Smoking and infertility

The Practice Committee of the American Society for Reproductive Medicine

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Approximately 30% of reproductive age women and 35% of reproductive age men in the United States smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent but are not generally appreciated. (Fertil Steril® 2008;90:S254–9. ©2008 by American Society for Reproductive Medicine.)

Approximately 30% of reproductive age women and 35% of reproductive age men in the United States smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent but are not generally appreciated. A survey of 388 female employees of a Connecticut hospital revealed that the major deleterious health effects of smoking are widely recognized. However, the majority of the women surveyed, including female health care providers, were unfamiliar with the reproductive risks associated with smoking (Table 1) (1).

This Educational Bulletin reviews the evidence linking cigarette smoking with reproductive hazards for both females and males. Health care providers who educate their patients about the risks of smoking will increase the likelihood that their patients can stop smoking (2, 3).

FEMALE REPRODUCTIVE CONSEQUENCES OF SMOKING

Conception Delay

Several comprehensive reviews have summarized the cumulative data on cigarette smoking and female fecundity and all support the conclusion that smoking has an adverse impact (4–9). However, because the available studies are largely observational and include diverse populations, there is considerable potential for bias from multiple sources (8, 9).

The most recent meta-analysis identified the pertinent literature available from Medline and Embase databases from 1966 through late 1997 and included 12 studies meeting strict inclusion criteria (9). Data from 10,928 exposed women and 19,179 unexposed women were entered into these analyses. The study yielded an overall odds ratio (OR) and 95% confidence interval (CI) for infertility in smoking compared to nonsmoking women across all studies designs of 1.60 (CI 1.34–1.91). In cohort studies, the OR for conception delay over one year in smoking versus nonsmoking women was 1.42 (CI 1.27–1.58), and in case control studies, the OR for infertility versus fertility in smokers compared to nonsmokers was 2.27 (CI 1.28–4.02). The narrow CI suggests that the summary OR is a reasonably accurate estimate of the effect and that the results are unlikely to have arisen by chance. Most of the studies excluded from the meta-analysis also support the findings that the prevalence of infertility is higher, fecundity is lower, and the time to conception is increased in smokers compared to nonsmokers. In some studies, the effects on fertility were only seen in women smoking more than 20 cigarettes per day, but a trend for all levels of smoking was identified.

Recently, the first large scale population based study to demonstrate that smoking negatively affects fecundity, independent of other factors, was published (10). The investigators studied data from nearly 15,000 pregnancies to determine time to conception. In addition to smoking, factors such as parental age, ethnicity, education, employment, housing, pre-pregnancy body mass index, and alcohol consumption were assessed for their possible confounding influences. Active smoking was associated with a failure to conceive within both 6- and 12-month durations of study. Increasing delay to conception correlated with increasing daily numbers of cigarettes smoked. The percentage of women experiencing conception delay for over 12 months was 54% higher for smokers than in nonsmokers. Active smoking by either partner had adverse effects, and the impact of passive cigarette smoke exposure alone was only slightly smaller than for active smoking by either partner (10).

Ovarian Follicular Depletion

Menopause occurs one to four years earlier in smoking women than in nonsmokers (11–13). The dose-dependent nature of the effect supports the contention that smoking may accelerate ovarian follicular depletion.

Chemicals in cigarette smoke appear to accelerate follicular depletion and the loss of reproductive function (11). Mean basal FSH levels are significantly higher in young smokers than in nonsmokers (14, 15). In one study, basal FSH levels were 66% higher in active smokers than in nonsmokers and 39% higher in passive smokers than in nonsmokers (15). Urinary estrogen excretion during the luteal phase in smokers is only about one third that observed in nonsmokers (16), possibly because constituents of tobacco smoke inhibit granulosa cell aromatase (17).

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TABLE 1

Public knowledge of the risks of smoking.

Smoking risk	Knowledge of risk
Lung cancer	99%
Respiratory disease	99%
Heart disease	96%
Miscarriage	39%
Osteoporosis	30%
Ectopic pregnancy	27%
Infertility	22%
Early menopause	17%

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Mean gonadotropin dose requirements for smokers receiving stimulation for in vitro fertilization (IVF) are higher when compared to those of nonsmoking women (16). The higher prevalence of abnormal clomiphene citrate challenge test (CCCT) results in smokers than in age-matched non-smokers provides further evidence that smoking has adverse effects on ovarian reserve (18). However, ovarian response to FSH stimulation and pregnancy rates are normal in smoking women having normal ovarian reserve test results. This observation implies that a smoking-related decrease in ovarian reserve may be only one explanation for decreased fecundity in smokers (18).

Assessment of Causality

Overall, the literature strongly supports an association between cigarette smoking and infertility. Two systematic reviews of the subject have analyzed the evidence to support a causal relationship (8, 9). Both concluded that causality cannot be excluded but would require more rigorous empiric evidence than is currently available to be established. The following briefly summarizes the criteria for causality and the status of existing information (8, 9):

Strength: The association between smoking and increased risk for infertility is statistically significant but not particularly strong in most studies.

Consistency: The association between smoking and decreased fertility is generally quite consistent across most studies.

Dose Response: A number of studies have demonstrated a dose-dependent adverse effect of smoking on fertility (19–21). Even at one-half pack use per day, female cigarette consumption has been consistently associated with decreased fecundity (22). An Oxford Family Planning Association study observed a return to normal fecundity in ex-smokers (23). The reversible nature of the effect supports a dose-dependent relationship between smoking and infertility and also provides an important educational and motivational tool that may help to convince current smokers to stop.

Specificity: The specificity of the association between smoking and infertility is not strong. The possibility remains that other confounding variables are involved, as suggested by the relationship between cigarette smoking and tubal factor infertility.

Temporal Sequence: Most studies that have examined the relationship between smoking and infertility have been retrospective and therefore unable to assess any exposure-to-effect sequence.

Biological Plausibility: Several lines of evidence provide biological plausibility for an adverse effect of smoking on the ovary, oocytes, and the reproductive tract (24). Various known toxins have been identified in the ovary and/or follicular fluid of smokers (4, 25). Smoking has been associated with short menstrual cycle length ($\leq$24 days) which could result in reduced fecundity (26). The evidence cited earlier suggesting accelerated follicular depletion and an earlier age of menopause further supports the biological plausibility of an adverse impact of smoking on fecundity (11–13).

If a causal relationship between cigarette smoking and female infertility is accepted, up to 13% of female infertility may be caused by smoking, based on the 1.6 OR from meta-analysis and assuming a 25% prevalence of smoking in women of reproductive age (9).

Mutagenic Potential

Gametogenesis appears to be vulnerable to damage from tobacco smoke (27). Both chromosomal and DNA damage to human germ cells may result from tobacco smoke exposure (28). The proportion of diploid oocytes in the ovary increases with the number of cigarettes smoked per day ($P<0.001$), an observation suggesting that smoking may disrupt function of the meiotic spindle in humans (28). Moreover, smoking in pregnant women is associated with an increased risk of trisomy 21 offspring resulting from maternal meiotic nondisjunction (29). The prevalence of Y chromosome disomy (two homologous Y chromosomes) in sperm correlates with urinary cotinine concentrations, a marker of recent exposure to cigarette smoke (30).

Evidence suggests that gene damage in sperm may relate to direct binding of tobacco smoke constituents or their intermediates to DNA (31, 32). When bound to DNA, some of these chemical "adducts" represent premutational lesions. Cigarette smoke contains toxic oxygen reactive species that help produce adducts and are mutagenic in their own right. Nuclear DNA damage and mitochondrial and cytoskeletal aberrations have been shown to result directly from oxidative stress in gametes, likely in part via adduct formation. These mechanisms are supported by the finding of increased chemical adducts in embryos from smokers compared to nonsmokers, indicating transmission of modified DNA originating from parental smoking (33).

Gamete DNA damage has the potential to underlie many of the recognized adverse reproductive effects of smoking such as increased miscarriages, accelerated onset of menopause, and reduced fecundity. Increases in birth defects have

variably been reported among the offspring of smoking parents, but the teratogenic effects of cigarette smoke during pregnancy confound whether DNA damage in gametes may play a role (33).

Early Pregnancy Effects

Smoking is associated with an increase in spontaneous miscarriage in both natural and assisted conception cycles (8, 34, 35). Five of seven heterogeneous studies (including the only prospective study) of natural conception in female smokers have found an increased miscarriage risk (9). In one study of inner-city women 14–39 years of age, smoking accounted for 16% of miscarriages (35). Mechanisms have not been completely elucidated. There are few data investigating chromosomal effects of smoking within abortus tissue, but the vasoconstrictive and antimetabolic properties of some components of cigarette smoke such as nicotine, carbon monoxide, and cyanide may lead to placental insufficiency and embryonic and fetal growth restriction and demise.

Smoking has also been associated with bacterial vaginosis (which in turn is associated with late pregnancy miscarriage) and with preterm labor (6, 7, 36). The risk of multiple gestation may also be increased in smokers (37, 38). Although it is difficult to control for involvement of other lifestyle factors, an association between ectopic pregnancy and smoking has also been reported (4, 39). A case-control study of inner-city African American women identified a dose-related risk for ectopic pregnancy among smokers (39). Women who smoked more than 20 cigarettes daily had an OR for ectopic pregnancy of 3.5 (95% CI 1.4–8.6) compared to nonsmokers. Pick-up of the oocyte cumulus complex and ciliary beat frequency were found to be inhibited in hamster oviduct subjected to cigarette smoke in a perfusion chamber (40). These abnormalities may contribute to increased incidences of ectopic pregnancy and tubal infertility in smoking women.

Effects of Maternal Smoking on Male Progeny

An epidemiologic study to identify the cause of decreasing sperm counts in Danish vs. Finnish men has suggested an effect of maternal smoking (41). After adjusting for confounding factors, men whose mothers had smoked more than 10 cigarettes per day had lower sperm densities than men with nonsmoking mothers. Paternal smoking was unrelated to semen parameters of the offspring. It is possible that these effects on male offspring could be mediated by cadmium or other contaminants of cigarette smoke. Together with a reduction in fecundity and early pregnancy effects, these effects on progeny may add substantially to the overall adverse reproductive burden from smoking.

Influence on Assisted Reproduction Outcomes

Ten retrospective and four prospective studies have been included in one or more of three meta-analyses that have examined the effects of smoking on the outcome of pregnancies achieved via IVF or gamete intrafallopian transfer (GIFT) (8, 9, 42). Most of these studies of assisted reproduction have low power and failed to adjust for confounders. Meta-analysis of nine of the studies identified an OR of 0.66 (95% CI 0.49–0.88) for conception among smokers undergoing IVF (9). Another meta-analysis of seven relevant studies in addition to the authors' own prospective data yielded an OR of 1.79 (95% CI 1.24–2.59) for the quotient of successful first IVF cycles for nonsmokers over smokers (42); the result suggested that smokers require nearly twice the number of IVF cycles to conceive as nonsmokers.

The specific reproductive processes antagonized by smoking cannot be precisely defined because reported outcomes have been heterogeneous. Yet studies of IVF and GIFT have variously reported an increased gonadotropin requirement for ovarian stimulation, lower peak E_2 levels, fewer oocytes retrieved, higher numbers of canceled cycles, lower implantation rates, and more cycles with failed fertilization in smokers compared to nonsmokers (8, 15, 38, 42–44). No study has specifically examined the effects of cigarette smoking on ovulation induction outcomes. The detrimental effect of smoking becomes more detectable in older women undergoing treatment (8, 18, 45, 46). The effects of smoking and advancing age may therefore synergize to accelerate the rate of oocyte depletion (27).

Possible mechanisms of compromised oocyte quality include the presence of toxins derived from tobacco smoke in follicular fluid. The follicular fluid concentrations of the heavy metal cadmium (47), a known ovarian toxin, are higher in smokers than in nonsmokers. Likewise, the concentrations of cotinine (a major metabolite of nicotine) in the follicular fluid aspirated from women at time of egg retrieval in IVF cycles relate directly to the number of cigarettes smoked (25). All women known to be exposed to passive smoke in the home also had detectable follicular fluid cotinine levels, albeit at lower concentrations. Also concerning was the finding that 84% of women who reported themselves as nonsmokers with nonsmoking partners had detectable levels of cotinine in their follicular fluids (47). These women were exposed environmentally, with all but one working outside the home. These data emphasize the potential hazards from passive tobacco smoke inhalation.

A more recent study not included in the meta-analyses also concluded that smoking has adverse effects on conception rates in assisted reproduction treatment (ART) cycles (38). Uniquely, this was a five-year prospective study that controlled for potential confounders to the effects of smoking and analyzed the quantity, frequency, and duration of smoking exposure among 221 couples. A dose-response effect for number of cigarettes smoked could not be demonstrated but was apparent for the duration of smoking. If a woman ever smoked during her lifetime, her risk of failing to conceive via ART more than doubled (relative risk = 2.5, 95% CI 1.38–4.55, $P<0.01$). Each year that a woman smoked was associated with a 9% increase in the risk of unsuccessful ART cycles (95% CI 1.02–1.15, $P<0.01$).

Overall, it appears that ART may not necessarily be able to overcome the reduction in natural fecundity associated with smoking.

MALE REPRODUCTIVE CONSEQUENCES OF SMOKING

The effects of smoking and passive smoke on various semen parameters have been evaluated (6, 8, 10, 37, 47, 48). Reductions in sperm density, motility, and a possible adverse effect on morphology have been demonstrated (4). The decrease in sperm concentration averaged 22% and was dose-dependent.

The effect of smoking on male fertility is more difficult to discern. The available data do not conclusively demonstrate that smoking decreases male fertility (6–8, 10, 46, 48). Few studies have or can address the question, because of the confounding effects of partner smoking habits and fecundity. Although sperm concentrations, motility, and/or morphology are often reduced compared to results observed in nonsmokers, they often remain within the normal range. Nevertheless, to the extent that the zona-free hamster egg penetration test reflects the ability of sperm to successfully fertilize a human oocyte, the available evidence suggests that smoking may have adverse effects on sperm function (49).

Although the effect of smoking on male fertility remains inconclusive, the potential consequences of passive and side-stream smoking on female partners and evidence of adverse effects of smoking on semen parameters suggest that smoking reasonably may be regarded as an infertility risk factor. Smoking should therefore be discouraged for both male and female partners in couples with a history of infertility or recurrent pregnancy loss, particularly when marginal or frankly abnormal semen parameters have been documented (4, 48).

SMOKING CESSATION

Unfortunately, even among pregnant women who may understand the risks of smoking, concerted efforts to help them quit smoking have been only modestly effective (2). Smoking cessation rates generally are better for infertile women than for pregnant women. The only study to examine the effectiveness of a specific method for smoking cessation in infertile women found that a relatively simple and inexpensive approach was reasonably effective, increasing the proportion of women who quit smoking from 4% at baseline to 24% after 12 months of intervention (3).

A recommended approach to smoking cessation for infertile women includes several minutes of counseling, education, and encouragement during each clinic visit, according to their individual stage of readiness to quit. Providing educational materials and website addresses alone is helpful but unlikely to achieve cessation without other methods of intervention (3). In general populations, various interventions including behavior modification, group counseling, feedback, advice, and nicotine weaning with patches and gum have proven effective. However, only 5% of women referred to a specialty smoking cessation clinic actually attended. Regularly scheduled office visits and use of multiple interventions are more effective, albeit resource-intensive. In infertile women, carbon monoxide (CO) monitoring using an inexpensive hand-held spirometer may also be of benefit. Results correlate well with the self-reported number of cigarettes smoked and offer feedback to patients. Serum and urine cotinine concentrations have also been used effectively for the same purpose (7, 50).

The Public Health Service and National Cancer Institute offer validated office-based intervention guidelines for smoking cessation that incorporate and extend the above-described recommendations (51, 52). A five-step approach is suggested: 1) Ask about smoking at every opportunity, 2) Advise all smokers to stop, 3) Assess willingness to stop, 4) Assist patients in stopping (including the use of pharmaceuticals and CO monitoring), 5) Arrange follow up visits (7, 49). Specific smoking cessation protocols for pregnant women have been outlined in several recent reviews (2, 50, 53). Other helpful resources for smoking cessation for health care providers and patients are available from various organizations (Centers for Disease Control, American Cancer Association) via their websites.

Although medical adjunctive therapy for smoking cessation has not been studied in infertile women, it may be justified for some. When behavioral approaches fail, the use of nicotine replacement therapy (NRT) and/or bupropion has resulted in a two-fold increase in the proportion of non-pregnant women able to quit smoking (50).

Available medical therapies include NRT in the form of gum and patches (both available over the counter) as well as nasal sprays and inhalers. Because the latter two have not been studied in pregnancy and are classified as category D agents (indicating adverse effects in animal models), NRT via nasal inhalers and sprays are best avoided in pregnant women and women attempting to conceive. Nicotine gum carries a category C classification and the nicotine patch is a category D agent, despite its reported safety in the limited clinical studies involving pregnant women that have been conducted to date.

The only non-nicotine FDA-approved smoking cessation agent is the aminoketone bupropion (Zyban). Bupropion is also available for use as an antidepressant (Wellbutrin), but is marketed differently (Zyban) for smoking cessation with a category B classification. The efficacy of bupropion appears similar to that of NRT strategies. Although studies of both bupropion and NRT in pregnant women have been limited, no adverse effects for pregnant women or their fetuses have been reported thus far. Ideally, however, pharmacological smoking cessation therapies are best used prior to conception.

When the likelihood of achieving smoking cessation is high and its benefits appear to outweigh the combined risks of smoking and NRT in pregnant or potentially pregnant women, NRT may be reasonable. The nicotine levels that

result from daily inhalation of 10 or more cigarettes are higher than those associated with recommended doses of nicotine gum and patches (50). Eliminating the exposure to the many other chemicals contained in cigarette smoke is one clear advantage of NRT (2). No studies have directly compared bupropion and NRT in infertile or pregnant women. However, given the relative safety and generally good compliance with prescribed bupropion treatment, it would appear to be an acceptable initial medical intervention, when needed.

On average, female smokers referred for evaluation and treatment of infertility have tried to quit smoking three times previously. Sadly, only 18% of such women have received advice on smoking cessation from their referring physicians (3). The likelihood of achieving smoking cessation appears to increase with each attempt (7, 53), and physicians who care for infertile women have another opportunity to help them quit smoking, beginning with their initial visit.

The substantial reproductive risks associated with smoking and the revelation that much of the reduced fecundity associated with smoking may be reversed within a year of cessation (3, 8, 23, 54) can be powerful incentives when included in physician counseling. When successful, smoking cessation represents an important part of effective treatment for infertility.

CONCLUSIONS

- The available biologic, experimental, and epidemiological data indicate that up to 13% of infertility may be attributable to cigarette smoking.
- Smoking appears to accelerate the loss of reproductive function and may advance the time of menopause by one to four years.
- Smoking is associated with increased risks of spontaneous abortion and ectopic pregnancy.
- Gamete mutagenesis is one possible mechanism whereby smoking may adversely affect fecundity and reproductive performance.
- Results of a meta-analysis examining the outcome of ART cycles indicate that smokers require nearly twice the number of IVF attempts to conceive as nonsmokers.
- Semen parameters and results of sperm function tests are generally poorer in smokers than in nonsmokers, but smoking has not yet conclusively been shown to reduce male fertility.
- The adverse effects of sidestream and passive smoking are now established, and nonsmokers with excessive exposure to tobacco smoke may have reproductive consequences as great as those observed in smokers.
- Clinicians can facilitate smoking cessation by providing education, monitoring, and consistent individualized support.
- The accumulated evidence supports the value of taking a preventive approach to infertility by discouraging smoking and helping to eliminate exposure to tobacco smoke in both women and men.

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