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.)

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 ($\leq$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).