

PREVENTION OF INFERTILITY SOURCE DOCUMENT

SMOKING AND INFERTILITY

Introduction

Approximately 30% of reproductive age women and 35% of reproductive age men in the United States smoke cigarettes, as do an increasing percentage of adolescent and teenage girls. This despite costly and long-standing national campaigns to limit their use. The percentage of cigarette use worldwide varies from culture to culture, but in many areas the percentage of reproductive age individuals who voluntarily, and then by habit - expose themselves to the recognized hazards of cigarette smoke is considerably higher than in the United States, and the campaigns against its use considerably less visible.

Given the high prevalence of smoking and the documented variety of deleterious health effects, C. Everette Koop, MD, the former U.S. Surgeon General had appropriately labeled smoking "the chief single avoidable cause of death in our society and the single most important health issue of our time." (1) Specifically addressing the adverse effects of smoking on reproductive health in the introduction to a *Seminars in Reproductive Medicine* issue devoted to a review of the this subject (2), Dr. Koop summarized the available data in stark terms:

"Women who smoke have decreased fertility.

The risk of spontaneous abortion is higher for pregnant women who smoke...

Babies born to smokers weigh, on average, 200 grams less than babies born to comparable women who do not smoke, with low birth weight being an important predictor of infant mortality"

In addition to smokers who inhale the bevy of toxic, carcinogenic and mutagenic substances known to be prevalent in cigarette smoke, many nonsmokers are regularly exposed by inhalation of 'sidestream' smoke from burning cigarettes and / or from 'passive' smoke exhaled by smokers. A recent study (3) documented cotinine, a major metabolite of nicotine, to be found in dose dependent concentrations relative to the number of cigarettes smoked in **100%** of the follicular fluids of infertility patients undergoing *in vitro* fertilization oocyte retrieval. One hundred percent (100%) of women known to be exposed to passive smoke in the home also had follicular fluid cotinine detected, albeit at lower concentrations. What was as alarming was that **84%** of women reporting themselves as non-smokers and with a non-smoking partner also had detectable levels of cotinine in their follicular fluids. These women were exposed environmentally, with all but one working outside the home. As the authors, who had previously reported the ovarian toxin heavy metal cadmium in the follicular fluid of smoking infertile patients (4), state regarding these women, "this constitutes an unsolicited hazard to their health and is an argument for smoke free public areas and workplaces"(3).

Given the wisdom of Dr. Koop's comments regarding smoking overall and reproductive health in particular and Dr. Zenzes' concerns regarding patients undergoing *in vitro* fertilization, what is it

that is known about the effects of cigarette smoking on female and male fertility?; what is the evidence for a causal relationship between smoking and infertility?; can practitioners provide this information to those already undergoing therapy for infertility (and thereby increase their likelihood of success in stopping smoking and subsequently conceiving)?; and, more importantly, how can this information serve health professionals and the public in the *prevention of infertility* in younger citizens currently smoking or those contemplating beginning?

The Association of Cigarette Smoking with Female Infertility and the Evidence for a Causal Relationship

A number of comprehensive reviews of the literature have been published (2,5,6,7) summarizing the cumulative data supporting an association between cigarette smoking and diminished female fecundity. The impact of cigarette smoking on early spontaneous abortion has been an important addition to these reviews on fertility, with the increase in pregnancy loss and ectopic pregnancies attributable to smoking adding to the overall adverse reproductive impact of this habit (2). It has led Joffe (8) to describe smoking as the foremost reproductive poison of the 20th Century - and, might we add, perhaps the 21st. In addition, evidence linking cigarette smoking to diminished fertility in the male has been reviewed (2, 9)

Additional publications have led to more recent systematic reviews. The first was by Hughes (10) reviewed evidence of cigarette smoking impairing natural *and* assisted fecundity; the second by Augood (11) performed a meta-analysis on the critically reviewed relevant literature available to date. Both have taken the compelling evidence linking cigarette smoking to impaired reproduction and reviewed how this evidence contributes to a case for causality. (It should be mentioned that the list of references found in these two articles (10,11) serve as a more complete compendium of the currently available literature on this subject than those listed following this document.)

Augood (11) carefully screened the literature available from Medline and Embase databases from 1966 through late 1997 and found twelve studies meeting the strict criteria for inclusion in their meta-analysis. The authors review each article in detail and in summary, including many excluded from the meta-analysis. They also review the inherent limitations and inherent strengths in the use of the meta-analysis itself. Their results include,

"The overall odds ratio (OR 95% CI) of infertility in smoking relative to non-smoking women across all studies in the meta-analysis was 1.60 (CI 1.34-1.91). In cohort studies the OR for conception delay over one year in smoking versus non-smoking women was 1.42 (CI 1.27-1.58), in case control studies the OR of infertility versus fertility in smokers relative to non-smokers was 2.27 (CI 1.28-4.02). *These results are strongly supportive of an association between active cigarette smoking and infertility* (italics mine). The narrow CI and the 95% confidence limits indicate the summary OR is a precise estimate of the effect and that the results are unlikely to have arisen by chance...Overall 10,928 exposed women and 19179 unexposed women were entered into these analyses...Most of the studies excluded from the meta-analysis also support the above conclusions: infertility rates are higher in smokers compared to nonsmokers, fecundability rates are reduced, time to conception is increased....In some studies the effects on fertility were only seen

for smoking more than 20 cigarettes per day, though there was a trend for all levels of smoking."

To make the case for causality between cigarette smoking and an adverse effect on female fertility, higher standards need be met than establishing even the statistically significant association reviewed by Augood's meta-analysis. This higher standard these same authors provide (11):

Strength: The strength of the association between smoking and increased infertility, although significant, is not overwhelming in most studies.

Consistency: The consistency of the association is very good throughout almost all studies.

Dose Response: A number of individual studies show a dose response effect. (12,13,14). In 1996 Bolumar (15) reported an important association between female cigarette use and diminished fecundity at even 1/2 pack use per day, an association they report consistent despite using different study groups from eight countries and using a variety of methods of data collection. A return to normal fecundity in ex-smokers was reported from the Oxford Family Planning Association study (16). This fact of reversibility, besides its importance in supporting a dose response relationship between smoking and infertility, is an important educational tool in the prevention of infertility in supporting current smokers to stop.

Specificity: The specificity of the association is not strong, and the possibility that confounding variables such as life-style choices remains unresolved, especially when reviewing cigarette smoking's relationship to tubal factor infertility and other life-style issues associated with both smoking and tubal infertility.

Temporal Sequence: Most studies are retrospective and therefore cannot prospectively evaluate individual fertility prior to and then after starting to smoke. The one prospective study following smokers and non-smokers until pregnancy could evaluate when the influence of smoking on fertility that was found took effect.

Biological Plausibility: Experimental data on animals support a biological plausibility of smoking's effect on the ovary, oocytes, and the reproductive tract (17). Chemicals in cigarette smoke increase the rate of follicular destruction and accelerate the loss of reproductive function (18) Smoking also affects meiotic maturation in oocytes resulting in abnormal diploid complement (19). Ovarian toxicity in humans is supported by finding of various known toxins in the ovary and or follicular fluid of smokers (2,3), and of the documented dose response effect on earlier age of menopause in women who smoke of up to 1 to 4 years (18,20,21,22). Smoking accelerates the development of diminished ovarian reserve as evidence by the Clomiphene Citrate Challenge Test and may be one reason for reduced fecundity in smokers since those smokers with normal ovarian reserve were found to have normal responses to ovarian stimulation (23,24). Cooper also found a diminished ovarian reserve based on markedly statistically significant higher mean basal FSH levels, particularly in younger women smokers. Smokers also required more gonadotropins for ovarian stimulation in *in vitro* fertilization cycles, had a higher number of canceled cycles, fewer oocytes retrieved in those cycles not canceled, more cycles with failed fertilization and a lower overall clinical pregnancy rate. This is one of several studies documenting diminished success in Assisted Reproduction among smokers compared to non-smokers. (10,25,26,27). Cooper found that basal FSH levels were 66% higher in active smokers compared to non-smokers and 39% higher in passive smokers than non-smokers (25).

Augood estimates that, if the conclusion for a causal relationship between cigarette smoking and female infertility is accepted, then the population-attributable risk percentage for smoking is 13%. In other terms, based on the meta-analysis risk estimate of 1.6 and smoking rate of 25% of the female reproductive age population (in Great Britain in 1996), ***up to 13% of female infertility is caused by cigarette smoking*** (11).

Summary

The available biologic, experimental and epidemiological data support a substantial increase in female infertility attributable to cigarette smoking. Stopping smoking in many women not already in earlier menopause and not permanently effected with tubal factor infertility returns the potential for fertility. Ex-smokers have fecundity similar to that of women who have never smoked, often when they quit even within a year of starting to try to conceive (28). The adverse effects of sidestream and passive smoking are notable and add to the urgency of addressing not only those who smoke in campaigns aimed at prevention of infertility, but those with whom they live and work or share the environment.

Those couples already suffering from infertility need to know that continuing to smoke adversely effects the success of therapy. In particular regarding Assisted Reproductive Technology (e.g. *in vitro* fertilization therapy), ovarian reserve, ovarian response to stimulation, the number of oocytes retrieved and fertilized, and the pregnancy rates are reduced in smokers compared to non-smokers (10,26,27). The Odds Ratio (95% CI, random effect model) calculated using Hughes meta-analysis (10) plus two more recent studies (26,27) for pregnancies per number of IVF treatment cycle in smokers versus non-smokers was 0.66 (0.49-0.88). The pregnancy rate in *in vitro* fertilization treatment cycles was thus reduced in smokers by 34%. (11). The deleterious effect of smoking becomes more detectable in older women undergoing therapy (29).

To add significant weight to the evidence in the literature, the most recently published study by Hull (31), using a large population-based sample of pregnant women, has concluded that smoking can significantly delay time to conception. This important study is the first large scale population based study to demonstrate that smoking negatively effects fertility, independently of other factors. Active smoking was associated with failure to conceive within 6 or 12 months with increase delay correlated to increase number of cigarettes smoked per day. **The percentage of women experiencing conception delay for over 12 months was 54% higher for smokers** compared to non-smokers. Exposure to passive smoke further increased the odds against a woman conceiving within 6 months. The investigators studied data from nearly 15,000 pregnancies. They determined time to conception, and in addition to smoking assessed factors such as parental age, ethnicity, education, employment, housing, the mother's Body Mass Index (BMI) and alcohol consumption. **Smoking by the mother, the father, or other exposure to tobacco smoke were all associated with a longer time to conception.** Active smoking by the man or the woman both had effects, and the impact of passive smoking was only slightly smaller than active smoking by either parent. While clearly, anyone interested in having children should not be smoking, even exposure to second hand smoke must be avoided. (31)

While smoking's adverse effects on female fertility and on infertility therapy have been reviewed, the well known negative effects of smoking on pregnancies and neonatal well being need also to be emphasized. Smoking is clearly associated with an increase in spontaneous miscarriage (10), with bacterial vaginosis (which is associated with late pregnancy miscarriage), with preterm labor (6,7), risk of multiple pregnancy (32) and with delivery of low birth weight infants at added risk of neonatal morbidity and mortality (30, 6). On top of the estimated 60% increase in female infertility, all of these adverse reproductive effects add substantially to the burden of adverse reproductive events on the prospective mothers, mothers and infants.

To the adverse effects of cigarette smoking on female fertility and pregnancy outcome must also be added the adverse effects of cigarette smoking by males on their own fertility (6,7,9,33), and on their partners through passive and sidestream smoke (4). Several studies over many years have evaluated the effect of smoking on semen parameters, especially density, motility and morphology. Summarized by Rosenberg (2), these studies collectively demonstrate a reduction in sperm density, motility and possibly morphology. The reduction in sperm count averaged 22%, and showed a dose response, with increased cigarette smoking correlating to a greater reduction in sperm count. What is more difficult to discern than an adverse effect on semen parameters, however, is the effect of smoking on male fertility. Few studies have or can address this adequately, especially since their partner's smoking habits and their partner's fertility confound the data collected. The difficulty is compounded by the fact that while the sperm counts, motility and or morphology are often reduced compared to non-smokers, they often remain within the normal range. The actual fertilizing capacity of the sperm, perhaps a better measure of fertilizing potential than count, motility and morphology, is quite difficult to assess and has not been addressed. These limitations aside, given the effect of passive and side-stream smoking on their partners, and the potential adverse effect on male fertility based on semen parameters and the myriad of known detrimental general health effects, boys and men must be strongly encouraged not to smoke. This is particularly true if they are part of a couple having difficulty conceiving or maintaining pregnancy, and especially if they have marginal semen parameters on semen analysis (2, 9).

Taken in toto, the adverse effects on female and male fertility and pregnancy outcome add to our burden and responsibility to provide the source documents, information and initiative to the public and to health care providers regarding these risks. If this imperative to educate needs more emphasis, it can come from an abstract presented in Toronto at the 1999 Annual Meeting of the American society of Reproductive Medicine by Roth et al (34). This abstract detailed the results of a questionnaire given to health professionals about knowing the risks associated or caused by cigarette smoking:

<u>SMOKING RISK</u>	<u>KNOWLEDGE OF RISK</u>
Lung Cancer	> 85%
Respiratory / Heart Disease	> 85%
Osteoporosis	30%

Miscarriage	39%
Early Menopause	17%
Ectopic Pregnancy	30%
Infertility	27%

Again, the most sobering part of this data is that this lack of knowledge about infertility, miscarriage, ectopic pregnancy and early menopause comes from *health care providers*, not the lay public. Clearly there is a need for education both of health care professionals at all levels and the public about the reproductive health risks caused by cigarette smoking. This information may help those seeking to conceive and carry a healthy full-term infant to do so by imploring them to stop, especially those already having difficulty conceiving or maintaining a pregnancy. And for those not currently seeking to conceive but with wishes and dreams for the future, if they are in need of yet one more health risk to add to the panoply of reasons to discontinue their habit or never start, this information and data may be most useful in the **prevention of infertility**.

Respectfully submitted to the Prevention of Infertility Committee by:
Robert J. Stillman, MD

References

1. U.S. Department of Health and Human Services: The health consequences of smoking: a report of the Surgeon General. Washington, D.C., U.S. Government Printing Office, 1984
2. Seminars in Reproductive Endocrinology: Smoking and Reproductive Health: Robert J. Stillman, M.D. Editor, Thieme Medical Publishers, Inc., New York, November 1989
3. Maria Teresa Zenzes, Ph.D., T. Edward Reed, Ph.D., Peng Wang, M.D., Julia Klein, M.Sc., Continine, a major metabolite of nicotine, is detectable in follicular fluids of passive smokers in in vitro fertilization therapy. *Fertil. Steril.*, 1996; 66:614-9
4. Zenzes MT, Krishnan S., Krishnan B., Zhang H., Casper R.F., Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. *Fertil. Steril.* 1995; 64, 599-603
5. Weisberg, E. Smoking and reproductive health. *Clin. Reprod. Fertil.*, 1985; 3, 175-186
6. Stillman, R.J., Rosenberg, M.J. and Sachs, B.P. Smoking and reproduction. *Fertil. Steril.*, 1986; 46, 545-566
7. Fredricsson, B. and Gilljam, H. Smoking and reproduction. Short and long term effects and benefits of smoking cessation. *Acta Obstet Gynecol. Scand.*, 1992; 71, 580-592
8. Joffe M., Zhimin L. Male and female factors in fertility. *Am. J. Epidemiol.* 1995; 140, 921-9
9. Vine M.F., Smoking and male reproduction: a review. *Int. J. Androl.* 1996 Dec/, 19(6):323-37
10. Edward Hughes, M.B., Ch.B., Barbara G. Brennan, M.D., Ph.D. Does cigarette smoking impair natural or assisted fecundity? *Fertil. Steril.* 1996; 66, 679-89
11. C. Augood, K. Duckitt, A.A. Templeton Smoking and female infertility: a systematic review and meta-analysis. *Hum. Reprod.* 1998; 13, 1532-1539
12. Baird, D.D. and Wilcox, A.J. Cigarette smoking associated with delayed conception. *J. Am. Med. Assoc.*, 1985; 253, 2979-2983
13. Suomo, S., Saarikoski, S., Kauhanen, O. et al. Smoking does affect fecundity. *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1990; 34, 89-95
14. Laurent, S.L., Thompson, S.J., Addy, C. et al. An epidemiologic study of smoking and primary infertility in women. *Fertil. Steril.*, 1992; 57, 565-572
15. Bolumar, F., Olsen, J. and Boldsen, J. Smoking reduces fecundity: a European multicenter study on infertility and subfecundity. The European Study Group on Infertility and Subfecundity. *Am. J. Epidemiol.*, 1996; 143, 578-587
16. Howe, G., Westhoff, C., Vessey, M. and Yeates, D. Effects of age, cigarette smoking and other factors on fertility: findings in a large prospective study. *Br. Med. J.*, 1985; 290, 1697-1700
17. Weathersbee, P.S. Nicotine and its influence on the female reproductive system. *J. Reprod. Med.*, 1980; 25, 243-250
18. The Effect of Smoking on Oogenesis, Fertilization, and Implantation. Donald R. Mattison, M.D., David R. Plowchalk, B.S., M. Jane Meadows, Ph.D., Michael M. Miller, M.D., Antoine Malek, Ph.D., and Steve London, M.D. Seminars in Reproductive

- Endocrinology, Smoking and Reproductive Health, Robert J. Stillman, M.D., Editor. Thieme Medical Publishers, Inc. November 1989, Volume 7, Number 4, page 291
19. Racowsky, C., Hendricks, R.C., Baldwin, K.V. Direct effects of nicotine on the meiotic maturation of hamster oocytes. *Reprod. Toxicol.* 1989; 3, 13-21
 20. MacMahon, B., Trichopoulos, D., Cole, P. Cigarette smoking and urinary estrogens. *N. Engl. J. Med.* 1982; 307, 1062-5
 21. Baron, J.A., LaVecchia, C. and Levi, F. The antioestrogenic effect of cigarette smoking in women. *Am. J. Obstet. Gynecol.* 1990; 162, 502-514
 22. Adeno, M., Gallagher, H. Cigarette smoking and the age of menopause. *Ann. Hum. Biol.* 1982; 9, 121-30
 23. Fady I. Sharara, M.D., Scott N. Beatse, M.D., Michael R. Leonardi, M.D., Daniel Navot, M.D., Richard T. Scott, Jr., M.D. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test. *Fertil. Steril.* 1994; 62, 257-62
 24. A. El-Nemr, T. Al-Shawaf, L. Sabatini, C. Wilson, A.M. Lower and J.G. Grudzinskas Effect of smoking on ovarian reserve and ovarian stimulation in in vitro fertilization and embryo transfer. *Hum. Reprod.* 1998; 13, 2192-2198
 25. Cooper, G.S., Baird, D.D., Hulka, B.S., Weinberg, C.R., Savitz, D.A., Hughes, C.L. Follicle-stimulating hormone concentrations in relation to active and passive smoking. *Obstet. Gynecol.* 1995; 85, 407-11
 26. Van Voorhis, B.J., Syrop, C.H., Hammitt, D.G. et al. Effects of smoking on ovulation induction for assisted reproductive techniques. *Fertil. Steril.* 1992; 58, 981-985
 27. Sterzik, K., Strehler, E., De Santo, M. et al. Influence of smoking on fertility in women attending an in vitro fertilization program. *Fertil. Steril.*, 1996; 65, 810-814
 28. Curtis, K.M., Savitz, D.A. and Arbuckle, T.E. Effects of cigarette smoking, caffeine consumption and alcohol intake on fecundability. *Am. J. Epidemiol.*, 1997; 146, 32-41
 29. Zenzes, M.T., Reed, T.E., and Casper, R.F. Effects of cigarette smoking and age on the maturation of human oocytes. *Hum. Reprod.* 1997; 12, 1736-1741
 30. Llahi-Camp, J.M., Rai, R., Ison, C. et al. Association of bacterial vaginosis with a history of second trimester miscarriage. *Hum. Reprod.* 1996; 11, 1575-1578
 31. Hull, M., North K., Taylor, H., Farrow, A., Ford, W.C., et al., Delayed conception and active and passive smoking. *Fertil Steril* 2000; 74, 724 - 732.
 32. Parazzini, F., Chatenoud, L., Benzi, G. et al. Coffee and alcohol intake, smoking and risk of multiple pregnancy. *Hum. Reprod.* 1996; 11, 2306-2309
 33. K.A. Joesbury, W.R. Edirisinghe, M.R. Phillips, and J.L. Yovich Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. *Hum. Reprod.* 1998; 15, 1506-1513
 34. Roth, L., Taylor, H.S., Yale University School of Medicine, New Haven, CT., USA. Smoking Risks to Reproductive Health: Assessment of Women's Knowledge. P 235 Conjoint Annual Meeting of the American Society for Reproductive Medicine and the Canadian Fertility and Andrology Society. September 25-30, 1999 Toronto, Ontario, Canada