

Smoking and infertility: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

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Approximately 21% of women of reproductive age and 22% of men of reproductive age in the United States smoke cigarettes. Substantial harmful effects of cigarette smoke on fecundity and reproduction have become apparent but are not generally appreciated. This committee opinion reviews the potential deleterious effects of smoking on conception, ovarian follicular dynamics, sperm parameters, gamete mutations, early pregnancy, and assisted reproductive technology (ART) outcomes. It also reviews the current status of smoking cessation strategies. This document replaces the 2012 ASRM Practice Committee document of the same name (Fertil Steril 2012;98:1400–6). (Fertil Steril® 2018;110:611–8. ©2018 by American Society for Reproductive Medicine.)

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While the prevalence of smoking has declined over time, 17.8% of adults in the United States smoke cigarettes. Overall, the proportion of adult women who smoke is 15.3%; the proportion of women who smoke between 25 and 44 years of age is 20.7%. Smoking is more common among men in whom the prevalence is 20.5% overall and is 21.9% in the 25–44 age category (1). Smoking is an established modifiable risk factor for a number of serious complications in pregnancy and a public health challenge to maternal-fetal health (2). These complications include, but are not limited to: preterm delivery, intrauterine growth restriction, placental abruption, placenta previa, preterm premature rupture of membranes, and perinatal mortality. In addition to known risks during pregnancy, 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) (3).

This document 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 will stop smoking (4, 5).

ASSESSMENT OF CAUSALITY

Overall, the literature strongly supports an association between cigarette smoking and infertility. Two systematic reviews have analyzed the evidence to support such a relationship (6, 7). Both concluded that causality cannot be excluded but would require more rigorous empiric evidence. The following briefly summarizes the criteria for causality and the status of existing information (6, 7).

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 (8–10). Even at one-half pack per day use, female cigarette consumption has been associated consistently with decreased fecundity (11). An Oxford Family Planning Association study observed a return to normal fecundity in ex-smokers (12). 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.

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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

ASRM. *Smoking and infertility. Fertil Steril* 2018.

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 (13). Various known toxins have been identified in the ovary and/or follicular fluid of smokers (14, 15). Smoking has been associated with short menstrual cycle length (≤ 24 days), which could result in reduced fecundity (16). The evidence suggesting accelerated follicular depletion and an earlier age of menopause further supports the biological plausibility of an adverse impact of smoking on fecundity (17–19).

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 (6, 7, 14, 20–22). However, because the available studies are observational (given the nature of the research question) and include diverse populations, there is potential for bias from multiple sources (6, 7).

A 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 (7). 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 with nonsmoking women across all studies designs of 1.60 (CI 1.34–1.91). In cohort studies, the OR for conception delay over 1 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 with 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 with nonsmokers. In some studies, the effects on fertility were seen only in women smoking more than 20 cigarettes per day, but a trend for all levels of smoking was identified.

Since this meta-analysis was published, additional large-scale population-based studies have emerged supporting the negative association between smoking and fecundity, independent of other factors (23, 24). In the largest of these studies, investigators evaluated 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 increased 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 for 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 (23).

Ovarian Follicular Depletion

Menopause occurs 1–4 years earlier in smoking women than in nonsmokers (17–19, 25). 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 (17, 26–28). Mean basal follicle-stimulating hormone (FSH) levels are significantly higher in young smokers than in nonsmokers (29, 30). In one study, basal FSH levels were 66% higher in active smokers than in nonsmokers and 39% higher in passive smokers than in nonsmokers (30). Urinary estrogen excretion during the luteal phase in smokers is only about one third that observed in nonsmokers (31), possibly because constituents of tobacco smoke inhibit granulosa cell aromatase (32) and induce oxidative metabolism of estrogens (33). Significantly lower concentrations of antimüllerian hormone (AMH) have been described in association with current smoking in subjects pursuing in vitro fertilization (IVF) and in population-based studies (34–36). In a community sample of 284 women between 38 and 50 years of age, AMH levels were 44% lower in current smokers compared to never smokers; former smoking and passive smoking were not significantly associated with AMH (36). Longitudinal studies have described that AMH levels fall more rapidly in reproductively aging women who smoke. In one series, levels declined 21% faster per year in smokers compared with nonsmokers (37). Mean gonadotropin dose requirements for smokers receiving stimulation for IVF are higher when compared with those of nonsmoking women (29). The higher prevalence of abnormal clomiphene citrate challenge test (CCCT) results in smokers than in age-matched nonsmokers further provides evidence that smoking has adverse effects on ovarian reserve (38).

Effects on Sperm Parameters

The effect of smoking on male fertility is more difficult to discern. The effects of smoking and passive smoke on various semen parameters have been evaluated (6, 21, 39–41). Reductions in sperm density, motility, antioxidant activity, and a possible adverse effect on morphology have been demonstrated (14, 42). The decrease in sperm concentration averaged 22% and was dose-dependent. Use of smokeless tobacco also has a dose-dependent negative effect on multiple semen parameters (43). Although sperm concentration, motility, and/or morphology often are reduced compared with results observed in nonsmokers, they often remain within the normal range. However, available evidence suggests that smoking may have adverse effects on sperm binding to the zona pellucida based on a study involving the zona-free hamster egg penetration test (44). Available data on the effect of smoking on male fertility have been difficult to assess due to the confounding effect of the partner's smoking habits and fecundity (6, 21–23, 45).

Mutagenic Potential

Gametogenesis appears to be vulnerable to damage from tobacco smoke (46). Both chromosomal and DNA damage to human germ cells may result from tobacco smoke exposure (47). The proportion of diploid oocytes in the ovary increases with the number of cigarettes smoked per day ($P < .0003$), an observation suggesting that smoking may disrupt function of the meiotic spindle in humans (47). Moreover, smoking in pregnant women is associated with an increased risk of trisomy 21 offspring resulting from maternal meiotic nondisjunction (48). The prevalence of Y chromosome disomy (two homologous Y chromosomes) in sperm correlates with urinary cotinine concentrations, a major metabolite of nicotine and a marker of recent exposure to cigarette smoke (49).

Evidence suggests that gene damage in sperm may relate to direct binding of tobacco smoke constituents or their intermediates to DNA (50, 51). 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 additives in embryos from smokers compared with nonsmokers, indicating transmission of modified DNA originating from parental smoking (52).

Although it is plausible that gamete DNA damage may cause many of the recognized adverse reproductive effects of smoking such as increased miscarriages, accelerated onset of menopause, and reduced fecundity, the exact mechanism has yet to be determined. Increases in birth defects verifiably have 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 (50).

Early Pregnancy Effects

Smoking is associated with an increase in spontaneous miscarriage in both natural and assisted-conception cycles (6, 53, 54). Five of seven heterogeneous studies (including the only prospective study) of natural conception in female smokers have found an increased miscarriage risk (7). In one study of inner-city women 14–39 years of age, smoking, as assessed by presence of cotinine in the urine, was independently and significantly related to an increased risk of spontaneous abortion (OR 1.8, 95% CI 1.3–2.6) (54). 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. However, smokeless tobacco also is associated with increased risk of pregnancy loss (55, 56), suggesting that substances other than the combustible by products of tobacco may also cause pregnancy loss.

Although it is difficult to control for involvement of other lifestyle factors, an association between ectopic pregnancy and smoking also has been reported (14, 57). A case-control study showed an increased risk of ectopic pregnancy in women who smoked more than 20 cigarettes daily compared with nonsmokers (OR 3.5, 95% CI 1.4–8.6) (57). Pickup of the oocyte cumulus complex and ciliary beat frequency were found to be inhibited in hamster oviducts subjected to cigarette smoke in a perfusion chamber (58). These abnormalities may contribute to increased incidences of ectopic pregnancy and tubal infertility in smoking women.

Smoking also has been associated with bacterial vaginosis (which in turn is associated with second-trimester miscarriage) and with preterm labor (59). The risk of multiple gestations also may be increased in smokers (60, 61).

Effects of Maternal Smoking on Male Progeny

An epidemiologic study to identify the cause of decreasing sperm counts in Danish versus Finnish men has suggested an effect of maternal smoking (62). 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. The authors suggested 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 Infertility Treatments and Outcomes of Assisted Reproduction

Evidence suggests that self-reported smoking during ovulation induction for polycystic ovary syndrome (PCOS) is associated with diminished odds of live birth. A secondary analysis of the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) study, a randomized, controlled trial comparing

effectiveness of clomiphene citrate to letrozole in the treatment of infertility in women with PCOS, described 80% lower odds of live birth when both members of a couple smoked but no significant association with treatment outcomes when either the male or the female partner smoked (63). The association between couple smoking and diminished live-birth rate was independent of the effects of age, body mass index, sperm concentration, intercourse frequency, and study drug randomization. The observation that smoking in both partners was required to see an effect on live birth is important for preconception counseling about smoking cessation efforts.

Three meta-analyses have been published examining the relationship between smoking and the outcomes of assisted reproductive technology (ART) cycles (6, 7, 64). One meta-analysis that included nine studies identified an OR of 0.66 (95% CI, 0.49–0.88) for conception among smokers undergoing IVF (7). 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 successful first IVF cycles in nonsmokers over smokers (65), a result suggesting that smokers require nearly twice the number of IVF cycles to conceive as nonsmokers.

Additional studies support the conclusion of these earlier meta-analyses in demonstrating the adverse effects of smoking on conception rates in ART cycles (61, 65, 66). Among these is a prospective cohort study that analyzed the quantity, frequency, and duration of smoking exposure among 221 couples at various time points (including lifetime, week prior to treatment, and during procedures) (61). In a multivariate analysis, a woman who ever smoked during her lifetime was more likely to fail to conceive, (relative risk [RR] 2.71, 95% CI 1.37–5.35, $P < .01$) or achieve a live birth (RR 2.51, 95% CI 1.11–5.67, $P = .03$) with ART when compared with a non-smoker. This association was still significant even when adjusting for the effects of age, race, educational attainment and numerous other confounding variables. Each year that a woman smoked was associated with a 9% increase in the risk of unsuccessful ART cycles (95% CI 1.0–1.16, $P = .02$). Similar negative associations between ART outcomes and smoking were observed when couple smoking was evaluated. Studies evaluating donor-oocyte cycles are limited but evidence suggests that donor-egg recipients who were described as moderate-to-heavy smokers, were significantly less likely to achieve pregnancy than light or nonsmoking donor-egg recipients (34.1% vs 52.2% respectively, $P = .02$). These results suggest that alterations in uterine receptivity may also contribute to diminished ART success in smokers (65).

The specific adverse effects of smoking on reproductive processes cannot be defined precisely because reported outcomes have been heterogeneous. Yet studies have variously reported an increased gonadotropin requirement for ovarian stimulation, lower peak estradiol levels, elevated testosterone, fewer oocytes retrieved, higher numbers of canceled cycles, thicker zona pellucida, lower implantation rates, and more cycles with failed fertilization in smokers compared with nonsmokers (6, 30, 61, 64, 67–71). The detrimental effect of smoking becomes more detectable in

older women undergoing treatment (6, 38, 45, 72). The effects of smoking and advancing age may therefore synergize to accelerate the rate of oocyte depletion (46).

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 (73), a known ovarian toxin, are higher in smokers than in nonsmokers. Lipid peroxidation, a marker of intrafollicular oxidative stress is more abundant in the follicular fluid of smokers undergoing IVF than nonsmokers (74). Likewise, the concentrations of cotinine in the follicular fluid aspirated from women at the time of egg retrieval in IVF cycles relate directly to the number of cigarettes smoked (15). All women with known exposure 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 (15). These women were exposed environmentally, with all but one working outside the home. These data emphasize the potential hazards from passive tobacco smoke inhalation. Additional evidence suggests an association between exposure to sidestream smoke and impaired reproductive outcomes in IVF cycles such that clinical pregnancy rates are comparable to that of active smokers and significantly lower than nonsmokers (75).

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

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 (4). Smoking cessation rates generally are better for infertile women than for pregnant women. The only study to examine smoking cessation in infertile women found that a relatively simple and inexpensive approach based on individualized counseling regarding the risks of smoking was reasonably effective, increasing the proportion of women who quit smoking from 4% at baseline to 24% after 12 months of intervention (5). This study method involved several minutes of counseling, education, and encouragement during each clinic visit, according to the patient's individual stage of readiness to quit. This method was more successful than just providing educational materials and website addresses alone (5).

In general populations, various interventions including behavior modification, group counseling, feedback, advice, and weaning nicotine 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 also may be of benefit. Results correlate well with the self-reported number of cigarettes smoked and offer feedback to patients. Serum and urine cotinine

concentrations also have been used effectively for the same purpose (22, 76).

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 (77, 78). 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); and 5) Arrange follow-up visits (21, 44). Specific smoking-cessation protocols for pregnant women have been outlined in several reviews (4, 76, 79). 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) bupropion, and/or varenicline have resulted in a two-fold increase in the proportion of nonpregnant women able to quit smoking (76).

Available medical therapies include NRT in the form of gum, lozenges, and patches (available over the counter) as well as nasal sprays and inhalers (prescription only). Because the latter two have not been studied in pregnancy and are classified as Food and Drug Administration (FDA) category D agents (there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans), NRT via nasal inhalers and sprays are best avoided in pregnant women and women attempting to conceive. Nicotine gum carries a category C classification, the nicotine lozenge is pregnancy category D, 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. Electronic cigarettes are also an inhaled form of nicotine replacement but have not been adequately studied in pregnancy or in women attempting pregnancy (80).

Two non-nicotine FDA-approved smoking cessation agents are currently available: varenicline (pregnancy category C) and bupropion sustained release (pregnancy category B). Varenicline is a partial agonist at the alpha-4 beta-2 subunit of the nicotinic acetylcholine receptor and as such, reduces nicotine withdrawal symptoms and diminishes the rewarding effects of cigarettes (81). Bupropion is believed to upregulate noradrenergic and dopaminergic activity in the central nervous system which also may limit the rewarding effects of smoking. The United States Public Health Service considers varenicline, bupropion, and combination nicotine therapy (transdermal nicotine patch in combination with nicotine gum, lozenge, inhaler, and/or spray) to be first-line therapies for smoking cessation (82), and all approaches are approximately twice as effective as placebo in randomized trials. One review summarized results of 267 randomized trials involving more than 100,000 patients and described the comparative effectiveness of these treatments (83). Nicotine-replacement therapies and bupropion had similar

efficacy. While varenicline was 50% more effective than single-agent nicotine replacement, it was comparable to combination nicotine-replacement therapy (83). In head-to-head comparisons with bupropion, varenicline was 60% more effective for smoking cessation (83). Individual nicotine-replacement options achieved similar treatment effects and combination nicotine replacement was superior to any single nicotine-replacement treatment (83). Studies evaluating risk of teratogenicity in pregnant women prescribed bupropion and NRT are limited. While some evidence suggests that bupropion exposure has low risk to the fetus (84), there is debate in the literature regarding the risk of left ventricular outflow tract obstruction with first-trimester exposure (85–87). Studies evaluating pregnancies in which nicotine therapy was prescribed have failed to demonstrate increased fetal anomalies with the exception of one report suggesting a higher risk of congenital respiratory tract anomalies with nicotine treatment (88–90). While significant evidence argues for the safety of smoking cessation therapies in pregnancy, ideally 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 (76). Eliminating exposure to the many other chemicals contained in cigarette smoke is one clear advantage of NRT (4). 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 (5). The likelihood of achieving smoking cessation appears to increase with each attempt (22, 79), 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 (6, 12, 91) can be powerful incentives when included in physician counseling. When successful, smoking cessation represents an important part of effective treatment for infertility.

SUMMARY

- There is good evidence that smoking in the female is associated with impaired fecundity and increased risks of spontaneous abortion and ectopic pregnancy.
- Smoking appears to accelerate the loss of reproductive function and may advance the time of menopause by 1–4 years.

- There is good evidence that smoking is negatively associated with ART outcomes such that smokers require nearly twice the number of IVF attempts to conceive as nonsmokers.
- There is fair evidence that semen parameters and results of sperm function tests are lower in smokers than in nonsmokers and the effects are dose-dependent, but smoking has not yet been conclusively shown to reduce male fertility.
- The adverse effects of sidestream and passive smoking are now established, and there is good evidence that nonsmokers with excessive exposure to tobacco smoke may have reproductive consequences as great as those observed in smokers.
- Varenicline, bupropion, and combination nicotine therapy should be considered first-line therapies for smoking cessation; all approaches are approximately twice as effective as placebo in randomized trials.

CONCLUSIONS

- 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.
- Clinicians can facilitate smoking cessation by providing education, monitoring, and consistent individualized support.

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