Tobacco or marijuana use and infertility: a committee opinion

Practice Committee of the American Society for Reproductive Medicine

American Society for Reproductive Medicine, Washington, D.C.

In the United States, approximately 21% of adults report some form of tobacco use, although 18% report marijuana use. Although the negative impact of tobacco use in pregnancy is well documented, the impact of tobacco and marijuana on fertility and reproduction is less clear. This committee opinion reviews the potential deleterious effects of tobacco, nicotine, and marijuana use on conception, ovarian follicular dynamics, sperm parameters, gamete mutations, early pregnancy, and assisted reproductive technology outcomes. It also reviews the current status of tobacco smoking cessation strategies. This document replaces the 2018 American Society for Reproductive Medicine Practice Committee document entitled Smoking and Infertility: a committee opinion (Fertil Steril 2018). (Fertil Steril® 2024;121:589-603. ©2023 by American Society for Reproductive Medicine.)

El resumen está disponible en Español al final del artículo.

Key Words: Smoking, tobacco, marijuana, fertility, fertility preservation

Although the prevalence of cigarette smoking has declined over time, the use of other inhaled products, such as electronic nicotine delivery systems (ENDS; vaping or electronic cigarettes [e-cigarettes]), and recreational marijuana use have increased. In 2019, approximately 21% of adults in the United States used any tobacco product. Cigarettes remain the most commonly used tobacco product at 14%, followed by e-cigarettes at 4.5%. Cigarette smoking is more frequent among men, of whom the prevalence is 25% in those aged 25–44 years old. The prevalence of cigarette use in women aged 25–44 years old is 14%, although 8% report use during pregnancy (1). An analysis of 2016 Behavioral Risk Factor Surveillance System data reported a 9.9% prevalence of current marijuana use among women of reproductive age (2). Current cigarette use and e-cigarette use were significantly associated with marijuana use, raising the importance of screening for each of these substances individually.

This document reviews the evidence linking cigarette smoking, ENDS, and marijuana use with reproductive hazards for both females and males. Health care providers who educate their patients about the potential reproductive risks associated with these products will increase the likelihood that their patients will discontinue use before conception (3, 4).

CIGARETTE SMOKING AND INFERTILITY

Cigarette smoking is an established modifiable risk factor for a number of serious complications in pregnancy and a public health challenge to maternal-fetal health (5). 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, most of the women surveyed, including female health care providers, were unfamiliar with the reproductive risks associated with cigarette smoking (Table 1) (6).

REPRODUCTIVE CONSEQUENCES OF CIGARETTE SMOKING

Conception Delay

Multiple comprehensive reviews have summarized the cumulative data on cigarette smoking and female fecundity, and all support the conclusion that smoking has an adverse impact (Table 2) (7–11). 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 (7, 8).

A meta-analysis identified the pertinent literature available from 1966 through late 1997 and included 12 studies meeting strict inclusion criteria (8). 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 study designs of 1.60 (95% CI 1.34–1.91). In cohort studies, the OR for

Received December 21, 2023; accepted December 21, 2023; published online January 27, 2024.
Correspondence: Practice Committee, American Society for Reproductive Medicine, Washington, DC (E-mail: asrm@asrm.org).

Fertility and Sterility® Vol. 121, No. 4, April 2024 0015-0282/$36.00

https://doi.org/10.1016/j.fertnstert.2023.12.029

conception delay over 1 year in smoking vs. nonsmoking women was 1.42 (95% CI 1.27–1.58), and in case-control studies, the OR for infertility vs. fertility in smokers compared with nonsmokers was 2.27 (95% 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 resulted from 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 >20 cigarettes per day, but a trend for all levels of smoking was identified. Because this meta-analysis was published, additional large-scale, population-based studies have emerged supporting the negative association between cigarette smoking and fecundity, independent of other factors (12, 13). In the largest of these studies, investigators evaluated nearly 15,000 pregnancies to determine the time to conception. In addition to cigarette smoking, factors such as parental age, ethnicity, education, employment, housing, prepregnancy body mass index, and alcohol consumption were assessed for their possible confounding influences. Active smoking was associated with increased failure to conceive within both the 6- and 12-month durations of study. Increasing delay to conception is 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 (12).

Ovarian Follicular Depletion

Menopause occurs 1–4 years earlier in women smoking cigarettes than in nonsmokers (14–17). The dose-dependent nature of the effect supports the contention that smoking may accelerate ovarian follicular depletion, although this relationship has not been observed in all studies (18). Chemicals in cigarette smoke appear to accelerate follicular depletion and the loss of reproductive function (14, 19–21). Mean basal follicle-stimulating hormone (FSH) levels are significantly higher in young smokers than in nonsmokers (22, 23). In one study, basal FSH levels were 66% higher in active smokers than in nonsmokers and 39% higher in passive smokers than in nonsmokers (23). Urinary estrogen excretion during the luteal phase in smokers is only about one-third of that observed in nonsmokers (24), possibly because constituents of tobacco smoke inhibit granulosa cell aromatase (25) and induce oxidative metabolism of estrogens (26). Significantly lower concentrations of antimüllerian hormone (AMH) have been described in association with current cigarette smoking in subjects pursuing in vitro fertilization (IVF) and in population-based studies (27–29). In a community sample of 284 women between 38 and 50 years of age, AMH levels were 44% lower in current smokers compared with never-smokers; former smoking and passive smoking were not significantly associated with AMH levels (29). A recent cross-sectional study (30) demonstrated an increases risk of diminished ovarian reserve (AMH <1 ng/mL) for each additional cigarette currently smoked (OR: 1.08; 95% CI 1.01–1.15). 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 (31). Mean gonadotropin dose requirements for smokers receiving stimulation for IVF are higher when compared with those of nonsmoking women (48.1 ± 15.6 vs. 38.9 ± 13.6 ampules, 75 IU/ampule; $P<.0001$) (22).

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

Hayes. Tobacco or marijuana use and infertility. Fertil Steril 2024.

Effects on Sperm Parameters

The effect of cigarette smoking on male fertility is more difficult to discern. The effects of smoking and passive smoking on various semen parameters have been evaluated (7, 10, 32–35). Reductions in sperm density, motility, antioxidant activity, and a possible adverse effect on morphology have been demonstrated (36, 37). The decrease in sperm concentration averaged 22% and was dose-dependent. The use of smokeless tobacco also has a dose-dependent negative effect on multiple semen parameters (38). Although sperm concentration, motility, and/or morphology 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, on the basis of a study involving the zona-free hamster egg penetration test (39). Available data on the effect of cigarette smoking on male fertility have been difficult to assess because of the confounding effect of the partner's smoking habits and fecundity (7, 10–12, 40).

Mutagenic Potential

Gametogenesis appears to be vulnerable to damage from tobacco smoke (41). Both chromosomal and DNA damage to human germ cells may result from tobacco smoke exposure (42). 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 the function of the meiotic spindle in humans (42). Moreover, smoking in pregnant women is associated with an increased risk of trisomy 21 offspring resulting from maternal meiotic nondisjunction (43). The prevalence of Y chromosome disomy (two homologous Y chromosomes) in sperm correlates with urinary

TABLE 2

Adverse reproductive effects of tobacco use.

Adverse effect	Degree of effect	Other information
Conception delay	OR 1.4–2.3	Dose-dependent effect; active use by either partner showed an adverse effect
Earlier menopause	1–4 years earlier	Dose-dependent effect
Lower antimüllerian hormone levels	44% lower than nonsmokers; falls 21% faster per year	Effect greatest with current use
Decreased sperm concentration, motility, and/or morphology	Variable	Reduced compared with nonsmokers but may remain in normal range overall
Increase in spontaneous miscarriage	OR 1.8–2.2	The effect can be also seen with smokeless tobacco
Increased risk of ectopic pregnancy	OR 1.7–3.5	May alter the pickup of the oocyte cumulus complex and ciliary beat frequency
Decreased live birth rate with ovulation induction	OR 0.2	Impact seen when both partners actively using
Decreased live birth rate with ART	OR 0.59–0.66	Effect more notable in older women

Notes: ART = assisted reproductive technology; OR = odds ratio.

Hayes, Tobacco or marijuana use and infertility. Fertil Steril 2024.

cotinine concentrations, a major metabolite of nicotine, and a marker of recent exposure to cigarette smoke (44).

Evidence suggests that gene damage in sperm may relate to the direct binding of tobacco smoke constituents or their intermediates to DNA (45, 46). When bound to DNA, some of these chemicals "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 the transmission of modified DNA originating from parental smoking (47). A more recent study additionally demonstrated elevated reactive oxygen species levels and increased global methylation of sperm DNA in smoking normozoospermic men. This indicates that paternal tobacco smoke exposure alters epigenetic characteristics in sperm, potentially contributing to the noted reproductive risks (48).

Although it is plausible that gamete DNA damage may cause many of the recognized adverse reproductive effects of cigarette smoking, 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 (47).

Early Pregnancy Effects

Cigarette smoking is associated with an increase in spontaneous miscarriage in both natural and assisted conception cycles (4, 49, 50). Five of seven heterogeneous studies (including the only prospective study) of natural conception in female smokers have found an increased miscarriage risk (8). In one study of inner-city women 14–39 years of age, smoking, as assessed by the 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) (50). There are few studies investigating the chromosomal effects of cigarette 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 is also associated with an increased risk of pregnancy loss (51, 52), suggesting that substances other than the combustible by-products of tobacco may also cause pregnancy loss.

Although it is difficult to control for other lifestyle factors, an association between ectopic pregnancy and cigarette smoking has been consistently reported (36, 53, 54). 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) (53). A more recent prospective cohort study noted an increased risk of ectopic pregnancy in current smokers (OR 1.73, 95% CI 1.28–1.32). The risk of ectopic pregnancy fell to the same

level as that of never-smokers 10 years after quitting (54). 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 (55). Analysis of an oviductal epithelial cell line (OE-E6/E7) and explants of human Fallopian tubes exposed to cotinine demonstrated significant changes in Fallopian tube epithelial morphology and altered epithelia cell turnover (56). These abnormalities may contribute to increased incidences of ectopic pregnancy and tubal infertility in smoking women.

Effects of Maternal Cigarette 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 cigarette smoking (57). After adjusting for confounding factors, men whose mothers had smoked >10 cigarettes per day had sperm densities that were 48% lower than men with nonsmoking mothers (95% CI −69% to −11%). Paternal smoking was unrelated to the semen parameters of the offspring. The investigators 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 cigarette smoking during ovulation induction for polycystic ovary syndrome is associated with diminished odds of live birth (LB). A secondary analysis of the Pregnancy in Polycystic Ovary Syndrome II (PPCOS II) study, a randomized, controlled trial comparing the effectiveness of clomiphene citrate to letrozole in the treatment of infertility in women with polycystic ovary syndrome, described 80% lower odds of LB when both members of a couple smoked but no significant association with treatment outcomes when either the male or the female partner smoked (58). The association between couple smoking and diminished LB rate was independent of the effects of age, body mass index, sperm concentration, intercourse frequency, and study drug randomization. The observation that cigarette smoking in both partners was required to see an effect on LBs is important for preconception counseling about smoking cessation efforts.

The impact of cigarette smoking on intrauterine insemination (IUI) success has not been evaluated extensively, with studies demonstrating mixed results. Several studies were unable to find a significant association between male or female smoking and IUI outcomes (59–62). One study demonstrated that smokers who underwent ovarian stimulation required significantly higher gonadotropin dosing. Another study reported that male smoking resulted in a statistically significant reduction in clinical pregnancy rate (CPR) for partner insemination (10.9% CPR for male nonsmokers vs. 5.9% for male partner smokers). The investigators also demonstrated the impact of female smoking on donor insemination cycles. Female nonsmokers and those smoking <15 cigarettes a day had a higher CPR than women smoking >15 cigarettes daily (16.8% and 24.5% vs. 5.6%, $P=.01$). A third study also demonstrated the impact of male partner smoking in homologous IUI cycles (63), as well as females smoking >15 cigarettes a day on donor IUI cycles (64).

Several meta-analyses have been published examining the relationship between cigarette smoking and the outcomes of assisted reproductive technology (ART) cycles (7, 8, 65–67). One early meta-analysis that included nine studies identified an OR of 0.66 (95% CI, 0.49–0.88) for conception among smokers undergoing IVF (8). Another meta-analysis of seven relevant studies in addition to the investigators' own prospective data yielded an OR of 1.79 (95% CI, 1.24–2.59) for successful first IVF cycles in nonsmokers over smokers (68), a result suggesting that smokers require nearly twice the number of IVF cycles to conceive as nonsmokers. Two more recent meta-analyses published in 2018 demonstrated similar results, with a significantly reduced chance of LB per cycle for smoking patients (OR 0.59, 95% CI 0.44–0.79) as well as a significantly increased risk for spontaneous miscarriage (OR 2.22, 95% CI 1.10–4.48) (66, 67).

Additional studies support the conclusion of these meta-analyses by demonstrating the adverse effects of cigarette smoking on conception rates in ART cycles (68–70). 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 before treatment, and during procedures) (69). 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 LB (RR 2.51, 95% CI 1.11–5.67, $P=.03$) with ART when compared with a nonsmoker. 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, $P=.02$). 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 therapy success in smokers (68).

The specific adverse effects of cigarette 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 levels, 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 (7, 23, 65, 69, 71–75). The detrimental effect of smoking becomes more detectable in older women undergoing treatment (7, 40, 41, 76, 77).

The effects of smoking and advancing age may therefore synergize to accelerate the rate of oocyte depletion (41).

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 (78), 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 (79). 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 (80). All women with known exposure to passive smoke in the home also had detectable follicular fluid cotinine levels, albeit at lower concentrations. These data emphasize the potential hazards of passive tobacco smoke inhalation. Additional evidence suggests an association between exposure to side stream smoke and impaired reproductive outcomes in IVF cycles, such that CPRs are comparable to those of active smokers and significantly lower than those of nonsmokers (81). 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 cigarette smoking, concerted efforts to help them quit smoking have been only modestly effective (3). Smoking cessation rates are generally better for infertile women than for pregnant women. One study that examined smoking cessation in infertile women found that a relatively simple and inexpensive approach on the basis of 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 (4). 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 (4). A more recent study from the Netherlands reported on the use of an mHealth tool (a mobile phone with internet access) to support healthy nutrition and lifestyle behaviors in couples planning pregnancy. A subsequent randomized controlled trial demonstrated an improvement in the lifestyle risk score (smoking and alcohol use) both 24 weeks after the start of the program and 12 weeks after completion of the program (82).

The Public Health Service and National Cancer Institute offer validated evidence-based intervention guidelines for smoking cessation that incorporate and extend the above-described recommendations (83, 84). A five-step approach is suggested: ask about smoking at every opportunity; advise all smokers to stop; assess willingness to stop; assist patients in stopping (including the use of pharmaceuticals and CO monitoring); and arrange follow-up visits (10, 85). Specific smoking cessation protocols for pregnant women have been outlined in several reviews (3, 86, 87). 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 (Table 3).

Although pharmacotherapy for cigarette smoking cessation has not been studied specifically in infertile women, it may be justified for some. When behavioral approaches fail, the use of nicotine replacement therapy (NRT), bupropion, and/or varenicline has resulted in a twofold increase in the proportion of nonpregnant women able to quit smoking (86). Varenicline is a partial agonist at the α-4 β-2 subunit of the nicotinic acetylcholine receptor and, as such, reduces nicotine withdrawal symptoms and diminishes the rewarding effects of cigarettes (88). Bupropion is believed to up-regulate noradrenergic and dopaminergic activity in the central nervous system, which may also limit the rewarding effects of smoking. A review summarized the results of 267 randomized trials involving >100,000 patients and described the comparative effectiveness of these treatments in nonpregnant adults (89). Nicotine replacement therapy and buproprion had similar efficacy, although varenicline was 60% more effective for smoking cessation (89). Studies evaluating the risk of teratogenicity in pregnant women prescribed bupropion, varenicline, and NRT are limited. Although some evidence suggests that buproprion exposure has a low risk to the fetus (90), there is debate in the literature regarding the risk of left ventricular outflow tract obstruction with first-trimester exposure (91–93). Studies evaluating pregnancies in which nicotine therapy was prescribed have failed to demonstrate increased fetal anomalies, with the exception of one report suggesting

TABLE 3

Resources for smoking cessation.

Agency for Healthcare Research and Quality
Treating Tobacco Use and Dependence – 2008 Update Clinical Practice Guideline
https://www.ahrq.gov/prevention/guidelines/tobacco/clinicians/update/index.html
Smoking Cessation: A Report of the Surgeon General
https://www.hhs.gov/surgeongeneral/reports-and-publications/tobacco/2020-cessation-sgr-factsheet-key-findings/index.html
U.S. Preventive Services Task Force
Tobacco Smoking Cessation in Adults, Including Pregnant Persons: Interventions
https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/tobacco-use-in-adults-and-pregnant-women-counseling-and-interventions
NIH National Cancer Institute Smoking Cessation
Includes link to smokefree.gov Initiative (SFGI) – free information and support
https://cancercontrol.cancer.gov/brp/tcrb/smoking-cessation
American Cancer Society
How to Quit Using Tobacco
https://www.cancer.org/healthy/stay-away-from-tobacco/guide-quitting-smoking.html
American Lung Association
Lung Helpline and Tobacco Quitline
https://www.lung.org/help-support/lung-helpline-and-tobacco-quitline
U.S. Food and Drug Administration
Quitting Smoking and Other Tobacco Public Health Resources
https://www.fda.gov/tobacco-products/health-effects-tobacco-use/quitting-smoking-and-other-tobacco-public-health-resources

Hayes. Tobacco or marijuana use and infertility. Fertil Steril 2024.

a higher risk of congenital respiratory tract anomalies with nicotine treatment compared with smokers (OR 4.65, 95% CI 1.76–12.25) (94–96). Two recent observational studies failed to demonstrate any increased risk of a major congenital anomaly or adverse perinatal event with maternal varenicline use in pregnancy (97, 98). Despite this information, the United States Preventive Services Task Force recently updated their guidelines regarding smoking cessation in pregnant adults and concluded that the evidence is insufficient to assess a balance of the risks and benefits of pharmacotherapy (99).

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 (4). The likelihood of achieving smoking cessation appears to increase with each attempt (11, 87), 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 (7, 100, 101) can be powerful incentives when included in physician counseling. When successful, smoking cessation represents an important part of effective treatment for infertility.

ELECTRONIC NICOTINE DELIVERY SYSTEMS

Electronic nicotine delivery systems, more colloquially known as e-cigarettes or vaping, are battery-powered products used to heat and aerosolize a solution that contains nicotine and other toxic substances (102, 103). Electronic nicotine delivery systems are often touted as a "safer" or "cleaner" alternative to cigarettes (104) or as a bridge to cigarette smoking cessation (105, 106). Despite the perception that ENDS are less harmful than traditional tobacco products, increasing data show that the aerosolized particles contain toxic substances that may be harmful to both the user and nonusers who are exposed secondhand (102). The World Health Organization has stated that the use of ENDS may lead to an increased risk of some diseases, such as cardiovascular disease, cancer, and adverse reproductive outcomes (103). In particular, there is increasing recognition of lung injury because of the use of ENDS, termed e-cigarette product-use-associated lung injury (107).

Although found to contain fewer toxic components than traditional cigarettes, the aerosol in ENDS has been found to contain metals (chromium, nickel, and lead) and carbonyls (formaldehyde, acetaldehyde, acrolein, and glyoxal) (103). Heavy metals may act as endocrine disruptors (108) and have been linked to male infertility (109); carbonyl exposure has been linked with infertility (110) and miscarriage (111). Additionally, given that ENDS contain nicotine, any harmful exposure to nicotine itself is not avoided by its use. There is a dearth of evidence regarding the effect of ENDS on reproductive health with regard to conception, ovarian reserve depletion, sperm parameters, or ART outcomes in humans. Most currently available literature involves animal studies (112). However, despite the lack of conclusive evidence in humans, there is a theoretical basis on which ENDS may harm reproductive function.

Fecundity and Implantation

Studies in mouse models have shown that female mice exposed to vapors from ENDS have a delayed time to first litter, suggesting lower fecundity and impaired implantation compared with female mice exposed to sham vapors (113). Exposure to ENDS vapors in mice has been shown to impair placental trophoblast function (114). So far, only one study has evaluated the impact of ENDS use on fecundability in humans; its findings suggested that ENDS use was associated with lower fecundability, although it was difficult to differentiate between independent use of ENDS and joint use with traditional combustible cigarettes (115). There are no studies that evaluate the effect of ENDS use on early miscarriage in humans.

Male Reproduction and Sperm Parameters

There is a small body of literature that exists that suggests that ENDS has an effect on male reproductive function. Although no studies exist to compare the effect of ENDS with traditional combustible cigarettes on erectile dysfunction, studies have shown that ENDS result in similar vascular damage, albeit at lower levels, compared with traditional combustible cigarettes (116). Additionally, nicotine itself has been implicated as a contributor to erectile dysfunction (117), thus putting those who use ENDS at risk. A recent systematic review of animal studies suggested that ENDS impact sperm parameters, although less than traditional combustible cigarettes (116, 118). Animal studies have found exposure to ENDS aerosolizing liquid to be associated with decreased sperm density and viability in rodent models, regardless of whether or not nicotine was present in the liquid, suggesting that the liquid that gets aerosolized with ENDS use may itself cause oxidative imbalance and impact steroidogenesis (119, 120). A single epidemiological study in humans exists that examines testicular function in men using ENDS. This study found that men who reported the use of ENDS had lower sperm concentration and total sperm count compared with nonusers (121).

Assisted Reproductive Technology Treatment Outcomes

No studies exist yet that look specifically at the effect of ENDS use on ART success or outcomes.

Embryological Development

Most studies regarding the effects of ENDS on embryological development come from animal models. These animal studies show complications related to fetal development that range from physical morphology to major developmental and functional abnormalities of organ systems that have the ability to impact offspring exposed in utero into their adult life (122–126). Animal studies have demonstrated abnormal lung

growth, airway branching, and alveolar development (127). One study on embryonic development included human stem cells and found exposure of embryonic stem cells to ENDS fluid to be cytotoxic; moreover, this study found that cytotoxicity was not because of nicotine but was correlated with the number and concentration of chemicals used in ENDS flavor fluids (128).

Pregnancy Outcomes

Most of the current literature surrounding ENDS in humans pertains to the negative health consequences of ENDS exposure in pregnancy from epidemiological studies, but data are still scarce. Both the American College of Obstetricians and Gynecologists and the Centers for Disease Control and Prevention recommend against the use of ENDS in pregnancy and the postpartum period (129). Despite this recommendation, there is a perception among pregnant women that smoking e-cigarettes is a safer alternative than smoking traditional combustible cigarettes (130–133), and the use of ENDS in pregnancy is increasing (134). Additionally, most pregnant women who use ENDS also use combustible cigarettes rather than exclusively using ENDS (135–137), so it is difficult to differentiate health effects during pregnancy between traditional combustible cigarette use and ENDS alone. Two studies have attempted to look at pregnancy outcomes, notably birth weight and ENDS use. Regan and Pereira (135) used data from the Pregnancy Risk Assessment Monitoring System to compare the pregnancy outcomes of former smokers (those who quit combustible cigarette smoking before pregnancy and did not use ENDS) to those of exclusive ENDS users, combustible cigarette smokers, and dual ENDS + cigarette smokers. They found that ENDS users had a similar prevalence of preterm birth (adjusted prevalence ratio [aPR] 0.85; 95% CI 0.55–1.31), small-for-gestational-age (aPR 0.56; 95% CI 0.29–1.08), and low birth rate (aPR 0.81; 95% CI 0.54–1.21) compared with current smokers (135). Moreover, ENDS users had a higher prevalence of low birth weight (aPR 1.52; 95% CI 1.01–2.29) compared with former smokers (135). The investigators concluded that the prevalence of low birth weight was higher for those who used e-cigarettes, even exclusively, compared with women who quit smoking cigarettes entirely. These findings were not replicated in a smaller prospective observational study by McDonnell et al. (138), which found that birth weights of infants born to women who were exclusive ENDS users (mean 3,470 ± 555 g) were similar to those of women who were nonsmokers (mean 3,471 ± 504 g), whereas birth weights of infants born to combustible cigarette smokers were significantly less (3,166 ± 502 g) (138).

Long-Term Effects on Offspring

No human studies exist that detail the long-term outcomes of offspring from women who used ENDS during pregnancy, but some studies in animals have suggested long-term consequences. Animal models have shown the effects of ENDS on the female offspring of female mice exposed, although in utero, to ENDS, as these offspring were more likely to have decreased weight gain and were significantly smaller than mice not exposed to ENDS (114). Vascular compromise in offspring of female rats with ENDS exposure during pregnancy has been also demonstrated; middle cerebral artery reactivity by endothelial-dependent dilation to acetylcholine was found to be 51%–56% reduced in offspring of female rats exposed to ENDS as well as when exposed to nicotine-free versions of electronic cigarette vapors compared with ambient air exposure (139). Electronic nicotine delivery systems have been linked with behavioral changes including memory and cognition, altered brain development, and deficits in neurotransmission in murine models (140).

Conclusions

Although touted as a safe alternative to traditional combustible cigarettes, early data from animal studies involving ENDS suggest overall harm to reproductive health and that use by pregnant women may be detrimental to fetuses.

MARIJUANA

Since 2012, 18 states, two territories, and the District of Columbia have legalized marijuana for adult recreational use, with an accompanying increase in the number of people reporting initiating use from 2.2 million people in 2002 to 3.5 million people in 2019 (141, 142). Up to 17% of men and 12% of women report using marijuana during the preconception period, with lower reported use in women during pregnancy (143–147), with a longer time to pregnancy, and infertility (148–152). In studies investigating perceptions of marijuana during preconception and pregnancy, participants report that marijuana is risky, is safe in pregnancy at low doses, poses no risks to offspring, or does not impact fertility (152–156).

The American College of Obstetrics and Gynecology and the American College of Pediatricians recommend against the use of marijuana during preconception and pregnancy because of the risks to offspring, although they acknowledge that supporting evidence is incomplete, conflicting, and largely theoretical (157, 158). Evidence on the potential associations between marijuana use and fertility is likewise incomplete and conflicting. Studies conducted thus far are potentially hindered by issues including a small number of exposed participants, misclassification of the exposure because of retrospective and participant self-report, lack of information regarding type of marijuana use (e.g., smoking vs. edibles), heterogeneity in study designs, study populations, and dose and timing of marijuana use.

Female Reproductive Hormones

Thus far, no appreciable associations have been found between marijuana use and most examined female reproductive hormones (FSH, progesterone, estradiol, testosterone (total and free), prolactin, estrone-1-glucuronide, pregnanediol-3-glucuronide, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate, and AMH) (143, 149, 159–161).

Luteinizing hormone (LH), the only exception, has been inconsistently associated with marijuana use across a small number of existing studies that are heterogeneous in size, population, and timing of exposure. In a trial consisting of 5 and 16 (respectively) female marijuana users, Mendelson et al. (159) in 1986 and Mendelson and Mello (162) in 1984 found that marijuana use during the periovulatory and luteal phases of the menstrual cycle was associated with a short-term suppression of LH up to 180 minutes after exposure to one 1-g marijuana cigarette. In a subsequent small (n = 56) retrospective cohort study, no association was found between weekly chronic marijuana use and LH level (mean LH nonusers 10 mIU/mL, infrequent 11 mIU/mL, moderate 16 mIU/mL, frequent 9 mIU/mL). The phase of participants' menstrual cycles was not specified and measures of statistical significance were not provided in the text (160). Conversely, in a prospective study of 1,228 female participants with a history of pregnancy loss, any marijuana use in the year before conception was associated with higher LH across the menstrual cycle (median level users 1.7 mIU/mL, interquartile range [IQR] 0.2, 3.7 mIU/mL) (nonusers 0.5 mIU/mL, IQR 0.2, 1.7 mIU/mL) and a higher LH-FSH ratio (median ratio users 0.2, IQR 0.2–0.8) (nonusers 0.3, IQR 0.2–0.6). However, the number of exposed participants was low (n exposed = 62) (143).

Male Reproductive Hormones

Male testosterone, FSH, LH, SHBG, and inhibin have all been assessed for associations with marijuana; however, studies are difficult to compare because of heterogeneity in findings, size, population, and dose or timing of marijuana exposure (160, 163–167). Smoking marijuana was associated with lower testosterone levels in an early small case-control study (n exposed = 20) (nonusers group mean 742 ± 29 ng/100 mL), (users 5–9 joints/wk group mean 503, SEM ± 40 ng/100 mL) (164). Although subsequent, larger studies found positive associations between greater testosterone concentrations and more recent use (165, 167). Similarly, in a 2019 prospective cohort study enrolling men presenting at an infertility clinic, although there were no differences in testosterone levels among men who were current, past, never, or ever marijuana smokers, men who had ever smoked marijuana at higher intensity had higher levels of serum testosterone than ever smokers at a lower intensity (20 additional joint years adjusted difference 8.22 ng/dL, 95% CI 2.02–14.8) (n ever exposed = 365) (150).

Inhibin and SHBG have not been studied widely, and no appreciable associations were found between LH and FSH levels and marijuana use in studies comprising men from the general population (160, 163, 164, 166). In an ongoing prospective cohort study enrolling men presenting to an infertility clinic, although no appreciable associations were found with LH and FSH levels, modestly depressed among marijuana smokers (never 7.77 IU/L, 95% CI 6.23–9.68), (ever 6.49 IU/L, 95% CI 5.28–7.98), and inhibin and SHBG elevated (inhibin adjusted difference 10.9 pg/mL, 95% CI, 0.30–22.6) (SHBG adjusted difference 9.00 nMol/L, 95% CI 1.65–16.9) (150).

Anovulation and Menstrual Cycles Abnormalities

Although evidence is scarce, findings from existing studies suggest a potential association between marijuana use, anovulation, and menstrual cycle abnormalities. A case-control study comprising 171 women exposed to marijuana between 1975 and 1982 found a positive association between both ever using marijuana (adjusted RR [aRR] ever vs. never 1.7, 95% CI 1.0–3.0) and use within a year of trying to conceive (aRR of use within a year vs. never 2.1, 95% CI 1.1–4.0) and anovulatory infertility (167). This finding is supported by results from a cohort study of women with pregnancy loss in which there was a trend toward an increased risk of anovulatory cycles in women who had ever used marijuana (aRR ever vs. never 1.75, 95% CI 0.85–3.60) (143). Two studies have assessed marijuana use and menstrual cycle abnormalities. In a prospective cohort study of 201 US women in North Carolina, marijuana use was associated with a longer follicular phase compared with nonuse (P=.04) (168). However, there was no evidence of a dose-response relationship between occasional use (a 3.5-day increase) and frequent use (a 1.7-day increase) compared with nonusers, and the number of exposed participants was low (n exposed = 29) (168). Similarly, in a 2018 case-control study of women who smoke tobacco, women who concurrently used marijuana (n = 13) had a shorter luteal phase (mean 16.8 days, SD 11.3 days) than the 39 women who only smoked tobacco (mean 11.4 days, SD 2.2 days) (P=.002) (169).

Semen Quality

Thus far, studies comprising men from the general population have found positive associations between marijuana use and diminished semen quality across all parameters aside from semen volume (count, morphology, motility, concentration) (164, 167, 170). However, only one study contained a larger sample size (n = 545) (167). Studies conducted in geographically diverse populations of men presenting to infertility clinics are more numerous and have found either no appreciable associations or inconsistent associations between marijuana use and examined semen parameters (sperm volume, concentration, motility, progressive motility, morphology, count, and ejaculatory volume) (147, 149, 150, 156, 171).

Among studies comprising men presenting to infertility centers, sperm morphology and motility were the most widely studied parameters. Marijuana use (current, past 3 months, and any past) was associated with an increased risk of abnormal sperm morphology across three studies conducted in the UK, Pacific Northwest, and Jamaica (147, 156, 171). Contrary to this, in a study comprising men presenting to an infertility center in New England, no appreciable associations were found with never, ever, past, or current use of marijuana and % normal morphology (150), and a modestly lower risk of abnormal morphology was found in men who had ever smoked vs. never smoked marijuana among Jamaican men (adjusted OR [aOR] abnormal morphology 0.4, 95% CI 0.2–0.9) (156). Findings from three studies examining sperm motility are likewise inconsistent. Although use of a large quantity of marijuana or recent marijuana use was associated

with increased odds of "abnormal motility" among Jamaican men (156), no appreciable associations were found between never, ever, past, or current marijuana use and % total sperm motility among men presenting to an infertility center in New England (150). Contrary to popular beliefs, current marijuana use was associated with a lower risk of abnormal motility among men in the Pacific Northwest (aOR of % abnormal motility 0.4, 95% CI 0.25–0.91) (147).

Female Marijuana Use and Pregnancy Delay

Results from the few studies investigating associations between female fecundability and marijuana are conflicting. The most recently published study found that any past-year use of marijuana was associated with reduced fecundability (aOR 0.59, 95% CI: 0.38–0.92). However, the sample contained 1,228 women with a history of pregnancy loss, and the number of exposed participants was low (n exposed = 62) (143). Conversely, in an internet-based prospective cohort study of 4,194 North American female pregnancy planners conducted in 2013–2017 with a higher number of exposed participants (n exposed = 485), no appreciable association was found between marijuana use < or ≥ once per week compared with nonuse (adjusted fecundability ratio [aFR] <once/wk aFR 0.99, 95% CI: 0.85–1.16, ≥once/wk aFR 0.98, 95% CI: 0.80–1.20) (144). Similarly, no appreciable association was found between marijuana use and time to pregnancy in a cross-sectional sample of 1,076 women trying to conceive who responded to the National Survey of Family Growth between 2002 and 2015 (n exposed = 124) (adjusted time ratio for daily users 0.92, 95% CI: 0.4–2.0; weekly 1.7, 95% CI 0.9–3.3; monthly 1.1, 95% CI 0.6–2.2, <once per month 1.0 (0.7–1.3) (172). In a retrospective cohort study, the time to pregnancy was shorter (3.7 vs. 5 months) for women who reported smoking ≥1 joint/wk (n exposed = 379) compared with women who reported no use (173). However, the association was modest (aRR of conception 1.1, 95% CI 1.0–1.2), and no appreciable associations were found between smoking ≥1 joint/wk and primary infertility in a related case-control study (aOR of infertility 1.1, 95% CI 0.8–1.4) (173).

Male Marijuana Use and Pregnancy Delay

Similar to female marijuana use, there is no clear association between male marijuana use and fecundability in the few existing studies on this topic. In an internet-based prospective cohort study of 1,125 male North American pregnancy planners conducted in 2013–2017, no appreciable association was found between any marijuana use at baseline and fecundability vs. nonuse (aFR 1.01, 95% CI 0.81–1.27). In subgroup analyses, marijuana use <1 time/wk trended toward decreased fecundability and use ≥1 time/week toward increased fecundability relative to nonuse (aFR <1 time/wk 0.87, 95% CI 0.66–1.15) (aFR ≥1 time/wk 1.24, 95% CI 0.90–1.70) (146). In a smaller cross-sectional study containing a sample of 758 US men responding to the National Survey of Family Growth (2002, 2006–2010, and 2011–2015), no appreciable associations were found between any, daily, weekly, or monthly marijuana use and time to pregnancy compared with never use (adjusted time ratio daily 1.1, 95% CI 0.79–1.5, weekly 1.0, 95% CI 0.3–2.9, monthly 0.9, 95% CI 0.5–1.8) (172).

Female Marijuana Use and ART Treatment Outcomes

Findings from three studies assessing associations between female marijuana use and outcomes of ART treatment are equivocal; however, the number of exposed participants in each study was low (149–151). In a 2021 retrospective cohort study conducted in Canada, implantation rate per embryo transfer and ongoing pregnancy rate per cycle started were higher in couples where only the female smoked marijuana (n light marijuana smokers = 13) compared with couples where neither partner smoked (implantation rate/embryo transfer female light smoker 53.85%, nonsmoker 41.3%) (ongoing pregnancy rate/cycle started female light smoker 43.75%, nonsmokers 29.1%) (149). In a prospective cohort study conducted in the United States comprising 421 females (current users at baseline = 12), no appreciable association was found between marijuana use at the study baseline (never, ever, past or current) and implantation, pregnancy, or LB (adjusted marginal probability implantation users at baseline 67.9, 95% CI: 46.0–81.7 vs. nonusers 54.0, 95% CI 50.2–57.7; clinical pregnancy 55.1, 95% 37.6–71.5 vs. 47.0, 95% CI 43.3–50.7; LB 30.3, 95% CI 18.1–46.1 vs. 39.1, 95% CI 35.5–42.9) (152). Likewise, in a prospective cohort study conducted in the US in a sample of 221 women undergoing IVF treatment between 1993 and 1997, though marijuana smokers in the year before treatment had slightly fewer oocytes retrieved (25% less, P=.03) and embryos transferred (1 fewer, P=.04), there were no statistically significant associations between marijuana use (year, month, week, and day before IVF treatment) and pregnancy or LB (measures of association not provided in the article text), (n exposed in the year before treatment = 22, month = 11, week = 6, day = 6) (151).

Male marijuana Use and ART Treatment Outcomes

Similar to studies investigating female use and ART outcomes, studies investigating associations between male marijuana use and ART treatment outcomes are few, comprising a small number of exposed participants, and have equivocal results. A retrospective cohort study conducted from 2016–2019 reported "no statistically significant differences" in implantation rate or ongoing pregnancy rate between couples in which only the male used marijuana and couples in which neither partner used marijuana (implantation rate in couples with only a male user (light) 47.1% (heavy) 27.8% vs. nonuser couples 41.1%) (ongoing pregnancy rate in couples with only a male user (light) 40.0% (heavy) 25% vs. nonuser couple 29.1%) (P value for subgroup analyses not provided in article text) (n light users = 26, heavy users = 14) (149). Likewise, in a prospective cohort study conducted in the US between 1993 and 1997, male marijuana use within a year of IVF treatment

was associated with one fewer embryo transferred; however, no association was found with pregnancy or LB (measures of associations are not provided in the article text) (n exposed = 39) (151). In contrast, in a sample of 200 men participating in the EARTH study, a prospective cohort study conducted in the US, the probability of implantation, clinical pregnancy, and LB was higher in couples where the male used marijuana at baseline (n = 23) than in couples where the male was not a user at baseline (adjusted marginal probability implantation users 77.9, 95% CI 53.5–91.5 vs. nonusers 56.9, 95% CI 31.0–79.5) (adjusted marginal probability clinical pregnancy users 60.1, 95% CI 42.6–75.4 vs. nonusers 45.1, 95% CI 30.0–61.3) (adjusted marginal probability LB users 47.6, 95% CI 32.4–63.3 vs. nonusers 29.2, 95% CI 18.0–43.5) (150).

SUMMARY

- There is good evidence that tobacco use in females is associated with impaired fecundity and increased risks of spontaneous abortion and ectopic pregnancy.
- Cigarette smoking appears to accelerate the loss of reproductive function and may advance the time to menopause by 1–4 years.
- There is good evidence that tobacco use 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 cigarette smokers than in nonsmokers, and the effects are dose-dependent. However, cigarette smoking has not yet been conclusively shown to reduce male fertility; rather, it appears to increase the risk of pregnancy loss.
- 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 nicotine replacement therapy should be considered first-line therapies for cigarette smoking cessation preconceptionally; all approaches are approximately twice as effective as placebo in randomized trials.
- Although touted as a safe alternative to traditional combustible cigarettes, early data suggest ENDS are harmful to reproductive health, and use by pregnant women is not safe for fetuses.
- Marijuana use has not been consistently associated with male or female fecundity, time to pregnancy, reproductive hormone levels, semen parameters, or ART outcomes.

CONCLUSIONS

- Accumulated evidence supports the value of taking a preventive approach to infertility by discouraging tobacco use and helping to eliminate exposure to cigarette smoke in both women and men.
- Clinicians can facilitate smoking cessation by asking about smoking and providing education, monitoring, and consistent, individualized support for identified smokers.
- Currently available data do not support the safety of ENDS as an alternative to traditional combustible cigarettes.
- Marijuana use has been inconsistently associated with fertility and IVF outcomes. Men and women should be informed of recommendations by the American College of Obstetrics and Gynecology and the American College of Pediatricians encouraging the reduction or cessation of marijuana use during preconception and pregnancy.

Acknowledgments

This report was developed under the direction of the Practice Committee of the American Society for Reproductive Medicine (ASRM) as a service to its members and other practicing clinicians. Although this document reflects appropriate management of a problem encountered in the practice of reproductive medicine, it is not intended to be the only approved standard of practice or to dictate an exclusive course of treatment. Other plans of management may be appropriate, taking into account the needs of the individual patient, available resources, and institutional or clinical practice limitations. The Practice Committee and the Board of Directors of the American Society for Reproductive Medicine have approved this report. This document was reviewed by ASRM members and their input was considered in the preparation of the final document. The following members of the ASRM Practice Committee participated in the development of this document: Alan Penzias, M.D.; Jacob Anderson, M.B.A.; Kristin Bendikson, M.D.; Clarisa Gracia, M.D., M.S.C.E.; Tommaso Falcone, M.D.; Jessica Goldstein, R.N.; Karl Hansen, M.D., Ph.D.; Micah Hill, D.O.; Sangita Jindal, Ph.D.; Suleena Kalra, M.D., M.S.C.E.; Tarun Jain, M.D.; Michael Thomas, M.D.; Richard Reindollar, M.D.; Jared Robins, M.D.; Chevis N Shannon, Dr.Ph., M.B.A., M.P.H.; Anne Steiner, M.D., M.P.H.; Cigdem Tanrikut, M.D.; and Belinda Yauger, M.D.. The Practice Committee acknowledges the special contribution of Belinda Yauger, M.D.; Elizabeth Sanderman, M.P.H., M.S.N.; and Lisa Shandley, M.D. in the preparation of this document. All committee members disclosed commercial and financial relationships with manufacturers or distributors of goods or services used to treat patients. Members of the Committee who were found to have conflicts of interest on the basis of the relationships disclosed did not participate in the discussion or development of this document.

REFERENCES

1. Cornelius ME, Wang TW, Jamal A, Loretan CG, Neff LJ. Tobacco product use among adults — United States, 2019. MMWR Morb Mortal Wkly Rep 2020;69:1736–42.
2. Ewing AC, Schauer GL, Grant-Lenzy AM, Njai R, Coy KC, Ko JY. Current marijuana use among women of reproductive age. Drug Alcohol Depend 2020;214:108161.
3. Klesges LM, Johnson KC, Ward KD, Barnard M. Smoking cessation in pregnant women. Obstet Gynecol Clin North Am 2001;28:269–82.
4. Hughes EG, Lamont DA, Beecroft ML, Wilson DM, Brennan BG, Rice SC. Randomized trial of a ''stage-of-change'' oriented smoking cessation intervention in infertile and pregnant women. Fertil Steril 2000;74:498–503.
5. ACOG Committee on Health Care for Under deserved Women; ACOG Committee on Obstetric Practice. ACOG committee opinion. Number 316, October 2005. Smoking cessation during pregnancy. Obstet Gynecol 2005;106:883–8.

6. Roth LK, Taylor HS. Risks of smoking to reproductive health: assessment of women's knowledge. Am J Obstet Gynecol 2001;184:934–9.
7. Hughes EG, Brennan BG. Does cigarette smoking impair natural or assisted fecundity? Fertil Steril 1996;66:679–89.
8. Augood C, Duckitt K, Templeton AA. Smoking and female infertility: a systematic review and meta-analysis. Hum Reprod 1998;13:1532–9.
9. Weisberg E. Smoking and reproductive health. Clin Reprod Fertil 1985;3:175–86.
10. Stillman RJ, Rosenberg MJ, Sachs BP. Smoking and reproduction. Fertil Steril 1986;46:545–66.
11. Fredricsson B, Gilljam H. Smoking and reproduction. Short and long term effects and benefits of smoking cessation. Acta Obstet Gynecol Scand 1992;71:580–92.
12. Hull MG, North K, Taylor H, Farrow A, Ford WC. Delayed conception and active and passive smoking. The Avon Longitudinal Study of Pregnancy and Childhood Study Team. Fertil Steril 2000;74:725–33.
13. Radin RG, Hatch EE, Rothman KJ, Mikkelsen EM, Sorensen HT, Riis AH, et al. Active and passive smoking and fecundability in Danish pregnancy planners. Fertil Steril 2014;102:183–91.e2.
14. Mattison D, Plowchalk D, Meadows M, Miller M, Malek A, London S. The effect of smoking on oogenesis, fertilization and implantation. Semin Reprod Endocrinol 1989;7:291–304.
15. Baron JA, La Vecchia C, Levi F. The antioestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162:502–14.
16. Adena MA, Gallagher HG. Cigarette smoking and the age at menopause. Ann Hum Biol 1982;9:121–30.
17. Freeman EW, Sammel MD, Lin H, Gracia CR. Anti-Mullerian hormone as a predictor of time to menopause in late reproductive age women. J Clin Endocrinol Metab 2012:1673–80.
18. Peck JD, Quaas AM, Craig LB, Soules MR, Klein NA, Hansen KR. Lifestyle factors associated with histologically derived human ovarian non-growing follicle count in reproductive age women. Hum Reprod 2016;31:150–7.
19. Jurisicova A, Taniuchi A, Li H, Shang Y, Antenos M, Detmar J, et al. Maternal exposure to polycyclic aromatic hydrocarbons diminishes murine ovarian reserve via induction of Harakiri. J Clin Invest 2007;117:3971–8.
20. Matikainen T, Perez GI, Jurisicova A, Pru JK, Schlezinger JJ, Ryu HY, et al. Aromatic hydrocarbon receptor-driven Bax gene expression is required for premature ovarian failure caused by biohazardous environmental chemicals. Nat Genet 2001;28:355–60.
21. Matikainen TM, Moriyama T, Morita Y, Perez GI, Korsmeyer SJ, Sherr DH, et al. Ligand activation of the aromatic hydrocarbon receptor transcription factor drives Bax-dependent apoptosis in developing fetal ovarian germ cells. Endocrinology 2002;143:615–20.
22. El-Nemr A, Al-Shawaf T, Sabatini L, Wilson C, Lower AM, Grudzinskas JG. Effect of smoking on ovarian reserve and ovarian stimulation in in-vitro fertilization and embryo transfer. Hum Reprod 1998;13:2192–8.
23. Cooper GS, Baird DD, Hulka BS, Weinberg CR, Savitz DA, Hughes CL Jr. Follicle-stimulating hormone concentrations in relation to active and passive smoking. Obstet Gynecol 1995;85:407–11.
24. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. N Engl J Med 1982;307:1062–5.
25. Barbieri RL, McShane PM, Ryan KJ. Constituents of cigarette smoke inhibit human granulosa cell aromatase. Fertil Steril 1986;46:232–6.
26. Michnovicz JJ, Hershcopf RJ, Naganuma H, Bradlow HL, Fishman J. Increased 2-hydroxylation of estradiol as a possible mechanism for the anti-estrogenic effect of cigarette smoking. N Engl J Med 1986;315:1305–9.
27. Sowers MR, McConnell D, Yosef M, Jannausch ML, Harlow SD, Randolph JF Jr. Relating smoking, obesity, insulin resistance, and ovarian biomarker changes to the final menstrual period. Ann N Y Acad Sci 2010;1204:95–103.
28. Freour T, Masson D, Mirallie S, Jean M, Bach K, Dejoie T, et al. Active smoking compromises IVF outcome and affects ovarian reserve. Reprod Biomed Online 2008;16:96–102.
29. Plante BJ, Cooper GS, Baird DD, Steiner AZ. The impact of smoking on antimullerian hormone levels in women aged 38 to 50 years. Menopause 2010;17:571–6.
30. Oladipupo I, Ali T, Hein DW, Pagidas K, Bohler H, Doll MA, et al. Association between cigarette smoking and ovarian reserve among women seeking fertility care. PLOS ONE 2022;17:e0278998.
31. Butts SF, Sammel MD, Greer C, Rebbeck TR, Boorman DW, Freeman EW. Cigarettes, genetic background, and menopausal timing: the presence of single nucleotide polymorphisms in cytochrome P450 genes is associated with increased risk of natural menopause in European-American smokers. Menopause 2014;21:694–701.
32. Vine MF. Smoking and male reproduction: a review. Int J Androl 1996;19:323–37.
33. Richthoff J, Elzanaty S, Rylander L, Hagmer L, Giwercman A. Association between tobacco exposure and reproductive parameters in adolescent males. Int J Androl 2008;31:31–9.
34. Sharma R, Harlev A, Agarwal A, Esteves SC. Cigarette smoking and semen quality: a new meta-analysis examining the effect of the 2010 World Health Organization laboratory methods for the examination of human semen. Eur Urol 2016;70:635–45.
35. Bundhun PK, Janoo G, Bhurtu A, Teeluck AR, Soogund MZS, Pursun M, et al. Tobacco smoking and semen quality in infertile males: a systematic review and meta-analysis. BMC Public Health 2019;19:36.
36. Stillman RJ, editor. Seminars in reproductive endocrinology: smoking and reproductive health. New York: Thieme Medical Publishers; 1989.
37. Pasqualotto FF, Umezu FM, Salvador M, Borges E, Sobreiro BP, Pasqualotto EB. Effect of cigarette smoking on antioxidant levels and presence of leukocytospermia in infertile men: a prospective study. Fertil Steril 2008;90:278–83.
38. Said TM, Ranga G, Agarwal A. Relationship between semen quality and tobacco chewing in men undergoing infertility evaluation. Fertil Steril 2005;84:649–53.
39. Sofikitis N, Takenaka M, Kanakas N, Papadopoulos H, Yamamoto Y, Drakakis P, et al. Effects of cotinine on sperm motility, membrane function, and fertilizing capacity in vitro. Urol Res 2000;28:370–5.
40. Joesbury KA, Edirisinghe WR, Phillips MR, Yovich JL. Evidence that male smoking affects the likelihood of a pregnancy following IVF treatment: application of the modified cumulative embryo score. Hum Reprod 1998;13:1506–13.
41. Zenzes MT. Smoking and reproduction: gene damage to human gametes and embryos. Hum Reprod Update 2000;6:122–31.
42. Zenzes MT, Wang P, Casper RF. Cigarette smoking may affect meiotic maturation of human oocytes. Hum Reprod 1995;10:3213–7.
43. Yang Q, Sherman SL, Hassold TJ, Allran K, Taft L, Pettay D, et al. Risk factors for trisomy 21: maternal cigarette smoking and oral contraceptive use in a population-based case-control study. Genet Med 1999;1:80–8.
44. Rubes J, Lowe X, Moore D, , II, Perreault S, Slott V, Evenson D, et al. Smoking cigarettes is associated with increased sperm disomy in teenage men. Fertil Steril 1998;70:715–23.
45. Zenzes MT, Bielecki R, Reed TE. Detection of benzo(a)pyrene diol epoxide-DNA adducts in sperm of men exposed to cigarette smoke. Fertil Steril 1999;72:330–5.
46. Fraga CG, Motchnik PA, Shigenaga MK, Helbock HJ, Jacob RA, Ames BN. Ascorbic acid protects against endogenous oxidative DNA damage in human sperm. Proc Natl Acad Sci U S A 1991;88:11003–6.
47. Zenzes MT, Puy LA, Bielecki R, Reed TE. Detection of benzo[a]pyrene diol epoxide-DNA adducts in embryos from smoking couples: evidence for transmission by spermatozoa. Mol Hum Reprod 1999;5:125–31.
48. Liu Y, Chen S, Pang D, Zhou J, Xu X, Yang S, et al. Effects of paternal exposure to cigarette smoke on sperm DNA methylation and long-term metabolic syndrome in offspring. Epigenetics Chromatin 2022;15:3, 21.
49. Winter E, Wang J, Davies MJ, Norman R. Early pregnancy loss following assisted reproductive technology treatment. Hum Reprod 2002;17:3220–3.
50. Ness RB, Grisso JA, Hirschinger N, Markovic N, Shaw LM, Day NL, et al. Cocaine and tobacco use and the risk of spontaneous abortion. N Engl J Med 1999;340:333–9.
51. Krishna K. Tobacco chewing in pregnancy. Br J Obstet Gynaecol 1978;85:726–8.
52. Gupta PC, Subramoney S. Smokeless tobacco use and risk of stillbirth: a cohort study in Mumbai, India. Epidemiology 2006;17:47–51.

53. Saraiya M, Berg CJ, Kendrick JS, Strauss LT, Atrash HK, Ahn YW. Cigarette smoking as a risk factor for ectopic pregnancy. Am J Obstet Gynecol 1998; 178:493–8.
54. Gaskins AJ, Missmer SA, Rich-Edwards JW, Williams PL, Souter I, Chavarro JE. Demographic, lifestyle, and reproductive risk factors for ectopic pregnancy. Fertil Steril 2018;110:1328–37.
55. Knoll M, Talbot P. Cigarette smoke inhibits oocyte cumulus complex pick-up by the oviduct in vitro independent of ciliary beat frequency. Reprod Toxicol 1998;12:57–68.
56. Horne AW, Brown JK, Nio-Kobayashi J, Abidin HB, Adin ZE, Boswell L, et al. The association between smoking and ectopic pregnancy: why nicotine is BAD for your fallopian tube. PLOS ONE 2014;9:e89400.
57. Storgaard L, Bonde JP, Ernst E, Spano M, Andersen CY, Frydenberg M, et al. Does smoking during pregnancy affect sons' sperm counts? Epidemiology 2003;14:278–86.
58. Polotsky AJ, Allshouse AA, Casson PR, Coutifaris C, Diamond MP, Christman GM, et al. Impact of male and female weight, smoking, and intercourse frequency on live birth in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2015;100:2405–12.
59. Aydin Y, Hassa H, Oge T, Tokgoz VY. A randomized study of simultaneous hCG administration with intrauterine insemination in stimulated cycles. Eur J Obstet Gynecol Reprod Biol 2013;170:444–8.
60. Farhi J, Orvieto R. Influence of smoking on outcome of COH and IUI in subfertile couples. J Assist Reprod Genet 2009;26:421–4.
61. Hansen KR, He AL, Styer AK, Wild RA, Butts S, Engmann L, et al. Predictors of pregnancy and live-birth in couples with unexplained infertility after ovarian stimulation-intrauterine insemination. Fertil Steril 2016;105: 1575–83.e2.
62. Huang H, Hansen KR, Factor-Litvak P, Carson SA, Guzick DS, Santoro N, et al. Predictors of pregnancy and live birth after insemination in couples with unexplained or male-factor infertility. Fertil Steril 2012;97: 959–67.
63. Thijssen A, Creemers A, Van der Elst W, Creemers E, Vandormael E, Dhont N, et al. Predictive value of different covariates influencing pregnancy rate following intrauterine insemination with homologous semen: a prospective cohort study. Reprod Biomed Online 2017;34:463–72.
64. Thijssen A, Creemers A, Van der Elst W, Creemers E, Vandormael E, Dhont N, et al. Predictive factors influencing pregnancy rates after intrauterine insemination with frozen donor semen: a prospective cohort study. Reprod Biomed Online 2017;34:590–7.
65. Feichtinger W, Papalambrou K, Poehl M, Krischker U, Neumann K. Smoking and in vitro fertilization: a meta-analysis. J Assist Reprod Genet 1997; 14:596–9.
66. Budani MC, Fensore S, Di Marzio M, Tiboni GM. Cigarette smoking impairs clinical outcomes of assisted reproductive technologies: a meta-analysis of the literature. Reprod Toxicol 2018;80:49–59.
67. Zhang RP, Zhao WZ, Chai BB, Wang QY, Yu CH, Wang HY, et al. The effects of maternal cigarette smoking on pregnancy outcomes using assisted reproduction technologies: an updated meta-analysis. J Gynecol Obstet Hum Reprod 2018;47:461–8.
68. Soares SR, Simon C, Remohi J, Pellicer A. Cigarette smoking affects uterine receptiveness. Hum Reprod 2007;22:543–7.
69. Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Cigarette smoking as a risk factor for ectopic pregnancy. Hum Reprod 2001;16:1389–90.
70. Waylen AL, Metwally M, Jones GL, Wilkinson AJ, Ledger WL. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. Hum Reprod Update 2009;15:31–44.
71. Van Voorhis BJ, Dawson JD, Stovall DW, Sparks AE, Syrop CH. The effects of smoking on ovarian function and fertility during assisted reproduction cycles. Obstet Gynecol 1996;88:785–91.
72. Sterzik K, Strehler E, De Santo M, Trumpp N, Abt M, Rosenbusch B, et al. Influence of smoking on fertility in women attending an in vitro fertilization program. Fertil Steril 1996;65:810–4.
73. Barbieri RL, Sluss PM, Powers RD, McShane PM, Vitonis A, Ginsburg E, et al. Association of body mass index, age, and cigarette smoking with serum testosterone levels in cycling women undergoing in vitro fertilization. Fertil Steril 2005;83:302–8.
74. Shiloh H, LahavBaratz S, Koifman M, Ishai D, Bidder D, Weiner-Meganzi Z, et al. The impact of cigarette smoking on zona pellucida thickness of oocytes and embryos prior to transfer into the uterine cavity. Hum Reprod 2004;19:157–9.
75. Gruber I, Just A, Birner M, Losch A. Effect of a woman's smoking status on oocyte, zygote, and day 3 pre-embryo quality in in vitro fertilization and embryo transfer program. Fertil Steril 2008;90:1249–52.
76. Sharara FI, Beatse SN, Leonardi MR, Navot D, Scott RT Jr. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test. Fertil Steril 1994;62:257–62.
77. Zenzes MT, Reed TE, Casper RF. Effects of cigarette smoking and age on the maturation of human oocytes. Hum Reprod 1997;12:1736–41.
78. Zenzes MT, Krishnan S, Krishnan B, Zhang H, Casper RF. Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. Fertil Steril 1995;64:599–603.
79. Paszkowski T, Clarke RN, Hornstein MD. Smoking induces oxidative stress inside the graafian follicle. Hum Reprod 2002;17:921–5.
80. Zenzes MT, Reed TE, Wang P, Klein J. Cotinine, a major metabolite of nicotine, is detectable in follicular fluids of passive smokers in in vitro fertilization therapy. Fertil Steril 1996;66:614–9.
81. Neal MS, Hughes EG, Holloway AC, Foster WG. Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. Hum Reprod 2005;20:2531–5.
82. Oostingh EC, Koster MPH, van Dijk MR, Willemsen SP, Broekmans FJM, Hoek A, et al. First effective mHealth nutrition and lifestyle coaching program for subfertile couples undergoing in vitro fertilization treatment: a single-blinded multicenter randomized controlled trial. Fertil Steril 2020; 114:945–54.
83. National Cancer Institute. Tobacco and the clinician: interventions for medical and dental practice: Monograph 5 of smoking and tobacco control series. Bethesda, MD: United States Department of Health and Human Services, National Institutes of Health; 1998 [publication no 95–3693].
84. US Public Health Service. A clinical practice guideline for treating tobacco use and dependence: A US Public Health Service report. Rockville, MD: United States Department of Health and Human Services, Public Health Service; 2000.
85. Sofikitis N, Miyagawa I, Dimitriadis D, Zavos P, Sikka S, Hellstrom W. Effects of smoking on testicular function, semen quality and sperm fertilizing capacity. J Urol 1995;154:1030–4.
86. Windsor R, Oncken C, HenningField J, Hartmann K, Edwards N. Behavioral and pharmacological treatment methods for pregnant smokers: issues for clinical practice. J Am Med Womens Assoc (1972) 2000;55:304–10.
87. Okuyemi KS, Ahluwalia JS, Harris KJ. Pharmacotherapy of smoking cessation. Arch Fam Med 2000;9:270–81.
88. Hays JT, Ebbert JO. Varenicline for tobacco dependence. N Engl J Med 2008;359:2018–24.
89. Cahill K, Steves S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;2013:CD009329.
90. Briggs GG, Freeman RK, Yaffe SJ. Bupropion. Drugs in pregnancy and lactation. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2008.
91. Alwan S, Reefhuis J, Botto LD, Rasmussen SA, Correa A, Friedman JM, et al. Maternal use of bupropion and risk for congenital heart defects. Am J Obstet Gynecol 2010;203:52.e1.
92. Cole JA, Modell JG, Haight BR, Cosmatos IS, Stoler JM, Walker AM. Bupropion in pregnancy and the prevalence of congenital malformations. Pharmacoepidemiol Drug Saf 2007;16:474–84.
93. Thyagarajan V, Robin Clifford C, Wurst KE, Ephross SA, Seeger JD. Bupropion therapy in pregnancy and the occurrence of cardiovascular malformations in infants. Pharmacoepidemiol Drug Saf 2012;21:1240.
94. Swamy GK, Roelands JJ, Peterson BL, Fish LJ, Oncken CA, Pletsch PK, et al. Predictors of adverse events among pregnant smokers exposed in a nicotine replacement therapy trial. Am J Obstet Gynecol 2009;201:354.e1, 7.
95. Cooper S, Taggar J, Lewis S, Marlow N, Dickinson A, Whitemore R, et al. Effect of nicotine patches in pregnancy on infant and maternal outcomes at 2 years: follow-up from the randomised, double-blind, placebo-controlled SNAP trial. Lancet Respir Med 2014;2:728–37.

96. Dhalwani NN, Szatkowski L, Coleman T, Fiaschi L, Tata LJ. Nicotine replacement therapy in pregnancy and major congenital anomalies in offspring. Pediatrics 2015;135:859–67.
97. Pedersen L, Petronis KR, Nørgaard M, Mo J, Frøslev T, Stephansson O, et al. Risk of adverse birth outcomes after maternal varenicline use: a population-based observational study in Denmark and Sweden. Pharmacoepidemiol Drug Saf 2020;29:94–102.
98. Tran DT, Preen DB, Einarsdottir K, Kemp-Casey A, Randall D, Jorm LR, et al. Use of smoking cessation pharmacotherapies during pregnancy is not associated with increased risk of adverse pregnancy outcomes: a population-based cohort study. BMC Med 2020;18:15.
99. US Preventive Services Task Force, Krist AH, Davidson KW, Mangione CM, Barry MJ, Cabana M, et al. Interventions for tobacco smoking cessation in adults, including pregnant persons: US Preventive Services Task Force recommendation statement. JAMA 2021;325:265–79.
100. Howe G, Westhoff C, Vessey M, Yeates D. Effects of age, cigarette smoking, and other factors on fertility: Findings in a large prospective study. Br Med J (Clin Res Ed) 1985;290:1697–700.
101. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am J Epidemiol 1997; 146:32–41.
102. World Health Organization. Tobacco: E-cigarettes 2020. Available at: https://www.who.int/news-room/questions-and-answers/item/tobacco-e-cigarettes. Accessed March 17, 2023.
103. World Health Organization. Electronic nicotine and non-nicotine delivery systems: A brief Copenhagen, Denmark: World Health Organization. Available at: https://www.euro.who.int/en/health-topics/disease-prevention/tobacco/publications/2020/electronic-nicotine-and-non-nicotine-delivery-systems-a-brief-2020. Accessed March 17, 2023.
104. Popova L, Owusu D, Weaver SR, Kemp CB, Mertz CK, Pechacek TF, et al. Affect, risk perception, and the use of cigarettes and e-cigarettes: a population study of U.S. adults. BMC Public Health 2018;18:395.
105. Ghebreyesus TA. Progress in beating the tobacco epidemic. Lancet 2019; 394:548–9.
106. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A Randomized Trial of E-Cigarettes versus nicotine-replacement therapy. N Engl J Med 2019;380:629–37.
107. Centers for Disease Control and Prevention National Center for Chronic Disease Prevention and Health Promotion. Outbreak of lung injury associated with the use of e-cigarette, or vaping, products. Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.htmlm. Accessed March 17, 2023.
108. Yang J, Ma Z. Research progress on the effects of nickel on hormone secretion in the endocrine axis and on target organs. Ecotoxicol Environ Saf 2021;213:112034.
109. Lopez-Botella A, Velasco I, Acien M, Saez-Espinosa P, Todoli-Torro JL, Sanchez-Romero R, et al. Impact of heavy metals on human male fertility-an overview. Antioxidants (Basel) 2021;10:1473.
110. Taskinen HK, Kyyrönen P, Sallmén M, Virtanen SV, Liukkonen TA, Huida O, et al. Reduced fertility among female wood workers exposed to formaldehyde. Am J Ind Med 1999;36:206–12.
111. Duong A, Steinmaus C, McHale CM, Vaughan CP, Zhang L. Reproductive and developmental toxicity of formaldehyde: a systematic review. Mutat Res 2011;728:118–38.
112. Szumilas K, Szumilas P, Grzywacz A, Wilk A. The effects of e-cigarette vapor components on the morphology and function of the male and female reproductive systems: a systematic review. Int J Environ Res Public Health 2020;17:6152.
113. Wetendorf M, Randall LT, Lemma MT, Hurr SH, Pawlak JB, Tarran R, et al. E-cigarette exposure delays implantation and causes reduced weight gain in female offspring exposed in utero. J Endocr Soc 2019;3:1907–16.
114. Raez-Villanueva S, Ma C, Kleiboer S, Holloway AC. The effects of electronic cigarette vapor on placental trophoblast cell function. Reprod Toxicol 2018;81:115–21.
115. Harlow AF, Hatch EE, Wesselink AK, Rothman KJ, Wise LA. Electronic cigarettes and fecundability: results from a prospective preconception cohort study. Am J Epidemiol 2021;190:353–61.
116. Corona G, Sansone A, Pallotti F, Ferlin A, Pivonello R, Isidori AM, et al. People smoke for nicotine, but lose sexual and reproductive health for tar: a narrative review on the effect of cigarette smoking on male sexuality and reproduction. J Endocrinol Invest 2020;43:1391–408.
117. Harte CB, Meston CM. Acute effects of nicotine on physiological and subjective sexual arousal in nonsmoking men: a randomized, double-blind, placebo-controlled trial. J Sex Med 2008;5:110–21.
118. Bjurlin MA, Kamecki H, Gordon T, Krajewski W, Matulewicz RS, Malkiewicz B, et al. Alternative tobacco products use and its impact on urologic health – will the lesser evil still be evil? A commentary and review of literature. Cent Eur J Urol 2021;74:152–60.
119. El Golli N, Rahali D, Jrad-Lamine A, Dallagi Y, Jallouli M, Bdiri Y, et al. Impact of electronic-cigarette refill liquid on rat testis. Toxicol Mech Methods 2016;26:427–34.
120. Rahali D, Jrad-Lamine A, Dallagi Y, Bdiri Y, Ba N, El May M, et al. Semen parameter alteration, histological changes and role of oxidative stress in adult rat epididymis on exposure to electronic cigarette refill liquid. Chin J Physiol 2018;61:75–84.
121. Holmboe SA, Priskorn L, Jensen TK, Skakkebaek NE, Andersson AM, Jorgensen N. Use of e-cigarettes associated with lower sperm counts in a cross-sectional study of young men from the general population. Hum Reprod 2020;35:1693–701.
122. Orzabal M, Ramadoss J. Impact of electronic cigarette aerosols on pregnancy and early development. Curr Opin Toxicol 2019;14:14–20.
123. Alshareef M, Alrafiah A, Abed S, Basingab F, Alrofaidi A. Effect of e-cigarette flavoring agents on the neural retina of chick embryo: histological and gene expression study. Folia Histochem Cytobiol 2021;59:245–58.
124. Massarsky A, Abdel A, Glazer L, Levin ED, Di Giulio RT. Exposure to 1,2-propanediol impacts early development of zebrafish (Danio rerio) and induces hyperactivity. Zebrafish 2017;14:216–22.
125. Chang YS, Park SM, Rah YC, Han EJ, Koun SI, Chang J, et al. In vivo assessment of the toxicity of electronic cigarettes to zebrafish (Danio rerio) embryos, following gestational exposure, in terms of mortality, developmental toxicity, and hair cell damage: toxicity of E-cigs to zebrafish embryos. Hum Exp Toxicol 2021;40:148–57.
126. El-Merhie N, Kruger A, Uliczka K, Papenmeier S, Roeder T, Rabe KF, et al. Sex dependent effect of maternal e-nicotine on F1 Drosophila development and airways. Sci Rep 2021;11:4441.
127. Bednarczuk N, Williams EE, Dassios T, Greenough A. Nicotine replacement therapy and e-cigarettes in pregnancy and infant respiratory outcomes. Early Hum Dev 2022;164:105509.
128. Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. Reprod Toxicol 2012;34:529–37.
129. American College of Obstetricians and Gynecologists (ACOG). Lung injury associated with e-cigarettes ("vaping"). Available at: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2019/10/lung-injury-associated-with-e-cigarettes-vaping#:~:text=The%20American%20College%20of%20Obstetricians,do%20not%20use%20tobacco%20products. Accessed March 17, 2023.
130. Kapaya M, D'Angelo DV, Tong VT, England L, Ruffo N, Cox S, et al. Use of electronic vapor products before, during, and after pregnancy among women with a recent live birth - Oklahoma and Texas, 2015. MMWR Morb Mortal Wkly Rep 2019;68:189–94.
131. Wagner NJ, Camerota M, Propper C. Prevalence and perceptions of electronic cigarette use during pregnancy. Matern Child Health J 2017;21: 1655–61.
132. Dobbs PD, Lu Y, Maness S, Coleman L, Johnson A, Metz S, et al. Gestational women's perceptions about the harms of cigarette and e-cigarette use during pregnancy. Matern Child Health J 2021;25:1209–20.
133. Bowker K, Orton S, Cooper S, Naughton F, Whitemore R, Lewis S, et al. Views on and experiences of electronic cigarettes: a qualitative study of women who are pregnant or have recently given birth. BMC Pregnancy Childbirth 2018;18:233.
134. Whittington JR, Simmons PM, Phillips AM, Gammill SK, Cen R, Magann EF, et al. The use of electronic cigarettes in pregnancy: a review of the literature. Obstet Gynecol Surv 2018;73:544–9.

135. Regan AK, Pereira G. Patterns of combustible and electronic cigarette use during pregnancy and associated pregnancy outcomes. Sci Rep 2021;11:13508.
136. Savitz DA. Invited commentary: the epidemiology of electronic cigarettes and reproductive health begins. Am J Epidemiol 2021;190:362–4.
137. Cardenas VM, Fischbach LA, Chowdhury P. The use of electronic nicotine delivery systems during pregnancy and the reproductive outcomes: a systematic review of the literature. Tob Induc Dis 2019;17:52.
138. McDonnell BP, Dicker P, Regan CL. Electronic cigarettes and obstetric outcomes: a prospective observational study. BJOG 2020;127:750–6.
139. Burrage EN, Aboaziza E, Hare L, Reppert S, Moore J, Goldsmith WT, et al. Long-term cerebrovascular dysfunction in the offspring from maternal electronic cigarette use during pregnancy. Am J Physiol Heart Circ Physiol 2021;321:H339–52.
140. Sailer S, Sebastiani G, Andreu-Fernandez V, Garcia-Algar O. Impact of nicotine replacement and electronic nicotine delivery systems on fetal brain development. Int J Environ Res Public Health 2019;16:5113.
141. Substance Abuse and Mental Health Services Administration. "Key substance use and mental health indicators in the United States: results from the 2019 National Survey on Drug Use and Health,.". Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration; 2020.
142. National Conference of State Legislatures NCSL. NCSL state medical cannabis laws [internet]. Available at: https://www.ncsl.org/research/civil-and-criminal-justice/marijuana-overview.aspx. Accessed March 17, 2023.
143. Mumford SL, Flannagan KS, Radoc JG, Sjaarda LA, Zolton JR, Metz TD, et al. Cannabis use while trying to conceive: a prospective cohort study evaluating associations with fecundability, live birth and pregnancy loss. Hum Reprod 2021;36:1405–15.
144. Ko JY, Coy KC, Haight SC, Haegerich TM, Williams L, Cox S, et al. Characteristics of marijuana use during pregnancy— eight states, pregnancy risk assessment monitoring system, 2017. MMWR Morb Mortal Wkly Rep 2020;69:1058–63.
145. Young-Wolff KC, Sarovar V, Tucker LY, Conway A, Alexeeff S, Weisner C, et al. Self-reported daily, weekly, and monthly cannabis use among women before and during pregnancy. JAMA Netw Open 2019;2:e196471.
146. Volkow ND, Han B, Compton WM, McCance-Katz EF. Self-reported medical and nonmedical cannabis use among pregnant women in the United States. JAMA 2019;322:167–9.
147. Hehemann MC, Raheem OA, Rajanahally S, Holt S, Chen T, Fustok JN, et al. Evaluation of the impact of marijuana use on semen quality: a prospective analysis. Ther Adv Urol 2021;13:17562872211032484.
148. Wise LA, Wesselink AK, Hatch EE, Weuve J, Murray EJ, Wang TR, et al. Changes in behavior with increasing pregnancy attempt time: a prospective cohort study. Available at: Epidemiology 2020;31:659–67 https://journals.lww.com/10.1097/EDE.0000000000001220. Accessed March 17, 2023.
149. Har-Gil E, Heled A, Dixon M, Ahamed AMS, Bentov Y. The relationship between cannabis use and IVF outcome-a cohort study. J Cannabis Res 2021;3:42.
150. Nassan FL, Arvizu M, Mínguez-Alarcón L, Gaskins AJ, Williams PL, Petrozza JC, et al. Marijuana smoking and outcomes of infertility treatment with assisted reproductive technologies. Hum Reprod 2019;34:1818–29.
151. Klonoff-Cohen HS, Natarajan L, Chen RV. A prospective study of the effects of female and male marijuana use on in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) outcomes. Am J Obstet Gynecol 2006;194:369–76.
152. Jordan T, Ngo B, Jones CA. The use of cannabis and perceptions of its effect on fertility among infertility patients. Hum Reprod Open 2020;2020:hoz041.
153. Chang JC, Tarr JA, Holland CL, De Genna NM, Richardson GA, Rodriguez KL, et al. Beliefs and attitudes regarding prenatal marijuana use: perspectives of pregnant women who report use. Drug Alcohol Depend 2019;196:14–20.
154. Mark K, Gryczynski J, Axenfeld E, Schwartz RP, Terplan M. Pregnant women's current and intended cannabis use in relation to their views toward legalization and knowledge of potential harm. J Addict Med 2017;11:211–6.
155. Bayrampour H, Zahradnik M, Lisonkova S, Janssen P. Women's perspectives about cannabis use during pregnancy and the postpartum period: an integrative review. Prev Med 2019;119:17–23.
156. Carroll K, Pottinger A, Jackson M. Associations between marijuana use and sperm quality in jamaican men: implications for the subfertile male. West Indian Med J 2017;66:569–75.
157. Ryan SA, Ammerman SD, O'Connor ME. Committee On Substance Use And Prevention, Section On Breastfeeding, Gonzalez L, et al. Marijuana use during pregnancy and breastfeeding: implications for neonatal and childhood outcomes. Pediatric 2018;142:e20181889.
158. ACOG. Committee Opinion No. 722. Marijuana use during pregnancy and lactation. Obstet Gynecol 2017;130:e205.
159. Mendelson JH, Mello NK, Ellingboe J, Skupny AS, Lex BW, Griffin M. Marihuana smoking suppresses luteinizing hormone in women. J Pharmacol Exp Ther 1986;237:862–6.
160. Block RI, Farinpour R, Schlechte JA. Effects of chronic marijuana use on testosterone, luteinizing hormone, follicle stimulating hormone, prolactin and cortisol in men and women. Drug Alcohol Depend 1991;28:121–8.
161. White AJ, Sandler DP, D'Aloisio AA, Stanczyk F, Whitworth KW, Baird DD, et al. Anti-Müllerian hormone in relation to tobacco and marijuana use and sources of indoor heating/cooking. Fertil Steril 2016;106:723–30.
162. Mendelson JH, Mello NK. Effects of marijuana on neuroendocrine hormones in human males and females. NIDA Res Monogr 1984;44:97–114.
163. Cushman P. Plasma testosterone levels in healthy male marijuana smokers. Am J Drug Alcohol Abuse 1975;2:269–75.
164. Kolodny RC, Masters WH, Kolodner RM, Toro G. Depression of plasma testosterone levels after chronic intensive marihuana use. N Engl J Med 1974;290:872–4.
165. Thistle JE, Graubard BI, Braunlin M, Vesper H, Trabert B, Cook MB, et al. Marijuana use and serum testosterone concentrations among U.S. males. Andrology 2017;5:732–8.
166. Gundersen TD, Jørgensen N, Andersson AM, Bang AK, Nordkap L, Skakkebæk NE, et al. Association between use of marijuana and male reproductive hormones and semen quality: a study among 1,215 healthy young men. Am J Epidemiol 2015;182:473–81.
167. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. Epidemiology 1990;1:195–200.
168. Jukic AMZ, Weinberg CR, Baird DD, Wilcox AJ. Life-style and reproductive factors associated with follicular phase length. J Womens Health (Larchmt) 2007;16:1340–7.
169. Lammert S, Harrison K, Tosun N, Allen S. Menstrual cycle in women who co-use marijuana and tobacco. J Addict Med 2018;12:207–11.
170. Hembree WC, Nahas GG, Zeidenberg P, Huang HF. Changes in human spermatozoa associated with high dose marihuana smoking. Adv Biosci 1978;22–23:429–39.
171. Pacey AA, Povey AC, Clyma JA, McNamee R, Moore HD, Baillie H, et al. Modifiable and non-modifiable risk factors for poor sperm morphology. Hum Reprod 2014;29:1629–36.
172. Kasman AM, Thoma ME, McLain AC, Eisenberg ML. Association between use of marijuana and time to pregnancy in men and women: findings from the National Survey of Family Growth. Fertil Steril 2018;109:866–71.
173. Joesoef MR, Beral V, Aral SO, Rolfs RT, Cramer DW. Fertility and use of cigarettes, alcohol, marijuana, and cocaine. Ann Epidemiol 1993;3:592–4.

Consumo de tabaco o marihuana e infertilidad: opinión de un comité.

Comité de Práctica de la Sociedad Americana de Medicina Reproductiva

En Estados Unidos, aproximadamente el 21% de los adultos declara consumir algún tipo de tabaco, aunque el 18% declara consumir marihuana. Aunque el impacto negativo del consumo de tabaco en el embarazo está bien documentado, el impacto del tabaco y la marihuana en la fertilidad y la reproducción está menos claro. Esta opinión del comité revisa los posibles efectos nocivos del consumo de tabaco, nicotina y marihuana sobre la concepción, la dinámica folicular ovárica, los parámetros espermáticos, las mutaciones de gametos, el embarazo precoz y los resultados de la tecnología de reproducción asistida. También revisa el estado actual de las estrategias para dejar de fumar tabaco. Este documento sustituye al documento del Comité de la Sociedad Americana para la Práctica de la Medicina Reproductiva de 2018 titulado Fumar e infertilidad: una opinión del comité.