Lisa J. Zhang, Jeffrey Roberts, MD, FRCSC, Caitlin Dunne, MD, FRCSC

Optimizing fertility Part 2: Environmental toxins

This second article in a two-part series examines how exposure to caffeine, alcohol, tobacco, vaping, cannabis, pesticides, plastics, and mercury can affect natural fertility.

ABSTRACT: Environmental toxins have the potential to damage sperm, eggs, and the developing fetus. Exposure to common substances like alcohol, tobacco, cannabis, caffeine, and plastics, for example, can be controlled prior to conception to mitigate their negative effects on fertility. There is conflicting literature on caffeine and alcohol, including the recommendation that patients should limit their consumption of each to two servings per day. Evidence suggests that patients should avoid smoking and using electronic cigarettes and cannabis when trying to conceive. Environmental toxins such as plasticizers and mercury appear to have a negative effect on fertility and should also be avoided. Couples who are considering pregnancy should limit their exposure to toxins and follow evidence-based recommendations that optimize their fertility.

Ms Zhang is a medical student at the University of British Columbia. Dr Roberts is a clinical assistant professor in the Department of Obstetrics and Gynaecology at the University of British Columbia and a co-founder/director of the Pacific Centre for Reproductive Medicine. Dr Dunne is a clinical assistant professor in the Department of Obstetrics and Gynaecology at the University of British Columbia and a co-director of the Pacific Centre for Reproductive Medicine.

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Infertility is defined as the inability to conceive after 1 year of unprotected intercourse, and it affects approximately 12% to 15% of couples.[1] Given that most couples achieve pregnancy within the first 3 to 6 months of trying to conceive, it is understandable that some patients become discouraged when they encounter unanticipated difficulties with the process.[1] Many couples will go online to find information on how to boost their natural fertility before meeting with a community physician, and will often do so much earlier than the 12-month mark. Initiating a dialogue with patients about making healthy lifestyle choices to optimize conception may help avert frustration and misinformation. In Part 1, we reviewed the current literature on how coital practices, diet, body weight, and exercise can affect a couple's natural fecundability. Here in Part 2, we review the available evidence on the effects of lifestyle risk factors and environmental toxins on natural fertility.

Moderate caffeine consumption of one to two cups of coffee per day before or during pregnancy does not have any apparent adverse effects on fertility or pregnancy outcomes.

Caffeine

Caffeine is a pharmacologically active substance that is widely consumed by many individuals as part of their daily routine. It is considered to be relatively harmless, and its consumption has even been associated with numerous health benefits, including reduced all-cause mortality and reduced cancer risk.[2] However, in the context of fertility, there are contradicting results. An excess of caffeine (> 500 mg/day) has been related to reduced fertility, with a significantly increased odds ratio of 1.45 (95% CI, 1.03-2.04) for subfecundity.[3] A prospective study demonstrated that women who consumed > 200 mg of caffeine had a greater than double risk of miscarriage than women who did not consume caffeine (RR 2.23; 95% CI, 1.34-3.69).[4] In contrast, a recent prospective cohort study of 1708 women found that women who were undergoing intrauterine insemination treatment and who drank one to five cups of coffee per day were more likely to achieve clinical pregnancy (RR 1.49; 95% CI, 1.05-2.11) and live birth (RR 1.53; 95% CI, 1.06-2.21) than were coffee abstainers.[5] Furthermore, a randomized controlled trial that assigned decaffeinated and caffeinated beverages to pregnant women did not show a significant difference in the length of gestation or infant birth weight between groups.[6] Given the current literature, the American Society for Reproductive Medicine states that moderate caffeine consumption of one to two cups of coffee per day before or during pregnancy does not have any apparent adverse effects on fertility or pregnancy outcomes.[1]

The literature on caffeine's effect on male fertility is inconsistent and inconclusive. Caffeine has been theorized to increase the risk of aneuploidy and DNA breaks in sperm, but clinical results contradict this.[7] Men's consumption of coffee has been associated with prolonged time to pregnancy in some studies, but no associations were found in others.[7] One systematic review reported potential negative effects of caffeine-containing soft drinks on semen volume, count, and concentration, but the authors also presented studies that did not find any evidence to support this claim.[7]

Alcohol

Alcohol has clear deleterious effects on many aspects of health. Excessive use of alcohol is well known to increase the risk of cancer, stroke, heart failure, and death, but the effects on fertility are less conclusive. Some studies have reported no relationship between alcohol consumption and fecundability, whereas others have shown evidence of a significant association. A prospective study that examined 6120 women who were not receiving fertility treatments did not find evidence of a relationship between moderate alcohol consumption and fecundability.[8] Another recent study of 1708 women showed that low to moderate weekly alcohol intake was not significantly associated with achieving clinical pregnancy or live birth following infertility treatments.[9]

Conversely, some studies have demonstrated significant declines in fertility associated with alcohol consumption. A prospective survey of 7393 women found that heavy alcohol consumption (> 140 g of alcohol per week) was associated with a higher risk of infertility when compared with moderate consumption (50 to 140 g per week) (RR of 1.59, 95% CI, 1.09-2.31).[10] Women who consumed less than 50 g of alcohol per week had a significantly lower risk of infertility than women who were heavy consumers (RR 0.64, 95% CI, 0.46-0.90).[10]

Even low levels of alcohol consumption have been shown to reduce fertility. In a study of couples who were trying to achieve their first pregnancy, women who consumed one to five alcoholic drinks per week had an odds ratio of 0.61 (95% CI, 0.40-0.93) of achieving pregnancy when compared with women who did not consume alcohol.[11] The effects were even more significant in women who consumed more than 10 drinks per week (OR 0.34, 95% CI, 0.22-0.52).[11]

A study that examined the intake of various alcohols and time to conception among 29 844 women found that those who preferred wine had a shorter wait time to conception than non-wine drinkers, while there was no relationship between beer consumption and time to conception.[12] There was a weak J-shaped relationship associated with the consumption of spirits and wait time to conception: the moderate intake group had shorter wait times, while the higher intake group had longer wait times.

There is substantial evidence of the pernicious effects smoking has on both the female and male reproductive organs.

The American Society for Reproductive Medicine recommends no more than two drinks of alcohol per day when trying to conceive, but it is important to note that there is no safe level of alcohol consumption when pregnant.[1]

There is no strong evidence that alcohol affects men's sperm. No significant association has been found between alcohol and seminal volume, sperm concentration, or percentage of motile spermatozoa.[13]

Smoking

Cigarette smoke contains numerous toxic components, including nicotine, carbon monoxide, and cyanide.[14] The effects of smoking are not limited to the oropharynx and lungs. There is substantial evidence of the pernicious effects smoking has on both the female and male reproductive organs.

A meta-analysis found a significant association between smoking and infertility (OR 1.60; 95% CI, 1.34-1.91).[15] Among those who conceived, smokers experienced substantial delays in conception of 12 months or more compared to nonsmokers (OR 1.54; 95% CI, 1.19-2.01).[16] This delay was even evident in women who were exposed to secondhand smoke, although it was of a lesser magnitude (OR 1.14; 95% CI, 0.92-1.42).[16] There is good evidence to suggest that nonsmokers who have excessive exposure to tobacco smoke may experience reproductive consequences as significant as those experienced by smokers.[17] Smokers also have a higher risk of miscarriage (OR 1.8; 95% CI, 1.3-2.6), as well as an earlier onset of menopause by 1 to 4 years and a diminished ovarian reserve.[14] The impact of smoking on the ovaries appears to be transgenerational, as the effects have been seen in the mother, fetus, and fetal gametes.[18] Male offspring of female smokers have lower sperm concentrations.[19]

Smoking appears to have some repercussions on spermatogenesis. Genetic and epigenetic changes that are associated with smoking lead to reduced sperm function and subsequently fertility.[20] Sperm concentration is reduced on average by 22%, and sperm motility and morphology have also been found to be abnormal in smokers.[16,21] The effects on the male reproductive system are dose-dependent, but overall, there is still limited evidence of clinical infertility given that most affected parameters remain within the normal range.[16] Even so, smoking cessation and elimination of secondhand exposure should be encouraged among both men and women who are seeking to maximize their fecundability. Smoking cessation agents, including bupropion, varenicline, or combination nicotine therapy, appear to be safe as a first-line therapy for those who are ready to quit.[16]

Electronic cigarettes and vaping

Vaping and the use of electronic cigarettes or "e-cigs" are marketed as a safe alternative to smoking, and their use is increasing rapidly, especially among the younger generations. Electronic cigarettes supposedly contain fewer chemicals than cigarette smoke, but they also contain unique and novel chemicals. Diacetyl is used for flavoring purposes and has been associated with the chronic lung disease bronchiolitis obliterans.[22] The lung condition was observed in popcorn plant workers, where diacetyl is used to give popcorn its butter-like flavor; hence, the condition was coined "popcorn

lung."[22] Propylene glycol and/or glycerol functions as the smoke, "throat hit," and vehicle for nicotine.[23] It is used for ketosis in cows and appears to have limited reproductive effects, none of which have been studied in humans.[24,25]

Nicotine is the stimulant and addictive component of tobacco and electronic cigarettes; it works through the nicotinic acetylcholine receptors to increase blood pressure and heart rate and stimulate the central nervous system. It is a known teratogen and carcinogen and is highly addictive. During pregnancy, nicotine concentrates in the fetus and placenta due to its lipophilic nature.[26] It has been associated with multiple medical comorbidities in offspring, including sudden infant death syndrome, attention deficit hyperactivity disorder, substance abuse disorders, and aggressive behaviors.[27]

Given the novelty of electronic cigarettes, the literature on their effects on the reproductive system is scant and limited to animal models. One study on mice found that exposure to electronic cigarette smoke prior to conception significantly reduced fertility by causing delayed implantation of the fertilized embryo to the uterus.[28] Furthermore, exposure during pregnancy affected the growing fetus and led to significant weight reductions in female offspring. A study on rats revealed that exposure to electronic cigarette smoke induced significant malformations in spermatozoa and accelerated the degeneration of the testes.[23] More research is needed before definitive conclusions can be made, but given the current evidence, vaping should not be used as an antismoking treatment by men or women of reproductive age.

Cannabis

Since Canada's recent legalization of recreational *Cannabis sativa*, its use is now more popular than ever.[29] Whether cannabis is smoked or refined into other products, tetrahydrocannabinol (THC) is its most psychoactive component and attaches to cannabinoid receptors within the endocannabinoid system. These receptors are present in many organ systems, including both the male and female reproductive systems.[30] There is speculation that cannabis use interferes with the hypothalamic-pituitary-ovarian axis, but currently, the evidence linking its use to infertility is limited. A study published in 1990 reported that women who smoked cannabis had a slightly elevated risk of infertility due to ovulatory abnormality (RR 1.7; 95% CI, 1.0-3.0).[31] However, more recent large-scale cohort studies have failed to demonstrate an association between cannabis use and a prolonged time to pregnancy. A retrospective review found that the time ratio to pregnancy for women who never used cannabis compared to daily users was 1.08 in men (95% CI, 0.79-1.47) and 0.92 in women (95% CI, 0.43-1.95).[32] Similarly, a preconception study that tracked fertility rates and self-reported cannabis use did not find a significant relationship between female or male cannabis use and fecundability.[33]

Given the current literature it is reasonable to recommend that both male and female patients abstain from using cannabis when attempting to maximize fecundability.

One meta-analysis found that cannabis use during pregnancy was associated with an increased risk of low birth weight (RR 1.43; 95% CI, 1.27-1.62) and preterm delivery (RR 1.32; 95% CI, 1.14-1.54).[34] However, after controlling for confounding factors such as tobacco use, those risks were no longer statistically significant. The authors concluded that "the association between maternal marijuana use and adverse outcomes appears attributable to concomitant tobacco use and other confounding factors."

The literature on cannabis use and male fertility is conflicting. An in vitro study showed that sperm motility decreased dose-dependently by 2% to 21% when samples were exposed to varying concentrations of THC.[35] However, there is no evidence of an effect on clinical outcomes. A recent longitudinal study of 662 subfertile men found that men who had smoked cannabis had significantly higher sperm concentrations than men who had never smoked; however, both concentrations were within the normal reference range, and cannabis smoking was not associated with alterations in the integrity of sperm DNA.[36]

There is sufficient evidence about the effects of cannabis use for the Society of Obstetricians and Gynaecologists of Canada to advise women to avoid using cannabis when pregnant or breastfeeding. Although the effects of cannabis use on fertility are more ambiguous, given the current literature it is reasonable to recommend that both male and female patients abstain from using cannabis when attempting to maximize fecundability. A more thorough review of cannabis effects on male and female reproduction is available in the September 2019 issue of the *BC Medical Journal*.[37]

Environmental toxins

Certain environmental toxins contain endocrine-disrupting chemicals that can interfere with female and male fertility by acting on steroid receptors as both agonists and antagonists, thus disrupting hormone biosynthesis, signaling, and metabolism. Exposure to these highly persistent toxic chemicals should be avoided, especially by those trying to conceive.

Pesticides contain organochlorine compounds that are known to disrupt reproductive function. Their effects have been highlighted in agricultural workers who have had high-risk occupational exposures to these compounds. A pooled estimate from eight studies showed that the likelihood of pregnancy among this population was lower than among non-exposed populations, and was 0.89 for women (95% CI, 0.82-0.97) and 0.95 for men (95% CI, 0.84-1.08).[38] A recent prospective cohort study demonstrated that reducing dietary intake of pesticides can improve outcomes of in vitro fertilization.[39] The study classified fruits and vegetables into groups with low and high concentrations of pesticide residues. Strawberries, kale, apples, grapes, tomatoes, and green peppers were considered to have the highest concentrations. Compared to women in the lowest quartile of high-pesticide intake (< 1.0 servings/day), women in the highest quartile (2.3 servings/day) had an 18% (95% CI, 5%-30%) lower probability of clinical pregnancy and a

26% lower probability of live birth (95% CI, 13%-37%).[39] The effects of pesticides on sperm parameters have also been established: decreases in sperm concentrations and effects on sperm motility and morphology have been recorded in numerous studies.[40,41] One meta-analysis found an odds ratio of 1.98 (95% CI, 1.34-2.62) for abnormal sperm quality due to exposure to organochlorines.[41]

Another common household source of endocrine-disrupting chemicals is plasticizers. Phthalate esters are used mainly as spacers between polycarbons to make plastics soft and pliable, and they are the source of the "new car smell." However, they can also be found in cosmetics, fragrances, sunscreen, laundry detergent, bar soap, shampoo, conditioner, lotions, and toothpaste. Some phthalates have a low molecular weight and can act as endocrine disruptors. Similar to organochlorines, phthalates have been associated with a consistently increased risk of compromised sperm quality (OR 1.52; 95% CI, 1.09-1.95).[41] The use of plastics, especially #3 and #7, should be minimized, and the use of phthalate-free or alternative household products are preferred.

Bisphenol A (BPA), another frequently used plasticizer, is used in the polycarbonate plastics of bottles and sports equipment, and the coating of metal food containers such as cans and lids. BPA disrupts meiotic maturation of oocytes in mature animals, which leads to higher levels of aneuploidy.[42] BPA can have an effect at very low concentrations, and one study found detectable concentrations of BPA in most IVF patients.[43] These concentrations appeared to be consequential because they were inversely associated with the number of oocytes retrieved and peak estradiol levels.

Finally, mercury is a chemical contaminant that bioaccumulates in humans and has the potential to act as a reproductive toxin. Its widespread presence is attributable mainly to seafood consumption, although coal-burning power plants are another source. Given that there are many health benefits associated with the high consumption of a seafood diet, namely from omega-3 fatty acids like docosahexaenoic acid and eicosapentaenoic acid, the benefits may counter mercury toxicity to some degree. There is a provisional tolerable intake, which is lower in reproductive-age women than in other women. Health Canada recommends limiting servings of high-risk fish such as tuna, shark, marlin, and swordfish to 150 g or 5 oz per month.[44] The effects of mercury on the male and female reproductive systems are not directly known, but one study found that compared to fertile control subjects, higher mercury levels were recorded in both infertile males with abnormal sperm and infertile females with unexplained infertility.[45] The blood mercury concentrations of the infertile subjects were positively correlated with their seafood consumption, and the authors concluded that "higher blood mercury concentration is associated with male and female infertility."

Bisphenol A (BPA) can have an effect at very low concentrations, and one study found detectable concentrations of BPA in most IVF patients.

Summary

There are many evidence-based lifestyle changes that can optimize natural fecundability. Moderate caffeine consumption (two cups per day) and moderate alcohol consumption (one to two drinks per day) are considered safe during the preconception period. Patients should abstain from smoking, vaping, or using cannabis products in any capacity given evidence in the current literature. Patients should consider organic food options or thoroughly wash their produce before consumption. Canned food, bottled water, and fish with high mercury content should be avoided. The use of plastics should be minimized, and the use of phthalate-free or alternative household products are preferred. Part 1 of this review provides more information on lifestyle changes that can optimize natural fecundability; it focuses on the effects of coital practices, diet, body weight, and exercise on fertility. If the recommendations provided in this review fail and patients 35 years and younger are still experiencing difficulty conceiving after 12 months (or 6 months in women over 35 years), infertility investigations should be initiated and consultation with a gynecologist or fertility specialist should be considered. ■

Competing interests

Dr Dunne is a member of the *BCMJ* Editorial Board but did not participate in the review or decision making regarding this article. No competing interests have been declared.

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