, physical stress, lack of decision stress, demand stress, lack of support stress, coffee, tea, alcohol, age, parity; **industrial occupation, solvents, fumes, smoking; ***coital frequency.
BMI = body mass index; CI = confidence limits; HSG = hysterosalpingography; IUD = intrauterine devices; OCP = oral contraceptive; OR = odds ratio; PID = pelvic inflammatory disease; RR = relative ratio; TTP = time to pregnancy.

Table II. Studies excluded from the meta-analysis

Study	Participants	Exposure	Reported outcome (adjusted OR, 95% CI)
Tokuhata, 1968	Retrospective cohort of 2016 childless women who had died of cancer of the genitalia and breast	Smoking categories were: tobacco (any forms), cigarettes, snuff or chewing tobacco	OR for infertility in smokers versus non-smokers 1.46; adjusted for: cause, age, year of death, education, race, occupation, husband's tobacco use, education and occupation Information regarding voluntary childlessness or male infertility not available
Linn <i>et al.</i> , 1982	Retrospective cohort of 3214 ex-contraceptive users with a planned natural conception	Smoking during pregnancy Stopped before pregnancy Never smoked	OR for a time interval from cessation of contraception to conception >3 months for smoking during pregnancy versus never smoked before pregnancy was 1.0 (0.9–1.2) OR adjusted for: prior contraceptive use, age, DES use by patient's mother, spontaneous abortion, induced abortion, marijuana use in pregnancy, age at menarche, BMI, race, religion, prior PID, ectopic pregnancy, gravidity, education, income
Olsen <i>et al.</i> , 1983	1069 women treated for infertility of over 1 year. 4305 matched controls (fertile women)	Smoker/non-smoker in the year of hospital admission (for infertility treatment or for delivering a baby)	OR for controls with a conception delay of ≥ 1 year compared with controls with a conception delay <1 year: 1.8 (1.3–2.5) in smokers versus non-smokers for primary subfecundity 1.3 (1.0–1.8) in smokers versus non-smokers for secondary subfecundity OR adjusted for alcohol, contraception, age, residence, education, parity, male factor
Harlap and Baras, 1984	Retrospective study of contraceptive	Smoking exposure not described	Authors state that smoking had no effect on fertility (data not users who had planned their pregnancy shown). Relative fertility rates adjusted for method of contraception stopped: Never smoked 1.00 (reference group) 1–5 cigarettes/day 1.00 (0.90–1.11) 6–10 cigarettes/day 0.97 (0.88–1.07) 11–15 cigarettes/day 0.93 (0.84–1.04) 16–20 cigarettes/day 0.79 (0.70–0.89) ≥ 21 cigarettes/day 0.78 (0.62–0.97)
Howe <i>et al.</i> , 1985	Retrospective cohort of 4104 women who stopped contraception to become pregnant (total of 6199 periods at risk of becoming pregnant). Fertility assessed as time taken to give birth to a child	Smoking habits at the time of entering the study (rather than at the time of stopping contraception): Never smoked Ex-smoker Smoker 1–5 cigarettes/day, 6–10, 11–15, 16–20, ≥ 21	OR for heavy smokers compared with non-smokers 1.35 when adjusted for age, 1.33 when adjusted for obesity, 1.42 when adjusted for husband's education level
Hartz <i>et al.</i> , 1987	35 973 married women aged 30–59 in a weight-reduction programme who were nulliparous	Current smokers of 1–10 cigarettes/day, 11–20 cigarettes/day, >20 cigarettes/day (heavy smokers) Never smokers Former smokers excluded	RR for current smokers versus never smokers of primary diagnosis: - cervical factors 1.7 (1.0–2.7) - tubal disease 1.6 (1.1–2.2) - ovulatory factor 1.0 (0.8–1.4) - endometriosis 0.9 (0.6–1.3) RR adjusted for: centre, age at interview, time between interview and index date, education, number of sexual partners, religion, contraceptive use
Phipps <i>et al.</i> , 1987	901 women with infertility of different types. 1264 controls admitted for delivery of their first child	Smokers Non-smokers	RR also presented for former smokers versus never smokers, ever smokers versus never smokers and primary diagnoses of infertility Infertility rate in couples in which the wife smoked was 3.1 times higher than that in couples in which the wife neither smoked nor drank (14.9% versus 4.8%).
Li <i>et al.</i> , 1990	2578 infertile couples (had tried to conceive for ≥ 2 years). Infertility assessed by interview. Male factor not excluded	'Regular smokers' Non-smokers	OR of infertility ≥ 2 years in smokers versus non-smokers 1.2 (1.2–1.3), adjusted for age, parity. OR of infertility ≥ 5 years in smokers versus non-smokers 1.6 (1.5–1.7) OR of TTP ≥ 1 year in women who smoked and drank ≥ 8 cups coffee/day (or an equivalent amount of tea) 1.35 (1.02–1.48) Risk ratio of mother smoking versus non-smoking 0.89 (0.83–0.97); adjusted for mother's age, father's smoking; risk ratio <1 indicated an increase in TTP
Ghazi <i>et al.</i> , 1991	Retrospective case-control	Smoking at enrolment at pre-natal care centre: no smoking, <10 cigarettes/day, ≥ 10 cigarettes/day Smokers Non-smokers	Crude fecundability ratio for smokers versus non-smokers 0.83 (0.76–0.90). Fecundability ratio adjusted for husband's smoking, recent OCP use, age when beginning to try to conceive 0.90 (0.82–0.98)
Olsen, 1991	Survey of 10 866 women in last trimester of pregnancy	Smoking prior to conception: yes/no	
Joffe and Li, 1994a	Cohort of women aged 33; data on 3132 first pregnancies		
Curtis <i>et al.</i> , 1997	Retrospective cohort study of 1277 farm couples with 2607 planned pregnancies	Never smokers Former smoker (treated as non-smokers if they had quit smoking in year trying to conceive) Current smoker (number per day, number of years smoked)	

BMI = body mass index; DES = diethylstilboestrol; OCP = oral contraceptive; OR = odds ratio; RR = risk ratio; PID = pelvic inflammatory disease; TTP = time to pregnancy.

was over 12 months (Baird and Wilcox, 1985; de Mouzon *et al.*, 1988; Suonio *et al.*, 1990; Joffe and Li, 1994b; Alderete *et al.*, 1995; Spinelli *et al.*, 1997), or the cut-off point was 9.5 months (Bolumar *et al.*, 1996). More importantly, the potential for fertility of the women was not known in some studies (de Mouzon *et al.*, 1988) or was certainly present in others, defined by the women being either primiparous (Joffe and Li, 1994b), 20 weeks pregnant (Suonio *et al.*, 1990), 'pregnant' (Baird and Wilcox, 1985; Bolumar *et al.*, 1996), primigravidae (Alderete *et al.*, 1995), or 'mothers' (Spinelli *et al.*, 1997). In the case-control studies the cases are composed of women with primary infertility (Joesoef *et al.*, 1993), women with primary tubal infertility (Daling *et al.*, 1985), women in infertile couples (Cramer *et al.*, 1985) or women with secondary infertility (Tzonou *et al.*, 1993).

There are a number of sources of bias. The validity of self-reported smoking is often questioned but a meta-analysis of published studies comparing self-reported smoking status with biochemical validation suggested generally high levels of sensitivity and specificity for self-report (87% and 89%, respectively) (Patrick *et al.*, 1994). Moreover, the types of studies included here (observational) have lower rates of deception than intervention studies (Weissfeld *et al.*, 1989). In prospective studies, infertile couples seeking care may not be representative of all infertile couples regarding smoking habits. In retrospective studies some women in the delivery control group may have stopped smoking during pregnancy and therefore may be (mis)classified as non-smokers.

A potential source of bias is introduced by the selection of participants. Clinicians use the length of time that a

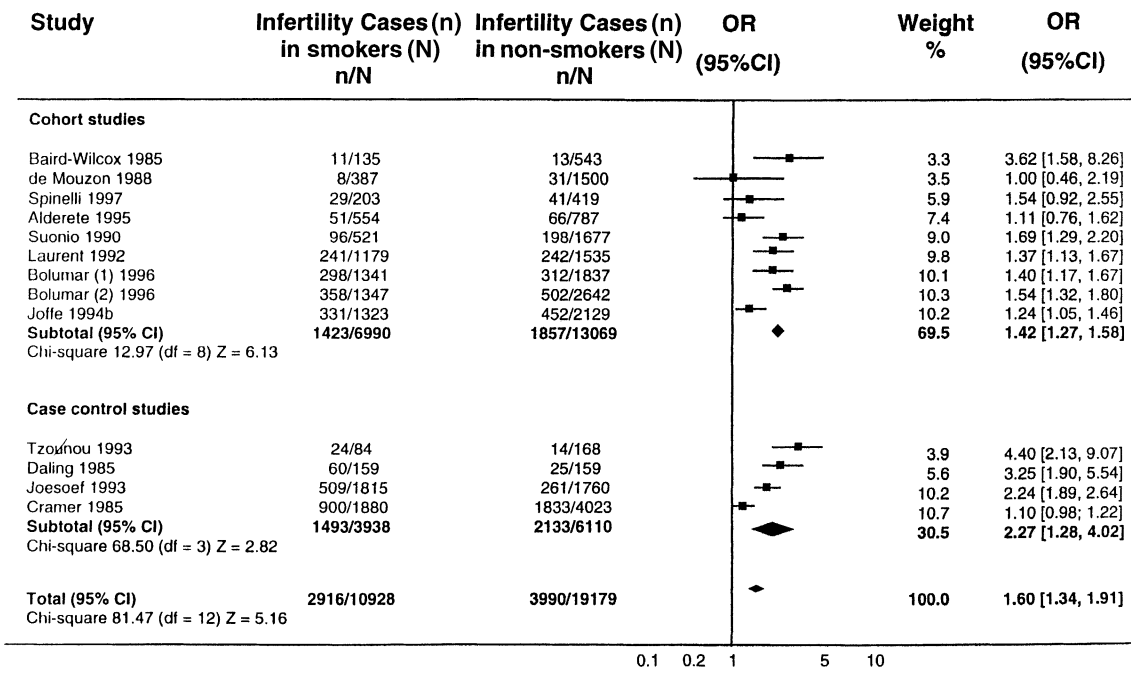


Figure 1. Meta-analysis of 12 studies of smoking exposure and female infertility. The odds ratio (OR) and 95% confidence interval (CI) for an effect of smoking on fertility are shown on a logarithmic scale.

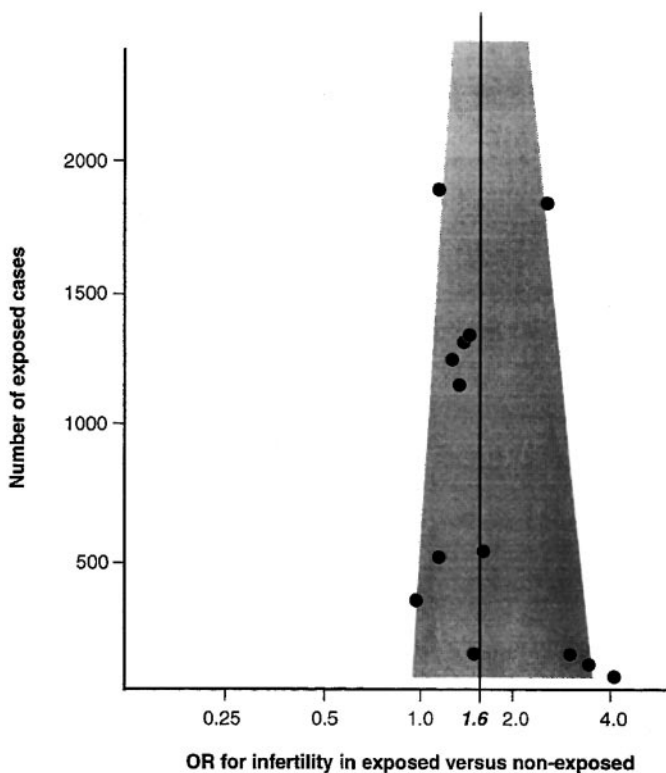


Figure 2. The ‘funnel plot’ to assess publication bias. Note the log scale on the x-axis; the vertical line at 1.6 and the shadowed area include most of the studies.

couple has been trying to conceive to identify those who might benefit from infertility services. Medical treatment, however, is not sought by all couples who are infertile. Less than one-half of the infertile couples seek medical help in some European countries (Olsen *et al.*, 1996). In a

study in the USA by Hirsch and Mosher (1987), though women with primary infertility represented only 30% of total infertile women, they were twice as likely to seek infertility services as women with secondary infertility (51% versus 22%). In the Danish health care setting, primary and secondary infertility was present in equal proportions but more women with primary infertility had sought treatment (Rachootin and Olsen, 1981). In a Scottish study (Templeton *et al.*, 1991), primary infertility was more frequently encountered than secondary infertility but the prevalences had remained the same over a decade. The study also indicated a significant increase over recent years in the uptake of medical services. Also, the demographic characteristics of women who seek infertility services differ significantly from those women who do not seek services (Hirsch and Mosher, 1987).

Another potential source of bias in the study design is the exclusion of unplanned pregnancies. Here the issue is not only of the reliability of information obtained on whether the pregnancies were planned, but also that women who did not plan their pregnancies may have different distributions of health-related behaviours compared with those who planned. For example, there is the possibility of overestimating the smoking-associated reduction in fertility if smokers use less effective birth control and therefore have more accidental pregnancies (Baird and Wilcox, 1985). The inclusion criterion that women took no longer than, say, 12 months to conceive may lead to an underestimate of the effect. If smoking causes extremely long delays in conception or total infertility in some women, the study would not detect that. In retrospective studies of pregnant women, infertile women are excluded completely. However, validity of recall of time to pregnancy is remarkably accurate, even

when the pregnancies in question had taken place a long time ago (Joffe and Li, 1994b).

Confounding factors may distort the association between smoking and infertility. There are still unanswered questions regarding the role of life-style factors, for example the timing and duration of exposures (lifetime or in the 12 months before attempting pregnancy) and the consistency of risk factors across subtypes of infertility (Buck *et al.*, 1997). Baird *et al.* (1986) identified over 25 potential confounders in infertility studies. Each of the studies found for the present review reported OR controlled for different confounding factors (e.g. age, alcohol or coffee consumption, education, care-seeking for treatment, working hours, parity, use of oral contraceptives, smoking habits of the male partner, frequency of sexual intercourse) and calculated using different statistical methods (Tables I and II). By recalculating the odds ratio of each individual study from the raw data, these potential confounders were not taken into account. Overall, however, 10 928 exposed women and 19 179 unexposed women were entered into these analyses, and in a study of this type 'it is difficult to imagine a single source of bias that would have influenced all the studies systematically' (Bracken, 1990).

Conclusions derived from meta-analyses depend on the acceptance of the validity of this procedure. The principal criticism is that studies and populations that are clearly different are being grouped together on the assumption that they are similar. Because of clinical heterogeneity between studies, for example, Hughes and Brennan (1996) did not attempt mathematically to combine data. Meta-analysis can result in adequate statistical power to detect meaningful differences, if they exist, and can lower the risk of missing true effects. The procedure, however, improves only the statistical power and does not correct for any biases in the individual studies. Also, meta-analyses do not consider the effects of confounding. The results of the present meta-analysis have to be interpreted within these limitations.

No attempt was made to weigh the studies according to quality criteria. At present, there is no universal system to evaluate the quality of any kind of study, although a large number of methods are in use. Moreover, in the present meta-analysis both case-control and cohort studies were used and the equivalence and combination of quality scores across different study designs can be determined (Spitzer, 1991) but was beyond the scope of this paper.

For all outcomes studied (primary infertility, tubal infertility, time to pregnancy over one year), there was a significantly increased risk of infertility in women who smoked. The association, however, may not be causal. In evaluating causation a number of questions have to be answered. The strength of association of smoking and increased infertility, although significant, is not overwhelming in most studies. The consistency of findings is good. The association of smoking to increased infertility is well supported, especially in relationship to primary tubal infertility.

A dose-response relationship between smoking and decreased fertility would provide further evidence for a

causal relationship. There were insufficient data available for such an analysis, but individual studies have shown this to be the case (Baird and Wilcox, 1985; Suonio *et al.*, 1990; Laurent *et al.*, 1992). In the recent study by Bolumar *et al.* (1996), a robust association between female smoking of more than half a pack of cigarettes per day and reduced fecundity was found. This association was seen in all samples from eight countries, regardless of sampling design and method of data collection. In the Oxford Family Planning Association study (Howe *et al.*, 1985), there was a return to normal fecundity in ex-smokers.

The specificity of the association is not great. The possibility that this association is related to the different life-style of smokers remains an important unresolved issue. At least part of smoking's apparent association to infertility may be its relationship to tubal disease (Olsen *et al.*, 1983).

The temporal sequence showing that exposure (to smoking) occurred before or during the time interval of interest improves the inferences that may be drawn from these data. In this meta-analysis there was only one prospective study (de Mouzon *et al.*, 1988), the rest had a retrospective design. In the case of women who were later classified as being infertile, selective recall may apply and they may be more likely to report exposures they believed to be related to infertility.

Biological plausibility of an effect of smoking on fecundity would further help the argument for causation. Reviews of experimental data on animals show this to be the case (Weathersbee, 1980). In humans, women who smoke have an earlier menopause than those who do not, usually by 1–1.5 years (MacMahon *et al.*, 1982; Baron *et al.*, 1990). Smoking could affect tubal or cervical function either directly or indirectly, and could be toxic to spermatozoa (Phipps *et al.*, 1987).

With these significant caveats in mind, if the conclusion of a causal relationship between cigarette smoking and infertility is accepted, the population-attributable risk percentage can be estimated. On the basis of the overall risk estimates for our meta-analysis of 1.60 and recent UK smoking rates of 25% (Department of Health, 1996), the population-attributable risk percentage for smoking and all types of infertility is 13%, i.e. up to 13% of female infertility cases would be due to smoking.

The present meta-analysis adds strength to previous studies suggesting that women attempting natural conception should be advised to stop smoking. Smoking is associated with a small increase in the risk of infertility. Stopping smoking returns the potential for fertility. Ex-smokers have a fecundability similar to that of never smokers, even when they quit within one year of starting trying to conceive (Curtis *et al.*, 1997). Studies of women undergoing in-vitro fertilization (IVF) treatment are contradictory with regards to fertilization rates or number of retrieved oocytes (Zenzes *et al.*, 1997), while the reduction in pregnancy rates among female smokers is not statistically significant in most cases. However, when two more studies (Van Voorhis *et al.*, 1992; Sterzik *et al.*, 1996) are added to the seven included in the meta-analysis by Hughes and Brennan (1996), the OR (95%

CI, random effect model) for pregnancies per number of IVF-treated cycles in smokers versus non-smokers is 0.66 (0.49–0.88). The deleterious effect of smoking becomes detectable in older women undergoing IVF treatment (Zenzes *et al.*, 1997). Even if the negative effect of smoking in natural or IVF-treated cycles is not as yet entirely convincing, there are well-known negative effects of smoking on an eventual pregnancy and on neonatal well-being. Smoking is associated with an increased risk of miscarriage (Hughes and Brennan, 1996), bacterial vaginosis which is associated with late miscarriage, preterm labour, and with delivery of low-birthweight infants (Llahi-Camp *et al.*, 1996), and increased risk of multiple pregnancy (Parazzini *et al.*, 1996).

The results of this meta-analysis point towards a significant association between smoking and infertility with a 60% increase in the risk of infertility among cigarette smokers. The overall value of the OR, at 1.60 (95% CI 1.34–1.91), is not impressive, given that it derives from studies of a weak methodological design. What is impressive, however, is the consistency of effects across study designs (cohort or case-control), sample size and types of outcomes (conception delay over one year, primary infertility, tubal infertility). The dose–response effect of smoking found in some of these studies and the variety of data supporting the biological credibility add strength to the possibility of a causal relationship between female smoking and increased risk of infertility. This association seems most clear for patients with tubal factor infertility.

There are two major questions that still need to be answered. Firstly, continued reassurance is needed that the calculated overall effect is not in fact due to one or more confounding variables, most importantly age. Secondly, due to the sensitive nature of the subject, there is a possibility that studies showing a negative association or no effect have not been published. Until such studies are performed (or published) the results of this study—consistent with those of previous reviews—indicate that, for the time being, infertility should remain on the list of diseases related to smoking and women attempting natural or assisted conception should be advised to stop smoking.

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