Toxicology in Reproductive Endocrinology

Roohi Jeelani, MD[a,*], Martin H. Bluth, MD, PhD[b,c], Husam M. Abu-Soud, PhD[a]

KEYWORDS

• Infertility • Reproductive outcomes • Subfertility • Toxicology • Alcohol • Drugs
• Environmental exposure • Health consequences

KEY POINTS

- Fertility relies on a series of time-dependent events, which are regulated by hormones. These hormones can be altered through exposure of consumed and environmental toxins.
- Reproductive dysfunction and infertility require laboratory evaluation, which involves serum hormone measurements.
- Infertility can be treatable through various assisted reproductive technologies. These can involve retrieval of the oocytes and insemination with sperm; however, if oocyte quality itself is disrupted through exposure through toxins, there is little that can be done to improve the quality.
- There are many toxins, including environmental, prescribed and illicit that can alter reproduction in the parent as well as future generations in a dose dependant manner.
- Currently there are no guidelines on laboratory testing for illicit drugs, alcohol, or environmental toxins in the scope of fertility testing. The best method remains to counsel and explain to patients at the first visit what impact it may have on their fertility.

INTRODUCTION

Reproduction is a dynamic process involving multiple pathways and signals throughout the body. If any of these steps are dysregulated, it can potentially lead to infertility. Many toxins and illicit drugs can impact and alter any part of these pathways, leading to difficulty in conceiving. Drugs such as opiates or cocaine have been known to disrupt oocyte quality, impacting fertilization and eventual fetal development and even childhood. Indeed, during in vitro fertilization, one may use genetic screening to biopsy and test the embryo for any chromosomal abnormalities, but other than that there is no laboratory test to detect the damage certain toxins may have caused. The

Disclosure: Nothing to disclose.

[a] Department of Obstetrics and Gynecology, The C.S. Mott Center for Human Growth and Development, Wayne State University School of Medicine, 275 East Hancock, Detroit, MI 48201, USA; [b] Department of Pathology, Wayne State University School of Medicine, 540 East Canfield, Detroit, MI 48201, USA; [c] Consolidated Laboratory Management Systems, 24555 Southfield Road, Southfield, MI 48075, USA
* Corresponding author.
E-mail address: rjeelani@med.wayne.edu

Clin Lab Med 36 (2016) 709–720
http://dx.doi.org/10.1016/j.cll.2016.07.011 **labmed.theclinics.com**

best and only intervention remains to consult patients at their first prenatal or even a preconception visit to discourage and eliminate potential exposure to any harmful toxins, drugs, or alcohol exposure because it may lead to detrimental effects on the fetus and even into adulthood for the child.

TOXICOLOGY AND REPRODUCTION

Behaviors such as illicit drug use, alcohol consumption, cigarette smoking, and excessive caffeine intake can alter reproductive health and fetal outcomes. Although the association remains loose and unclear, it is thought to be through the derangement of hormonal homeostasis and deterioration of oocyte milieu. In addition, toxin exposure to a variety of naturally occurring or man-made chemicals can alter hormone levels, resulting in an alteration in reproductive potential and possible fertility. Indeed, exposure to these toxins and its consequences are still not well understood, and many gaps still persist. As of yet, there are no guidelines regarding testing for these substances and at what level if any they can have an impact on reproduction. The optimal method to prevent any adverse effects on reproduction still remains to advise patients early on in their care to completely eliminate any substances of abuse and prevent any exposure to potential harmful toxins.

Illicit Drugs

Approximately 60% to 80% of adults use alcohol, and in addition to that, approximately 10% of adults may suffer from some type of substance use to the point of addiction.[1] In many instances there appears to be even higher rates of substance abuse as seen with analysis of meconium samples from newborns. Previously published studies, in certain cohorts, showed that neonates were 31% positive for cocaine, 18% positive for opiates, and 17% positive for cannabinoids, and out of these, many of them were positive for more than one of these drugs.[2,3] It becomes difficult to point to one drug to precipitate a certain outcome because many patients are multidrug abusers as noted by the study of meconium. Opiate and cocaine use while pregnant can lead to neonatal abstinence syndrome, which can persevere for months and lead to increased risk of neurobehavioral disorders and altered central nervous system (CNS) function later on.[4]

In women, the strongest evidence of the adverse impact of cocaine on reproduction is demonstrated by adverse obstetric outcomes, which include early and late pregnancy loss and placental abruption. Reproductive disturbances in substance-abusing adult women are evidenced by menstrual abnormalities, which predominantly consist of amenorrhea in heroin abusers.[5] On the contrary, the fact that many of these women who are regular narcotic abusers achieve pregnancy and deliver implies that the degree of reproductive insult is not enough to prevent the birth of an exposed and affected baby. However, use of narcotics in women who were on the edge of being infertile may push them into the infertility zone. Previous work has established that in adult mammals opiates bind in the hypothalamus and cause inhibition of the secretion of luteinizing hormone (LH), which can lead to mild to moderate gonadal suppression.[6,7] Not only that, but these drugs can impact fertility; however, it remains difficult to attribute a particular outcome to the use of a certain drug. Drug dependence can lead to varying effects, including malnutrition, increased risk of infectious diseases, poor health care, and poor pregnancy outcomes. These patients also have increased risk of physical and verbal abuse, which also affects the probability of successful fertility and fetal health. People addicted to drugs may be so compromised that the steps essential for normal reproductive hemostasis will be adversely affected leading

to reproductive failure. Currently, no specific guidelines have been developed in the field of reproductive endocrinology and toxicology because it remains very difficult to attribute a certain level or type of drug to a particular outcome. In addition, there has been sufficient evidence that addictive substances can pose a significant threat to the developing fetus and even continue throughout the neonatal period. Many disorders have been described, including but not limited to FAS, intrauterine growth restriction, and neonatal withdrawal syndrome. These insults not only alter the fetus in utero but also have been known to have a long-term impact on them as children.

Narcotics have a harmful impact on male reproduction as well. They have been shown to alter hormonal homeostasis through exerting their primary effect on the hypothalamic-pituitary axis, thus leading to effecting the gonads and sex accessory organs.[8] Narcotics can lead to a decrease in gonadotropin secretion and cause a stimulatory effect on prolactin secretion; both of these can cause an inhibitory effect on male sexual function. Previous studies have shown that in some patients, although hormone levels may remain normal or return to baseline after cessation of opiate use, semen parameters might still be altered. Men who abuse heroin have been shown to have asthenospermia and oligospermia.[9,10] An in vitro study done using human sperm and high concentrations of cocaine demonstrated a decrease in kinematics, straight line velocity, and linearity but no impact on overall sperm motility and fertilizing capability.[11] Many men have also claimed that abuse of cocaine leads to increased libido and sexual responsiveness.[12]

In animal models, adverse effects of drug use and fertility have been shown through a significant disturbance of spermatogenesis.[6] In addition to the impact of cocaine on reproductive function and sexual behavior of male rats, there has been some evidence for detrimental effects of long-term cocaine exposure on spermatogenesis and fertility in peripubertal male rats.[13] Chronic cocaine exposure in female rhesus monkeys also led to disruption of their menstrual cycles.[7] To summarize, the impact of narcotics and illicit agents such as cocaine on fertility still remain unclear and not well studied on human subjects. However, it is clear illicit drug use by individuals attempting to conceive is harmful and has consequences to their fertility, although the exact level of impact remains unknown. Furthermore, whereas the adverse effects of exposure to narcotics and illicit agents on the fetus are known, the specific future fertility effects of developmental exposure to these offspring remain unexplored. The relationship of selective agents and their effect on female and male reproductive health as well as general obstetrics, neonatology, and pediatrics, where applicable, follow.

Alcohol

Extensive evidence has shown that excessive ethanol consumption is harmful to both nongravid and gravid women in that even small amounts of exposure can adversely affect the fetus. Alcohol remains the substance most frequently abused by pregnant women, and fetal alcohol syndrome (FAS) has been well studied as well as described.[14] FAS is characterized by intrauterine growth retardation, facial abnormalities, congenital defects, musculoskeletal abnormalities, and dysfunction of the CNS.[14] Generally speaking, the amount of alcohol consumed will proportionally impact the fetus. An average daily maternal intake of 3 oz of alcohol is sufficient to significantly increase the incidence of FAS; however, consumption of less than 1 oz per day has little or no associated increased risk of FAS.[15] When taking into account birth defects, intake of 6 drinks of ethanol per day leads to a 50% chance of birth defects, or approximately 10 times the normal.[16] On the other hand, the impact of alcohol abuse and fertility remains uncertain. A study did show that if a woman consumed one or more drinks of ethanol per week, the probability of conception was reduced by

about 50% in each menstrual cycle. The primary site of action is still not clear; however, acute effects of ethanol appear to be due to hypothalamic impacts.[17] Ethanol can act at the level of the CNS to inhibit LH secretion by the pituitary and therefore inhibit ovulation.[17] There is clear evidence of the reproductive toxicity of ethanol consumption; however, no clear testing guidelines and limitations have been developed. It is strongly advised to eliminate or cut down as much as possible on alcohol intake when attempting to achieve pregnancy.

Alcohol has been studied far more than any other substance of abuse. It has been known to have a feminizing effect on men who abuse alcohol because it is related to liver dysfunction and leads to reduced hepatic clearance of estrogens.[18] In men who consume lower amounts of ethanol, some effects on sex steroids can still occur.[19] It has been well established not only in male animals but also in humans that chronic ethanol exposure even at low levels can be associated with lower serum testosterone levels, increased levels of plasma sex hormone–binding globulin, and higher prolactin, leading to increased estrogen levels.[19] The reduction in plasma testosterone levels correlate with decreased responsiveness to human chorionic gonadotropin (hCG), alluding to the possibility that ethanol damages the Leydig cell compartment of the testis. In a more recent study, significantly reduced plasma concentrations of testosterone, LH, and follicle-stimulating hormone (FSH) were reported in male alcohol abusers.[20] Alcohol can cause significant deterioration in sperm concentration, semen volume, and sperm quality.[20,21] Adverse effects of chronic ethanol consumption on male fertility have been demonstrated in experimental animals and human studies; however, no clear correlation has yet been established.

In addition, in animal studies ethanol has been reported to inhibit ovulation and suppress plasma estradiol; progesterone levels are also suppressed. In a nonhuman primate study, female monkeys were given a 7- to 10-oz glass of alcohol a day for up to 6 months and were noted to have disruptions in reproductive function, as demonstrated by amenorrhea, uterine atrophy, decreased ovarian weights, and suppression of LH levels.[22] These clinical findings seemed to mimic the findings in clinical studies of alcoholic women. Thus, there is clear evidence of the reproductive toxic effects of chronic alcohol exposure; however, the consequences of moderate alcohol use on fertility remain unclear. Therefore, the American Society of Reproductive Medicine states, “The effects of alcohol, marijuana and other recreational drugs have not been clearly established. Nevertheless, such drug use generally should be discouraged for both men and women, particularly because they have well-documented harmful effects on the developing fetus.” In addition, because there are no clear guidelines for when and who to test, it is always recommended to discourage such behavior at the initial fertility consult.

Cannabinoids

Cannabinoids have been extensively studied both in humans and in animal models. It has been proven that it or its major psychoactive constituent, tetrahydrocannabinol (THC), causes symptoms of neurobehavioral alterations, interrupts all phases of gonadal or reproductive function, and is toxic to the fetus. In women who abuse marijuana, they were noted to have shorter menstrual cycles (26.8 days) than those who did not (28.8 days).[23–25] In addition, marijuana users had more cycles that were anovulatory or had a shorter luteal phase when compared with nonusers. THC causes suppression of plasma LH levels and appears to be the primary mechanism by which THC exposure inhibits ovulation. Because gonadotropin-releasing hormone–induced LH secretion is not impacted by exposure to THC, the action of this drug appears at the hypothalamic axis rather than the actual hypophysial site. The

antiovulatory effect of THC results from an inhibition of LH secretion that does not involve the direct blockade of LHRH (LH-releasing hormone). In addition, when evaluating the levels, they did not reveal any statistically significant differences in serum LH, FSH, estrogen, or progesterone levels between marijuana users and non-marijuana users even though there were decreased luteal phase progesterone levels. Of note, serum prolactin levels were reduced, and serum testosterone levels were noted to be increased in the marijuana users. It has been suggested that the impact of THC may vary on the hormonal status of women. In menopausal women, THC did not alter the LH levels; however, in premenopausal women, there was a suppression of LH levels during the lute phase.[26] Although no clear long-term impact on fertility has been established, it is still recommended to avoid all marijuana use when trying to achieve pregnancy.

Marijuana use can impact fertility in men by decreasing plasma testosterone levels with chronic use. In chronic marijuana users, it has been shown that they have abnormal sperm morphology, including reduced nuclear size, increased condensation of chromatin, disorganization of acrosomal structure, and absence of acrosomes.[27] A study reported decreased testosterone plasma levels in men who had been smoking marijuana for 6 months before testing. However, giving hCG to marijuana users can increase testosterone levels, which indicates a functional Leydig cell response. In addition to this, if the man has a 2-week period of abstinence following marijuana use, their testosterone levels have been shown to increase or improve from the suppression caused by this abuse.[28] However, there has been little shown on the impacts of cannabinoids on the male reproductive tract. Changes in testis function have been noted after treatment with cannabinoids.

In an animal model, more specifically in rats, seminiferous tubule degeneration and degenerative changes in spermatocytes and spermatids were seen after exposure to marijuana. In mice that were given THC for only 5 days, there was a dose-dependent increase in abnormal sperm. In female rabbits, THC administration resulted in inhibition of ovulation.[29] In female rats, THC was shown to cause a delay of onset of puberty and reduce the number of ova.[30] Also, it has been shown that marijuana agonists can interfere with implantation of the mouse embryo in vitro. There is sufficient evidence to show that THC can act directly and impact the ovary. It has been shown that THC exposure reduces ovarian responsivity to LH in experimental animal models. THC-inhibited progesterone synthesis was seen in rat luteal cell cultures in in vitro experiments; however, when this was done in vivo, daily administration of THC had no effect on plasma progesterone levels or luteal phase length.[31] Other animal studies showed that tolerance develops to the disruptive effects of THC on the primate menstrual cycle and that despite chronic use of THC, reversible suppressive effects of the drug on the menstrual cycle can occur.[32] Long-term exposure of sexually mature female rhesus monkeys to 3 weekly injections of THC resulted in a disruption of the menstrual cycle that persisted for several months. The disruption in the menstural cycle was noted by the absence of ovulation and decreased basal concentrations of gonadotropin and sex steroids levels in plasma. After several months, despite continued twice weekly administration with THC, normal cycles and hormone concentrations were restored. The restoration of a normal menstural cycle in the setting of regular THC exposure helps to explain the lack of cycle disruption in many women who are chronic users of cannabis. In addition to the impact on women, it can be safely stated that testicular and ovarian toxicity result with use of marijuana; however, the impact it has on future fertility remains unknown because their function does resume after discontinuation.

Caffeine

Caffeine, although a natural compound, has been noted to have a significantly negative impact on fertility and pregnancy. Once consumed, it can be readily absorbed and distributed throughout the body. It has been noted in saliva, breast milk, embryos, and even in the blood of neonates.[33] It is known to cause numerous amounts of biologic effects in the human, including CNS stimulation, increase in heart rate, relaxation of smooth muscles, and increased secretion of catecholamines. There are data, based both on animal and human studies, associating caffeine intake with spontaneous abortion, intrauterine growth retardation, birth defects, and possibly other toxic effects to the fetus. However, the impact of caffeine on other reproductive processes, including fertility itself, has been a focus of concern, yet there is no clear association. Biologic credibility for this theory is suggested by information that there are significant alterations in the reproductive hormone profile of users, that caffeine may hinder ovulation, and that its intake is positively correlated with sex hormone–binding globulin concentrations.[34] The impact of caffeine on human reproduction is proven by reports that show that daily consumption of the typical amount of caffeine found in a cup of coffee was associated with a 50% decrease in per menstrual cycle conception when compared with nonusers.[35] Women consuming greater quantities of caffeine had consistently lower pregnancy rates, thus demonstrating a dose-related effect. The association between ovulatory disorder infertility and consumption of caffeinated beverages failed to demonstrate any causality relationship between caffeine consumption, impaired ovulation, and decreased fertility.[35] Studies on the association between caffeine and miscarriages showed that an increase in daily caffeine intake may be associated with an increased risk of recurrent pregnancy loss. It has been shown by one study that an increased dose of daily caffeine intake of 200 mg or more during pregnancy increased the risk of miscarriage in the general population independent of pregnancy-related symptoms.[36] However, there are conflicting findings because other sources have failed to demonstrate the correlation between caffeine and miscarriage. The relationship between caffeine consumption by pregnant women and risk of miscarriage, low birth weight, preterm delivery, and congenital malformations found no evidence that caffeine consumption at moderate levels has any discernible adverse effect on pregnancy outcome.[37] It is considered that the previous warning on caffeine consumption and the risk of reproductive hazards were based on findings that gavage feeding of large doses of caffeine to rats resulted in a particularly high incidence of facial cleft palate. However, the latest review on the effects of restricted caffeine intake by mother on fetal, neonatal, and pregnancy outcome in Cochrane Database System Review found insufficient evidence to confirm or refute the effectiveness of caffeine avoidance on birth weight or other pregnancy outcomes.[36] Lack of scientific evidence showing any association between caffeine consumption and adverse effect on pregnancy outcome led the US Food and Drug Administration agency to conclude that caffeine, as currently used in foods, does not carry a health risk. However, the agency continues to recommend that pregnant women consume caffeine in moderation.

Caffeine could impact male fertility by changing sperm mobility and viability. There is a decrease in these parameters when consuming more than 699 mg/d of caffeine. In addition, a recent study showed that caffeinated soda and energy drink intake was associated with reduced fecundability in men.[38] In an animal model, male rats were shown to have decreased reproductive organ weight, sperm characteristics, LH/FSH levels, and also testicular cytoarchitecture; however, these effects were reversible after caffeine withdrawal.[39]

In summary, the data regarding the effects of caffeine on reproduction in humans are still conflicting. Although it is not possible to give a clear recommendation on specific amounts that are deemed safe for couples trying to conceive, it would be best to consume no more than 3 cups of coffee per day. This recommendation should be discussed at the first infertility visit and reassured with the patient because there is no way to monitor caffeine levels. The American College of Obstetricians and Gynecologists recommends that pregnant women limit consumption to the caffeine equivalent of 1 to 2 cups of coffee (200 mg of caffeine). Given the high prevalence of caffeine intake by women of childbearing age, it is clear that further research is required and guidelines on testing are needed.

Tobacco

Smokers expose themselves and people around them to numerous amounts of toxins and carcinogens. Cigarette smoke has many carcinogens, including, cadmium, arsenic, butane, ammonia, lead, acetone, carbon monoxide, pesticide residue, polycyclic aromatic hydrocarbons, and formaldehyde.[40] The most addictive component, nicotine, can lead to problems such as vasoconstriction, can cause decreased tissue oxygenation, remain in blood, urine, saliva, and follicular fluid, and impact other reproductive functions.[41] Previous measurements in the serum and follicular fluid of cigarette smokers show correlation with decreased pregnancy rates in women exposed to smoke as compared with nonsmokers. In addition, the presence of cadmium has also been shown in human ovaries and follicular fluid of smokers, proving that essential organs responsible for reproduction are exposed and affected by the products of tobacco smoke in smokers.[42] It has been shown that cigarette smoke can alter reproduction as evidenced by numerous animal and human studies.

Animal studies have shown that cadmium can impact cellular processes leading to chromosomal anomalies in both oocytes and embryos which can lead to a decrease in the number of oocytes, potentially alter embryo development and thus decreasing fertility. Also, many animal studies have proven that cigarette smoke leads to an increased rates of follicular destruction and accelerates ovarian aging leading to premature reproductive failure.[43] This reproductive failure has been proven by human studies showing that women who smoke have an increased loss of ovarian follicles and decreased ovarian reserve, leading to an earlier menopause[44] as well as high basal or stimulated FSH levels signifying decreased ovarian function. Cigarette smoke has also been shown to decrease human granulosa cell aromatase production, leading to decreased estrogen levels, which cause the elevated FSH.[45,46] Cigarettes can also alter meiotic maturation of oocytes, which may cause chromosomal abnormalities and alter fetal health or even cause spontaneous abortions.[47] Surveys have shown that it takes smokers longer to conceive than nonsmokers, as noted with the decrease in fertility with increasing numbers of cigarettes smoked per day. In utero exposure to cigarette smoke also can result in a decreased fecundability in the man.[48] Smoking cessation products that contain the same concentrations of nicotine can cause the same sequelae as smoking cigarettes, including risk of low birth weight, overweight offspring, insulin resistance, and hypertension.[49]

Women who smoke while being treated with assisted reproduction have decreased gonadotropin-stimulated estradiol production, resulting in fewer numbers of oocytes retrieved and resultant embryos, a 50% decrease in implantation and ongoing pregnancy rate.[50,51] Spontaneous abortion rates are also increased in these patients.[52] In addition, these patients have an increased risk of ectopic pregnancy.[53] However,

this effect is temporary, because past smokers have pregnancy rates similar to nonsmokers after 3 months of quitting.[54]

Smoking also impacts male fertility, causing decreased volume, sperm density, total count, and normal forms, although the impact of smoking might not be sufficient to impact male fertility in a functional capacity.[55] Nonetheless, evidence strongly suggests that cigarette smoking leads to a decrease in fertility and impacts assisted reproductive technology success and outcomes due to ovarian toxicity and decreased implantation rates. Because of the aforementioned, women pursuing conception should be advised to avoid exposure to cigarette smoke. Because quitting completely may be impossible for some smokers, decreasing the amount should be encouraged. Cessation of smoking is an integral part of preconception counseling and even at the first prenatal visit. Despite all these facts, no test has been established or required to test the level of nicotine in a patient's blood or other body fluids at either preconception or during pregnancy.

Endocrine Disorders and Toxicology

Polycystic ovarian syndrome (PCOS) is a common disorder characterized by features of hyperandrogenism, obesity, acanthosis nigrans, possible insulin resistance, and polycystic or enlarged ovaries on ultrasound. There is no theory behind why one may be prone to developing PCOS. One possible cause is that environmental contaminants may play a role in the development of PCOS. Environmental toxins have been noted in follicular fluid, and bisphenol A (BPA) was seen in both the serum and the follicular fluid with a concentration between 1 and 2 ng/mL fluid.[56] Serum BPA concentrations of patients with PCOS were also higher in women with PCOS when compared to aged matched controls. Interestingly, there is also a positive correlation between higher BPA and serum testosterone, androstenedione, and dehydroepiandrosterone sulfate, which are androgens and tend to be higher in PCOS patients as well.[57] This may possibly be due to the effect of androgens on the metabolism of BPA. Although there is strong evidence of higher BPA levels in patients with PCOS, the exact pathophysiology remains unknown. Further research needs to be conducted to reveal the underlying relationship between the development of PCOS and role of environmental toxins. Although patients are advised to limit exposure to environmental toxins, there are currently no laboratory screening tests nor guidelines to determine what analytes in particular, and levels of such may be detrimental to reproduction.

Endometriosis, another disease that may cause infertility or potentially subfertility, is characterized by endometrial glands and stroma outside the uterine cavity. It causes infertility and affects about 14% of women of all reproductive ages.[58] There are several theories leading to the development of endometriosis, including coelomic metaplasia, proliferation of a progenitor stem cell, or retrograde menstruation of endometrial cells.[59] Despite which theory one looks at, they all are thought to lead to the implantation and proliferation of ectopic endometrial cells outside the uterine cavity. Because this disease is estrogen dependent, the role of environmental toxins has gained much attention over the recent years. Several studies have reported a strong relationship between dioxin in the pathophysiology of endometriosis.[60,61]

Several occupations may have an increased risk of infertility due to exposure of toxins, such as those involved in the agriculture and chemical industries.[62] At the initial visit, it is crucial to ask about occupation and to counsel patients to limit interaction with any potential harmful toxins. Because there are no currently developed guidelines or laboratory tests available, counseling remains the best mode of action to improve reproductive outcomes.

SUMMARY

Human reproduction depends on a complex series of time-sensitive events. Despite the crucial and time-dependent integration of these events achieved by hormonal signaling, exogenous factors do play a role and may dysregulate this process. Because it remains almost impossible to attribute a single outcome to a single substance, as one may abuse multiple ones such as alcohol and caffeine, the crucial part lies in the dose and timing of exposures and the mechanism of action of the agent to determine the insult. It is not uncommon for many reproductive age humans to be exposed over multiple years to high doses of ethanol, opiates, cannabinoids, nicotine, and caffeine. However, exposure to environmental toxins still remains low, and the association of such toxins to reproductive health is still difficult to establish. There is strong support from data that alcohol, opiates, cannabinoids, cigarette smoke, and caffeine can negatively impact reproductive homeostasis. To this end, toxicology testing for established substances (alcohol, opioids, cannabinoids, and other illicit agents) can provide an objective understanding of a patient's ingestion and exposure habits as it relates to general health and fertility counseling, in particular. However, further research needs to be conducted to establish the levels at which select current and emerging new agents might start impacting reproductive capabilities and how toxicology laboratory tests should be incorporated into the workup and management of an infertile patient.

REFERENCES

1. Anderson K, Nisenblat V, Norman R. Lifestyle factors in people seeking infertility treatment—a review. Aust N Z J Obstet Gynaecol 2010;50(1):8–20.
2. Sadeu JC, Hughes CL, Agarwal S, et al. Alcohol, drugs, caffeine, tobacco, and environmental contaminant exposure: reproductive health consequences and clinical implications. Crit Rev Toxicol 2010;40(7):633–52.
3. Nair P, Rothblum S, Hebel R. Neonatal outcome in infants with evidence of fetal exposure to opiates, cocaine, and cannabinoids. Clin Pediatr (Phila) 1994; 33(5):280–5.
4. Finnegan LP, Wapner RJ. Your CE topic this month (no. 3). Drug abuse in pregnancy. J Pract Nurs 1984;34(2):14–23.
5. Oei J, Lui K. Management of the newborn infant affected by maternal opiates and other drugs of dependency. J Paediatr Child Health 2007;43(1–2):9–18.
6. Abel EL, Moore C, Waselewsky D, et al. Effects of cocaine hydrochloride on reproductive function and sexual behavior of male rats and on the behavior of their offspring. J Androl 1989;10(1):17–27.
7. Mello NK, Mendelson JH, Kelly M, et al. The effects of chronic cocaine self-administration on the menstrual cycle in rhesus monkeys. J Pharmacol Exp Ther 1997;281(1):70–83.
8. Smith CG. Drug effects on male sexual function. Clin Obstet Gynecol 1982;25(3): 525–31.
9. Ragni G, De Lauretis L, Bestetti O, et al. Gonadal function in male heroin and methadone addicts. Int J Androl 1988;11(2):93–100.
10. Ragni G, De Lauretis L, Gambaro V, et al. Semen evaluation in heroin and methadone addicts. Acta Eur Fertil 1985;16(4):245–9.
11. Yelian FD, Sacco AG, Ginsburg K, et al. The effects of in vitro cocaine exposure on human sperm motility, intracellular calcium, and oocyte penetration. Fertil Steril 1994;61(5):915–21.

12. Cone EJ, Kato K, Hillsgrove M. Cocaine excretion in the semen of drug users. J Anal Toxicol 1996;20(2):139–40.
13. George VK, Li H, Teloken C, et al. Effects of long-term cocaine exposure on spermatogenesis and fertility in peripubertal male rats. J Urol 1996;155(1):327–31.
14. Spohr HL, Willms J, Steinhausen HC. Fetal alcohol spectrum disorders in young adulthood. J Pediatr 2007;150(2):175–9.e1.
15. Rementeria JL, Bhatt K. Withdrawal symptoms in neonates from intrauterine exposure to diazepam. J Pediatr 1977;90(1):123–6.
16. Hakim RB, Gray RH, Zacur H. Alcohol and caffeine consumption and decreased fertility. Fertil Steril 1998;70(4):632–7.
17. Rettori V, Skelley CW, McCann SM, et al. Detrimental effects of short-term ethanol exposure on reproductive function in the female rat. Biol Reprod 1987;37(5):1089–96.
18. Lloyd CW, Williams RH. Endocrine changes associated with Laennec's cirrhosis of the liver. Am J Med 1948;4(3):315–30.
19. Lester R, Van Thiel DH. Gonadal function in chronic alcoholic men. Adv Exp Med Biol 1977;85A:399–413.
20. Van Thiel DH, Gavaler JS, Lester R, et al. Plasma estrone, prolactin, neurophysin, and sex steroid-binding globulin in chronic alcoholic men. Metabolism 1975;24(9):1015–9.
21. Kucheria K, Saxena R, Mohan D. Semen analysis in alcohol dependence syndrome. Andrologia 1985;17(6):558–63.
22. Mello NK, Bree MP, Mendelson JH, et al. Alcohol self-administration disrupts reproductive function in female macaque monkeys. Science 1983;221(4611):677–9.
23. Brents LK. Marijuana, the endocannabinoid system and the female reproductive system. Yale J Biol Med 2016;89(2):175–91.
24. Mendelson JH, Mello NK, Ellingboe J, et al. Marijuana smoking suppresses luteinizing hormone in women. J Pharmacol Exp Ther 1986;237(3):862–6.
25. Alvarez S. Do some addictions interfere with fertility? Fertil Steril 2015;103(1):22–6.
26. Mendelson JH, Cristofaro P, Ellingboe J, et al. Acute effects of marihuana on luteinizing hormone in menopausal women. Pharmacol Biochem Behav 1985;23(5):765–8.
27. Hembree WC 3rd, Nahas GG, Zeidenberg P, et al. Changes in human spermatozoa associated with high dose marihuana smoking. Adv Biosci 1978;22–23:429–39.
28. Kolodny RC, Masters WH, Kolodner RM, et al. Depression of plasma testosterone levels after chronic intensive marihuana use. N Engl J Med 1974;290(16):872–4.
29. Asch RH, Fernandez EO, Smith CG, et al. Precoital single doses of delta9-tetrahydrocannabinol block ovulation in the rabbit. Fertil Steril 1979;31(3):331–4.
30. Wenger T, Croix D, Tramu G, et al. Marijuana and reproduction. Effects on puberty and gestation in female rats. Experimental results. Ann Endocrinol (Paris) 1992;53(1):37–43 [in French].
31. Symons AM, Teale JD, Marks V. Proceedings: effect of delta9-tetrahydrocannabinol on the hypothalamic-pituitary-gonadal system in the maturing male rat. J Endocrinol 1976;68(3):43P–4P.
32. Marks BH. Delta1-tetrahydrocannabinol and luteinizing hormone secretion. Prog Brain Res 1973;39:331–8.

33. Sieber SM, Fabro S. Identification of drugs in the preimplantation blastocyst and in the plasma, uterine secretion and urine of the pregnant rabbit. J Pharmacol Exp Ther 1971;176(1):65–75.
34. Petridou E, Katsouyanni K, Spanos E, et al. Pregnancy estrogens in relation to coffee and alcohol intake. Ann Epidemiol 1992;2(3):241–7.
35. Chavarro JE, Rich-Edwards JW, Rosner BA, et al. Caffeinated and alcoholic beverage intake in relation to ovulatory disorder infertility. Epidemiology 2009; 20(3):374–81.
36. Jahanfar S, Sharifah H. Effects of restricted caffeine intake by mother on fetal, neonatal and pregnancy outcome. Cochrane Database Syst Rev 2009;(2):CD006965.
37. Leviton A, Kuban KC, Pagano M, et al. Maternal toxemia and neonatal germinal matrix hemorrhage in intubated infants less than 1751 g. Obstet Gynecol 1988; 72(4):571–6.
38. Wesselink AK, Wise LA, Rothman KJ, et al. Caffeine and caffeinated beverage consumption and fecundability in a preconception cohort. Reprod Toxicol 2016;62:39–45.
39. Oluwole OF, Salami SA, Ogunwole E, et al. Implication of caffeine consumption and recovery on the reproductive functions of adult male Wistar rats. J Basic Clin Physiol Pharmacol 2016. [Epub ahead of print].
40. Jensen JA, Goodson WH, Hopf HW, et al. Cigarette smoking decreases tissue oxygen. Arch Surg 1991;126(9):1131–4.
41. Younglai EV, Foster WG, Hughes EG, et al. Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization. Arch Environ Contam Toxicol 2002;43(1):121–6.
42. Zenzes MT, Krishnan S, Krishnan B, et al. Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers. Fertil Steril 1995;64(3):599–603.
43. Watanabe T, Shimada T, Endo A. Mutagenic effects of cadmium on mammalian oocyte chromosomes. Mutat Res 1979;67(4):349–56.
44. Mattison DR, Singh H, Takizawa K, et al. Ovarian toxicity of benzo(a)pyrene and metabolites in mice. Reprod Toxicol 1989;3(2):115–25.
45. Sharara FI, Beatse SN, Leonardi MR, et al. Cigarette smoking accelerates the development of diminished ovarian reserve as evidenced by the clomiphene citrate challenge test. Fertil Steril 1994;62(2):257–62.
46. Barbieri RL, McShane PM, Ryan KJ. Constituents of cigarette smoke inhibit human granulosa cell aromatase. Fertil Steril 1986;46(2):232–6.
47. Windham GC, Von Behren J, Waller K, et al. Exposure to environmental and mainstream tobacco smoke and risk of spontaneous abortion. Am J Epidemiol 1999; 149(3):243–7.
48. Weinberg CR, Wilcox AJ, Baird DD. Reduced fecundability in women with prenatal exposure to cigarette smoking. Am J Epidemiol 1989;129(5):1072–8.
49. Gao YJ, Holloway AC, Zeng ZH, et al. Prenatal exposure to nicotine causes postnatal obesity and altered perivascular adipose tissue function. Obes Res 2005; 13(4):687–92.
50. Van Voorhis BJ, Dawson JD, Stovall DW, et al. The effects of smoking on ovarian function and fertility during assisted reproduction cycles. Obstet Gynecol 1996; 88(5):785–91.
51. Neal MS, Hughes EG, Holloway AC, et al. Sidestream smoking is equally as damaging as mainstream smoking on IVF outcomes. Hum Reprod 2005;20(9): 2531–5.

52. Maximovich A, Beyler SA. Cigarette smoking at time of in vitro fertilization cycle initiation has negative effect on in vitro fertilization-embryo transfer success rate. J Assist Reprod Genet 1995;12(2):75–7.
53. Waylen AL, Metwally M, Jones GL, et al. Effects of cigarette smoking upon clinical outcomes of assisted reproduction: a meta-analysis. Hum Reprod Update 2009; 15(1):31–44.
54. Howe G, Westhoff C, Vessey M, et al. Effects of age, cigarette smoking, and other factors on fertility: findings in a large prospective study. Br Med J (Clin Res Ed) 1985;290(6483):1697–700.
55. Vine MF, Tse CK, Hu P, et al. Cigarette smoking and semen quality. Fertil Steril 1996;65(4):835–42.
56. Jarrell JF, Villeneuve D, Franklin C, et al. Contamination of human ovarian follicular fluid and serum by chlorinated organic compounds in three Canadian cities. CMAJ 1993;148(8):1321–7.
57. Takeuchi T, Tsutsumi O, Ikezuki Y, et al. Positive relationship between androgen and the endocrine disruptor, bisphenol A, in normal women and women with ovarian dysfunction. Endocr J 2004;51(2):165–9.
58. Chedid S, Camus M, Smitz J, et al. Comparison among different ovarian stimulation regimens for assisted procreation procedures in patients with endometriosis. Hum Reprod 1995;10(9):2406–11.
59. Halme J, Hammond MG, Hulka JF, et al. Retrograde menstruation in healthy women and in patients with endometriosis. Obstet Gynecol 1984;64(2):151–4.
60. Rier S, Foster WG. Environmental dioxins and endometriosis. Toxicol Sci 2002; 70(2):161–70.
61. Foster WG, Agarwal SK. Environmental contaminants and dietary factors in endometriosis. Ann N Y Acad Sci 2002;955:213–29 [discussion: 230–2, 396–406].
62. Anger DL, Foster WG. The link between environmental toxicant exposure and endometriosis. Front Biosci 2008;13:1578–93.