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

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Abstract

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

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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.

Keywords

Caffeine; alcohol; smoking; assisted reproduction; fertility

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 upward 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 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).

ALCOHOL

Excessive alcohol consumption has long been known for its detrimental effect on human health, including increased risk of many cancers, stroke, heart failure, and death (30, 31). Moreover, numerous studies have shown that maternal alcohol consumption during pregnancy can have negative impacts on multiple fetal organ systems, the best studied being the adverse effects on the developing brain. Despite the knowledge of these links, preconception alcohol intake by women is still a very relevant exposure: 10% of pregnant women and 50% of nonpregnant women consume alcohol (32). Whether intake of alcohol reduces the ability to achieve a pregnancy is uncertain (11,33–38). For example, whereas some studies from the general population suggest that consumption of alcohol can reduce fecundability (33,35,39), others have not observed any detrimental effect (11,36–38).

To date, six studies have investigated the potential relationship between alcohol consumption and reproductive outcomes among women undergoing ART, and overall the results are quite conflicting (22,40–44); however, once studies are grouped by the timing of alcohol exposure (e.g., current intake vs. average intake over the past year) more consistent trends emerge. Regarding average intake before the start of ART, the first published study on the topic, by Klonoff-Cohen et al., found that alcohol intake in the year before ART was negatively related to oocyte retrieval but found no associations with other outcomes, including live birth, among 221 women undergoing ART in southern California (1993–1997) (40). Similarly, in a prospective cohort study of women undergoing fertility treatment in Boston (2006–2016), Abadia et al. also concluded that alcohol intake in the year before their first ART cycle (median 5.6 g/d) was not associated with any of the ART outcomes under study, including live birth (22).

Regarding alcohol consumption immediately before the ART cycle, the studies are more numerous and paint a potentially more hazardous picture. For example, although Klonoff-Cohen et al. did not find an association between long-term alcohol intake and ART outcomes, they did find an increased risk of miscarriage and decreased risk of becoming pregnant when participants were asked about their alcohol intake in the month or week before the ART cycle, despite relatively low intakes (mean intakes of 6.1 and 7.1 g/d, respectively). Wdowiak et al. also observed a detrimental effect of current alcohol intake (albeit at relatively high levels, >25 g/d) before the ART cycle on embryo quality among 54 women undergoing ART in Poland (41). Moreover, Rossi et al. reported that women who consumed >50 g of alcohol per week, assessed at the start of the ART cycle, had lower

peak E_2 levels and greater odds of failed fertilization in a large cohort study (n = 2,545) of U.S. women in the Boston area from 1994 to 2003 (42). They also found that compared with women who consumed fewer than four alcoholic drinks per week, those who consumed higher amounts had lower probabilities of live birth. In a large retrospective cohort study of women undergoing fertility treatment in Boston (2009–2013), Dodge et al. found increased risk of spontaneous abortion and a nonstatistically significant lower risk of live birth in the first ART cycle among daily alcohol drinkers compared with nondrinkers; however, they found no differences in ART outcomes by type of alcohol drinker (daily drinker vs. social drinker vs. nondrinker) when all of the ART cycles were included in the analyses (43). Finally, Firns et al. did not observe any association of alcohol consumption (mean of three drinks/week), assessed between days 4 and 10 of the cycle, with oocycte production and fertilization rate among 152 Australian women following ART during 1997–1998 (44).

Taken together, the findings from these studies suggest that moderate alcohol intake in the year before ART treatment does not seem to have an appreciable impact on the success of ART; however current alcohol intake immediately before the start of (and during) treatment may be harmful. These latter findings are in line with a recent statement from the Centers for Disease Control and Prevention reiterating that “there is no known safe amount of alcohol use during pregnancy or while trying to get pregnant.” Furthermore, our findings reinforce that the current recommendation for women undergoing ART treatment should be to err on the side of caution and abstain from alcohol. The results regarding alcohol intake over the year before infertility treatment initiation should provide some reassurance to women that low to moderate intake does not seem to have an adverse effect on their likelihood of ART success.

SMOKING

Tobacco smoking has been conclusively linked with higher risk of cardiovascular and lung diseases, as well as increased risks of cancer and mortality (45, 46). As such, tobacco is among the leading causes of death and disability worldwide (45), with >6 million people dying of tobacco-related causes per year (46). Smoking is also recognized to be one of the most important avoidable causes of adverse pregnancy outcomes, including restricted fetal growth, preterm birth, and increased perinatal and infant mortality rates (47, 48). Despite the knowledge of these health risks, smoking is still common in the U.S., being reported by approximately one out of four reproductive-age women and one out of eight women during pregnancy (49). Epidemiologic studies have consistently shown a detrimental impact of smoking on fecundity among women attempting to conceive without medical assistance (50, 51), despite substantial heterogeneity in study designs, sample sizes, and types of outcome examined. There is also increasing evidence that smoking is harmful for outcomes of ART.

A meta-analysis published in 2009 (52) of all available studies on smoking and ART outcomes concluded that a woman’s likelihood of success when undergoing assisted reproduction is negatively affected by smoking. Specifically, the pooled odds of clinical pregnancy and live birth per cycle for smokers was almost one-half that of never-smokers, the odds of miscarriage for smokers was more than double that of never-smokers, and the odds of ectopic pregnancy was more than 15 times higher in smokers compared with

never-smokers (52). Although not all epidemiologic studies have found negative associations between smoking and ART success (53, 54), these contradictory studies were often limited in power (owing to small sample sizes) and tended to analyze clinical outcomes only among cycles reaching the point of embryo transfer, which is susceptible to survival bias and would be expected to attenuate the observed effect of smoking (55).

As expected, given the known adverse effects of cigarette smoke on the ovary, many of these included studies also observed a negative impact on outcomes of controlled ovarian stimulation, including higher FSH levels, more frequent cancellation rates, and lower mean number of retrieved and mature oocytes (54, 56–59). Some authors have also reported lower implantation and pregnancy rates in smokers undergoing IVF cycles in which the number of transferred morphologically good embryos has been similar to that of nonsmokers (60), suggesting that uterine receptiveness may also be affected by cigarette smoking. This was later confirmed in an analysis of 785 first-time oocyte donation cycles performed at IVI-Valencia (2002–2005) which found that heavy smokers who received donor oocytes had lower pregnancy rates than nonheavy smokers (light smokers had no difference in pregnancy rates) (61). This finding is also supported by a recent study among 200 European women undergoing ART treatments (2010–2011) which found a negative effect of current smoking on endometrial thickness on the day of embryo transfer (62). Another interesting finding among multiple studies has been that the detrimental effect of smoking may be more pronounced in older women undergoing ART treatment, suggesting synergizing effects of age and smoking on the rate of oocyte depletion (63).

Given the relatively conclusive link between current smoking and worse ART outcomes, the more clinically relevant question becomes whether smoking cessation is beneficial to ART outcomes (or whether the damage from smoking is permanent) and if there is an optimal time window, before beginning ART, for cessation to occur. Unfortunately, very few studies have addressed this question. In general, former smokers have improved pregnancy rates following ART compared with current smokers. Yet most, if not all, of these studies have failed to account for a woman’s cumulative smoking history, which also tends to be higher in current smokers, and likely confounds comparisons of past smokers and current smokers. For example, in a prospective cohort study of 225 couples undergoing ART treatment from 2006 to 2014 in Boston, Vanegas et al. reported that smoking intensity among past and current female smokers was related to a higher risk of cycle failure before oocyte retrieval, even after accounting for duration of smoking and current smoking status. These results suggest that the effects of smoking on ovarian response to controlled ovarian stimulation may persist even after smoking cessation (64). This is similar to findings among women attempting to conceive without medical assistance which showed that higher cumulative exposure to active smoking was associated with reduced fecundability in both current and former regular smokers compared with never-smokers, and, among former smokers, time since quitting was not associated with fecundability (65).

In line with the most recent committee statement on smoking and infertility from the American Society for Reproductive Medicine, the best available advice is to discourage smoking and seek to eliminate exposure to tobacco smoke among women (66). Reassuringly, there is evidence that infertile women may be more motivated to quit smoking

than pregnant women, which makes the ART setting a potentially unique time window to help women initiate smoking cessation (67). More research is needed on the effectiveness of interventions for smoking cessation among women seeking infertility treatment and its influence on outcomes of ART, particularly among older women where pressures of reproductive aging are particularly relevant.

CAFFEINE, ALCOHOL, AND SMOKING IN THE MALE PARTNER

The literature on the relation between these three behaviors in the male partner of couples undergoing ART and treatment outcomes is even sparser. Meta-analyses have shown that caffeine and alcohol have no impact on semen quality (or at most very modest impact in the case of alcohol) (68, 69), whereas smoking has a very clear deleterious impact on semen quality (69, 70). Nevertheless, effects on semen quality, or lack thereof, does not imply effects on couple-based outcomes such as treatment outcomes with ART. To date, four studies (53, 64, 71, 72) have evaluated male partner smoking and three (20, 40, 73, 74) male partner intakes of alcohol and coffee in relation to infertility treatment outcomes with ART. Of the four studies evaluating male partner smoking, three (53, 64, 72) found no relation between male partner smoking status and ART outcomes, including one (72) where smoking status was determined with the use of urinary cotinine as an objective biomarker of exposure to cigarette smoke. Only the study by Klonoff-Cohen et al. (71) found that male partner smoking status was related to lower probability of pregnancy and live birth. Nevertheless, one of these studies suggested a beneficial effect of smoking cessation of the male partner, whereby the risk of treatment failure decreased by 4% for each additional year before ART that the male partner had stopped smoking (64). The picture is murkier for studies evaluating the role of male partner intakes of alcohol and caffeine. In the study by Klonoff-Cohen et al., male partner alcohol intake was associated with a lower probability of live birth, and intake of caffeine above “usual” was related to a higher risk of multiple gestation (20, 40). It should be noted that, as previously discussed, the study by Klonoff-Cohen et al. included a high proportion of GIFT cycles, so findings may not be directly relevant to current practice. On the other hand, a contemporary cohort of couples undergoing ART in Boston found that male partner usual alcohol intake in the year before ART was positively related to the probability of live birth but that usual caffeine intake was inversely related (73) despite a lack of association with semen quality in the same men. In contrast to those two studies, Braga et al. reported that intakes of both alcohol and caffeine were related to lower fertilization rate in intracytoplasmic sperm injection cycles, but it did not translate to significant differences in live birth rates (74). The best working conclusion is probably that additional data are needed to paint a clear picture of how men’s smoking, drinking, and caffeine habits affect infertility treatment outcomes.

CONCLUSION

In this paper, we have reviewed the available epidemiologic literature on caffeine, alcohol, smoking, and reproductive outcomes among couples following ART treatments. Despite many long-held beliefs that caffeine may be a reproductive toxicant, the ART literature on this topic does not support a link between low to moderate intakes of caffeine and poorer ART outcomes. It is worth noting, however, that the number of studies on this topic is

limited, all are observational, and most studies did not have enough high consumers to evaluate the risks of very high caffeine intake. Although alcohol intake during the year before treatment does not appear to have an appreciable impact on ART outcomes, current or short-term consumption of alcohol around the time of ART treatment appears to have a potentially negative effect. This evidence (though based on only a handful of studies) combined with the known harms of maternal alcohol intake on the development on the fetus suggests that women should err on the side of caution and abstain from alcohol immediately before undergoing ART treatment and throughout pregnancy. Finally, the epidemiologic research clearly shows, across many well conducted studies, that women who are current smokers have worse ART outcomes, including lower oocyte counts and quality and lower implantation, clinical pregnancy, and live birth rates. Initiation of ART treatment should be viewed as a unique window of opportunity to encourage smoking cessation among women. Future research should also be conducted to better understand the effects of duration and timing of smoking cessation on ART outcomes.

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