

Caffeine, alcohol, smoking, and reproductive outcomes among couples undergoing assisted reproductive technology treatments

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During the past decade, as the use of assisted reproductive technologies (ART) has continued to increase worldwide, research investigating whether modifiable lifestyle factors, such as alcohol, caffeine, and smoking, may affect ART outcomes has grown. Despite the vast literature, there is still uncertainty regarding the effects of some of these exposures on ART outcomes. The objective of this review is to summarize the epidemiologic literature on intakes of caffeine and alcohol, smoking, and reproductive outcomes among women undergoing ART. Of the five epidemiologic studies on caffeine intake and ART outcomes, only one found a significant negative effect of caffeine intake on live birth following ART. There have been six epidemiologic studies exploring whether alcohol intake is associated with fertility outcomes among women undergoing ART. Three studies assessed current alcohol consumption and observed a negative effect on outcomes such as fertilization, embryo quality, and implantation. When alcohol intake in the year before treatment was assessed, no relationships were observed with clinical outcomes following ART. Finally, numerous epidemiologic studies and a handful of meta-analyses have confirmed that female current smokers have worse ART outcomes compared with nonsmokers. Although former smokers tend to have better ART outcomes than current smokers, very few individual studies have investigated the influence of smoking cessation on ART outcomes. Literature on male smoking, drinking, and caffeine habits in relation to ART outcomes is even sparser and inconsistent, making it difficult to draw strong conclusions on that topic. In summary, there is little evidence supporting a detrimental effect of moderate caffeine intake on ART outcomes. Current consumption of alcohol may have a negative effect on ART outcomes, but at present the evidence is limited. Women who currently smoke cigarettes have been consistently found to have poorer ART outcomes, including reduced live birth rates, but a quantification of the benefits of smoking cessation is lacking. (*Fertil Steril*® 2018;110:587–92. ©2018 by American Society for Reproductive Medicine.)

Key Words: Caffeine, alcohol, smoking, assisted reproduction, fertility

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According to data from the Centers for Disease Control and Prevention, around 230,000 assisted reproductive technology (ART) treatments were performed in the United States in 2016 (1) compared with about 60,000 in 1995 (2). This up-

ward trend in the use of ART has been observed in other developed countries as well (3, 4). Despite the increasing use of these treatments among couples, the live birth rate per initiated cycle has remained relatively stable, at ~30% per cycle started, since

the early 2000s (5, 6). Therefore, identifying modifiable lifestyle factors that can predict human fertility and increase a couple's chances of success with the use of ART has become a major clinical and public health matter. Among infertility patients, smoking, alcohol, and caffeine are the top three modifiable factors perceived by women as being potentially detrimental to IVF cycle success (7). Cigarette smoking is in fact one of the best-characterized modifiable risk factors for female infertility, so much so that many insurance companies now require urine or serum cotinine levels to be obtained within the month of a

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requested infertility service for women (and their partners) who have acknowledged smoking within the past year. On the other hand, caffeine and alcohol have historically been two of the most studied dietary factors in relation to spontaneous fertility, and mixed findings in the existing literature have resulted in a less well defined understanding of their influence on ART success.

The purpose of this review is to summarize the available epidemiologic evidence on the effect of smoking, caffeine, and alcohol intake on ART outcomes with the hope of providing insights to clinicians who are advising patients on these exposures and to identify gaps in the literature where future research should be focused. One of the main strengths of including only ART studies in this review is the unique opportunity to study many early developmental outcomes, ranging from oocyte production, maturation, and fertilization to preimplantation embryo development and implantation, that are almost impossible to be observed in couples conceiving naturally. Moreover, because all of the women undergoing ART are planning pregnancy, these studies tend to suffer less from the biases relating to the intention of pregnancy that are inherent in studies relating smoking, alcohol, and caffeine to fertility in spontaneously conceived pregnancies.

CAFFEINE

Caffeine is a well known stimulant of the central nervous system, and several studies have linked its consumption to lower estrogen levels in the luteal phase in premenopausal women (8–11). However, findings of whether caffeine intake alters fecundability among women trying to conceive without medical assistance have been equivocal (12–19). To date, five studies have investigated the effect of caffeine consumption on fertility outcomes among women undergoing ART, and the evidence is mixed (20–24). The first study to address this question in an ART setting was published in 2002 by Klonoff-Cohen et al., who conducted a cohort study among 221 women attending seven fertility clinics in southern California. The authors found no effect of caffeine intake in the year before the cycle start on oocyte retrieval, fertilization, embryo transfer, or implantation after in vitro fertilization (IVF) or gamete intrafallopian transfer (GIFT) (20). However, they found that women with usual caffeine intakes of 2–50 and >50 mg/d had adjusted odds ratios (95% confidence interval [CI]) of not achieving a live birth of 3.1 (1.1–9.7) and 3.9 (1.3–11.6), respectively, compared with women consuming <2 mg/d. These findings raised concern, and the authors suggested that caffeine intake, which is common among reproductive-age women, should be minimized (essentially to zero) before and while undergoing IVF/GIFT.

Subsequent to that initial study, Choi et al. studied the relationship between current caffeine intake among 2,474 women with no history of IVF treatment who underwent 4,716 IVF treatment cycles at three clinics in the greater Boston area from 1994 to 2003 (24). Of all the IVF outcomes examined, only peak E_2 levels were negatively associated

with caffeine intake. Notably, no associations were observed with implantation and live birth rates, despite having a population of women with a wide range of caffeine intake. Consistent with the latter study, a follow-up study by Al-Saleh et al. among 619 Saudi Arabian women undergoing ART for the first time reported no relationship between current caffeine consumption and pregnancy rate, despite having a median caffeine intake of 456 mg/d (23). Abadia et al. also found no association between usual caffeine intake over the previous year (median 125 mg/d) and clinical ART outcomes among a cohort of 300 women (493 ART cycles) attending a fertility center in Boston from 2006 to 2016 (22). Finally, in the most recent study, including 340 women undergoing IVF at a university-affiliated center in Israel (2014–2016), Matchinger et al. failed to find an association between preconception caffeine intake (median 142 mg/d) and number of total, mature, and fertilized oocytes, embryo quality measures, implantation, clinical pregnancy, or live birth (21). The only significant association that was observed in this study was a detrimental effect of sugared soda on total and mature oocytes retrieved, number of fertilized oocytes, number of top-quality embryos, and live birth rates.

At present, little evidence supports a detrimental effect of caffeine consumption on reproductive outcomes among women undergoing ART treatments. In fact, only the Klonoff-Cohen et al. study found evidence that caffeine intake may be detrimental to live birth following ART. It is important to note, however, that 36% of the women in that study underwent GIFT, a procedure that has been largely phased out in the US (use was <1% in 2015), and the study was performed during a time when many more embryos were transferred, on average, than today (median in their study was four embryos vs. an average of less than two in the U.S. in 2015). Nevertheless, given the limited studies on this topic, it is difficult to completely rule out caffeine as a potential reproductive toxicant. For example, two recent meta-analyses conducted among all studies, regardless of infertility treatment use, reported that preconception caffeine was associated with a small but significant increased risk of spontaneous abortion (SAB) (25, 26). It was noted, however, that the studies had significant heterogeneity and risk of bias detected, including considerable risk of publication bias (e.g., smaller studies finding no association between caffeine and SAB were less likely to be published) (25). Therefore, the current guideline from the American Congress of Obstetricians and Gynecologists that suggests women who are pregnant and capable of pregnancy limit their caffeine intake to <200 mg/d (27) still seems to be the best advice to give patients. Given the known role of variants in the CYP1A2 gene affecting caffeine metabolism (28), future studies are needed that evaluate circulating caffeine levels and its metabolites (e.g., serum paraxanthine) in combination with targeted genotyping. Research into the role of sugar-sweetened beverages, specifically soda, on outcomes of ART also is warranted, given the recent findings that higher sugared soda intake was associated with decreased live birth in a prospective cohort of ART patients (21) and lower fecundability in a time-to-pregnancy study (29).

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