

SMOKING AND CONCEPTION



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In 1994 an article on smoking and conception was published in the magazine *Orgyn*. We have used this article as a source of patient information. The information contained within this article, which is attached, although now dated has been confirmed by numerous studies that have been carried out in the last 7 years.

Many studies have now confirmed that smoking is strongly associated with reduced conception rates both naturally and using artificial conception methods. One recent study (2000) showed that female smokers have their chances of success at IVF reduced by 44% compared to non-smokers. (If the expected conception rate of IVF is 25% then for smokers it will be 16.5%). The same study also showed a dose relationship between the number of cigarettes smoked per day and the reduction in conception rate (*Fertility and Sterility* Vol 74:725 October 2000).

However the **most disturbing new discovery** in recent years is the relationship between smoking and accelerated menopause among smokers. These studies have shown strong relationships between cigarette smoking and follicle (egg) density within the ovary. It has been established that there is **irreversible follicle depletion** perhaps due to the chemical constituents in cigarette smoke, which is responsible for the accelerated menopause in smokers. This finding has dire consequences as many women are now choosing to have children later in life, with a significant number having a first conception in their thirties. This coupled with accelerated depletion of follicles from the ovaries of smokers is a double risk for this group as follicle depletion is not treatable using current technology.

The message is clear. Stop smoking, and do it now.

"An increasingly large body of literature suggests that cigarette smoking, impairs natural fecundity in women. In addition, although the data relating smoking to outcomes of assisted reproductive technology are far less rigorous, they do suggest a significant impairment in concantion rate. Further large, well-designed studies are needed to more accurately assess this effect"

By DR EDWARD G HUGHES

HOW MANY PEOPLE BOARDING A PLANE WONDER WHETHER it has been adequately fuelled and serviced? Most people are concerned with safety when flying because crashes are frighteningly graphic. The trauma caused by cigarette smoking is much less evident but, in terms of human suffering, far more devastating. Approximately 340,000 Americans die annually as a direct result of cigarette smoking. This is the equivalent of about three 747 crashes per day.¹ In Canada, the equivalent of a Boeing 737 is lost every day. Despite these overwhelming statistics, smoking remains prevalent and is becoming relatively more common in young women. Already, smoking causes more deaths in women than breast cancer.

The association between smoking, various cancers and lung disease is understood even by those with only a limited interest in public or personal health. The effects of smoking on conception and pregnancy are less visible but, given the worrisome trend of increased smoking in young women, enormously important. The combination of the addictive substance nicotine with an alpha-emitting radioisotope polonium 210 and hundreds of other mutagens has made tobacco the foremost reproductive poison of the twentieth century. It has been estimated that the annual



burden of reproductive illness in North America alone from approximately 1,000,000 women smoking during pregnancy includes 100,000 fetal deaths, 4,000 infant deaths, 5,000 congenital malformations and 200,000 infants born with significant growth restriction.² Given the impact of these toxins on established pregnancy, it would be surprising if smoking did not in some way impair the ability to conceive.

EPIDEMIOLOGIC EVIDENCE

A large and fairly consistent body of epidemiologic evidence suggests that cigarette smoking among women stopping contraception in order to conceive reduces fecundity (Figure 1). This evidence has recently been reviewed in detail.³ The following criteria proposed by Sackett et al,⁴ may tell us more about the quality of evidence suggesting a causative association. These are listed in order of relative importance.

Is there evidence from true experiments in humans? Since it would be both unethical and impractical to expose women at random to cigarette smoke, clearly there can never be true experimental evidence of an effect on fecundity in the human.

Is the association strong? This question has two components: firstly, are the data valid or weak; and secondly, do they demonstrate a large or small effect? The best level of evidence possible is provided by prospective cohort studies. This design at least allows for the measurement of known prognostic factors and co-variables such as sexually transmitted diseases, previous pregnancy and caffeine use among smokers and non-smokers at the onset of observation. Also, it provides an opportunity for relatively accurate reporting of exposure. Retrospective studies are far more prone to incomplete and inaccurate data collection. Two prospective cohort studies have been published. The largest and most rigorous demonstrated a 22 per cent reduction of fecundity in women smoking more than 20 cigarettes per day.⁵ A dose-response effect was also shown, along with return to normal fecundity in ex-smokers. These data provide the most powerful evidence of a causal association. The only other prospective cohort study found no significant effect (odds ratio for conception 0.86, 95 per cent CI 0.63-1.19), but included only 45 per cent of eligible subjects in its analysis.⁶ Retrospective studies report odds ratios for conception of 0.33-1.0, suggesting at least a moderate effect.⁷⁻¹⁴

Is the association consistent from study to study? One of the prospective cohort studies reported no statistically significant effect.⁶ The eight other studies reporting relevant data suggested a consistent negative effect (Figure 1).

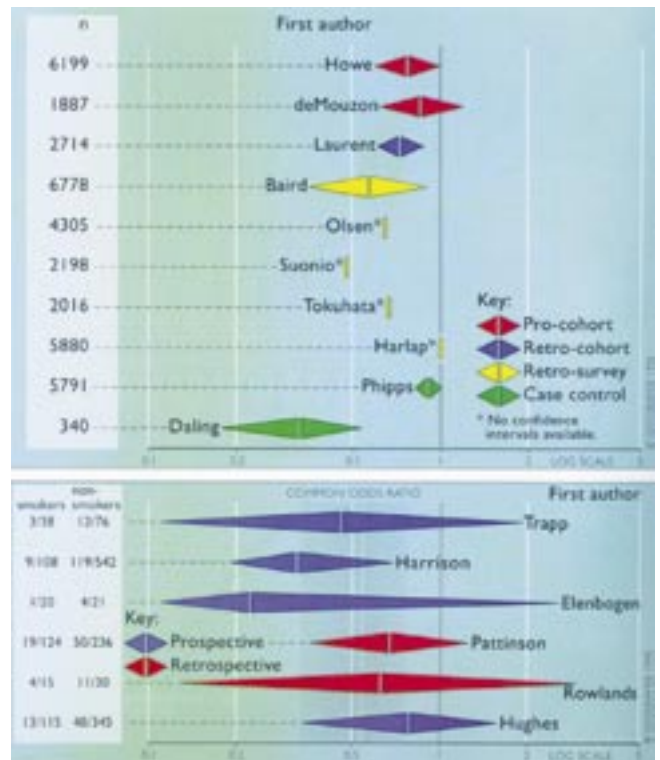



Figure 1 (top): The relative fecundity of smokers versus non-smokers expressed using odds ratios (Mantel-Haenszel method) with 95 per cent confidence limits. Where confidence limits cannot be calculated, a single point estimate has been made. Because of the clinical heterogeneity of these studies, data were not combined to give a common odds ratio.

Figure 2 (bottom): The likelihood of conception in smokers versus non-smokers undergoing IVF or GIFT. Data are presented from all published studies addressing this question as odds ratios (Mantel-Haenszel method) with 95 per cent confidence limits (Breslow-Day = 4.6; P = 0.466)

Is the temporal relationship correct? If outcome precedes exposure, clearly a causal association is impossible. In the two prospective studies,^{5,6} this question can be answered but it is more difficult to prove in those using a retrospective design.

Is there a dose-response effect? Whenever sufficient data were available for analysis, a dose-response effect was demonstrated. Does the association make epidemiological sense? This is difficult to answer because an apparent effect of increasing prevalence of smoking among young women may in fact be due to changing co-variables such as sexually transmitted disease and delayed childbearing.



Does the association make biological sense? Yes. Cigarette smoke has been shown to impair reproduction at various functional levels, including oocyte survival, sperm production, tubal motility, embryo cleavage, blastocyst formation and hatching, embryo development and implantation. Women who smoke have a higher rate of spontaneous abortion and an earlier menopause, by approximately two years, in “pack per day” smokers.

Is the association specific? A single effect of smoking on fecundity is unlikely, given the many potential pathways that exist. Is the association analogous to a previously proven causal association? Although the answer to this question is no, smoking during pregnancy has been proven to increase rates of abortion and growth restriction.

Cigarette smoke has been shown to impair reproduction at various functional levels

SMOKING AND INFERTILITY

These findings suggest that there is at least moderate evidence for causal association between smoking and reduced fecundity in women attempting spontaneous conception. We might then ask if these data can be extrapolated to the infertile population. The intuitive answer is yes, given that the same biological pathways should exist in both groups of women. However, the impact of cigarette smoking may be relatively small in the infertile population when compared with the effect of advancing female age, abnormal sperm quality, endometriosis and other factors known to impair fecundity.

Data on smoking in infertile populations comes largely from studies of IVF. Most of these have had insufficient power to assess small but clinically significant differences in conception rate.^{15,16} Also, their failure to consider important co-variates such as socio-economic status, male smoking, caffeine and alcohol consumption weakens conclusions. It is therefore hardly surprising that the existing literature on smoking and IVF is conflicting. Studies of less than 50 cycles have suggested a reduction in fertilization rates among smokers, resulting in a recent flurry of correspondence in *The Lancet*. Larger studies refute this finding.^{15,16} A retrospective study comparing IVF outcomes in 124 smokers with 236 non-smokers did demonstrate an increased spontaneous abortion rate (42 per cent versus 19 per cent), resulting in a reduced


live birth rate among smokers (9.6 per cent versus 17 per cent).¹⁵ Although the largest study of this question was prospective, IVF and GIFT cycles were combined, again without consideration of co-variates. This study did, however, demonstrate a significant reduction in conception rate from 22 per cent in non-smokers to eight per cent among smokers. Once again, an increased spontaneous abortion rate was seen in the latter group (55 per cent versus 20 per cent). Data from the author’s own centre demonstrate no statistically significant reduction in conception rate among smokers.¹⁶ Multi-variate analysis of as yet unpublished data suggests that female age is a far more powerful prognostic factor in this population.

Thus, the available data relating smoking and IVF are weakened by small sample size, retrospective study design and, in most cases, failure to consider co-variates. Any conclusions drawn from pooling of data must therefore be considered weak. Using the Mantel-Haenszel method, a common odds ratio 0.54 (95 per cent CI 0.386 - 0.717) (Figure 2) derived from the combined data may therefore be a significant overestimation of effect size. Larger well-designed studies are necessary to further test this question since the data include only 420 IVF or GIFT cycles among smokers, half of which were analyzed retrospectively.

The impact of male smoking on fecundity is even more uncertain. Previous studies of men undergoing subfertility investigation have demonstrated a reduction in semen volume among smokers but no effect on concentration, motility or morphology. The author’s own data suggest a reduction in sperm concentration among male smokers whose wives are undergoing IVF.¹⁶ Of studies examining 6,8 fecundity, two have shown no effect, while one study demonstrated a significant reduction in fecundity associated with male smoking (odds ratio 0.76, 95 per cent CI 0.71-0.83).¹⁰ This inconsistency suggests that the association is, at best, weak.

COLD TURKEY

The first challenge for caregivers is to understand the effects of smoking on general and reproductive health. The second challenge remains how best to help women with smoking cessation. Using data from the 1986 adult-use-of-tobacco survey, Fiore et al recently showed that more than 90 per cent of successful quitters did so on their own, twice as many as those who were successful following participation in group



programmes. Also, quitting “cold turkey” was more likely to succeed than gradually reducing the number of cigarettes or changing brand to a low-tar or nicotine product. Smokers of more than 25 cigarettes were more likely to use adjuncts such as nicotine patches. Last, and perhaps most importantly, those receiving advice from their physician were about twice as likely to succeed than those who did not. Thus, physicians have both potential and responsibility in helping women achieve the goal of smoking cessation. Physicians need to provide accurate information as well as a supportive environment which involves both partners. Educational information, both written and verbal, should be easily understandable and freely available in offices and clinics. In all of these ways, the active participation of physicians may significantly improve successful quitting among the 25 per cent of infertile and pregnant patients who currently smoke.

Finally, prevention remains the cornerstone of all public health issues. Taking the glamour out of smoking by forcing cigarette manufacturers to use generic packaging would no doubt reduce the appeal of cigarettes to adults and particularly children. Eliminating the sponsorship of glamorous sporting events would also reduce some of the positive exposure given to cigarettes. In Britain, where a voluntary agreement to control tobacco sponsorship of sport has been adopted, 64 per cent of children aged between nine and 15 still claim to see cigarette advertising on television. Snooker and motor racing are particularly important sources of this exposure. There is clear evidence that children smoke the brands most heavily promoted through sponsorship. The recognition of smoking as a major women’s issue may also help to hasten its control. Advertisers frequently misuse the “liberation message”, suggesting that cigarette smoking in some way enhances women’s equality. They fail to address the issues of women’s health. A recent study of 99 US magazines found that the probability of publishing information on the health risks of smoking was significantly reduced if the magazine also published advertisements for cigarettes. In other words, cigarette advertisement in magazines is associated with a reduction in coverage of its hazards, a finding particularly related to women’s magazines. Since much of the burden of illness resulting from smoking falls on women, this problem deserves the vigorous attention of women’s groups as well as health care providers.

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