Is coffee bad for reproduction? Maybe not, after all.

Coffee has a long history of being considered as a potential culprit for nearly every single human malady. Over the past decades, coffee drinking, the most important source of caffeine, has been suggested as a risk factor for cancer, heart disease, and every other common chronic disease, not to mention pregnancy complications and other adverse reproductive events, from infertility and pregnancy loss to preterm birth and adverse perinatal outcomes. Considering caffeine as a potentially harmful substance is not entirely without merits. For example, there is some evidence that caffeine may alter estrogen metabolism in premenopausal women (1), a potential biologic mechanism explaining some of its purported adverse reproductive effects. In addition, caffeine, a xanthine alkaloid with phosphodiesterase-inhibiting activity, acts as a natural pesticide protecting plants that produce it by inhibiting the growth of some bacterial and fungal species and by acting as a neurotoxin in some invertebrate herbivores (2).

Thankfully, human brains handle their relationship with caffeine on much better terms than the nervous systems of invertebrates. Moreover, over time it has become clear that many of the studies identifying coffee as a risk factor for adverse health outcomes had failed to properly account for smoking and other behaviors that commonly co-occur with coffee drinking. In 2015, the Dietary Guidelines for Americans Scientific Advisory Committee conducted the most comprehensive review of the health effects of coffee and caffeine to date (3). The Committee concluded that there is strong and consistent evidence that coffee intake is not related to increased risk of major chronic diseases or risk of premature death. In fact, the Committee concluded that there is consistent evidence that coffee may reduce the risk of type 2 diabetes, cardiovascular disease, cancers of the liver and endometrium, and premature mortality, as well as suggestive evidence that coffee may be protective against neurodegenerative conditions (3). Of most relevance for the readers of *Fertility and Sterility*, the Committee also concluded that there is consistent evidence that caffeine intake is not associated with risk of preterm delivery. They also concluded that there is limited evidence that caffeine intake is related to a higher risk of pregnancy loss; a conclusion for which they recommended cautious interpretation given that most studies addressing this question were highly susceptible to biases that would result in a spurious positive association (3).

In this issue of *Fertility and Sterility*, Lyngsø et al. (4) address another facet of the potential reproductive health effects of coffee consumption for which the evidence is still growing. They followed 1,708 couples presenting to the Aarhus University Hospital for infertility treatment and related the woman's pretreatment coffee consumption to the outcomes of infertility treatment with intrauterine insemination (IUI; 1,511 cycles), fresh in vitro fertilization or intracytoplasmic sperm injection (IVF/ICSI; 2,870 fresh cycles), or frozen embryo transfers (1,355 cycles). The study had several key advantages. The obvious strengths of the study included its large sample size and the assessment of coffee intake preceding treatment. Another advantage was conducting the study in Denmark, where coffee consumption is higher than in North America and where many pregnant women and women planning to conceive continue drinking coffee, in sharp contrast to North America where the default professional recommendations and cultural expectations are the opposite.

The authors report that coffee consumption was unrelated to the chances of attaining a clinical pregnancy or live birth in fresh or frozen IVF/ICSI cycles (4). This finding is consistent with the growing literature of the relationship between coffee and fertility, which, overall, shows no effect of coffee consumption on fertility in couples attempting conception without medical assistance or in couples seeking conception through assisted reproduction (or with semen quality parameters), as recently reviewed in this journal (5). Briefly, all but one of the studies evaluating the relationship between coffee consumption and outcomes or infertility treatment with assisted reproductive technologies (ART) have found no association between them, and the one study that reported potentially deleterious effects may not be comparable to other studies or relevant to the current practice of reproductive medicine (see discussions in references 4 and 5). Interestingly, the authors also report that higher coffee intake was related to a 50% higher chance of achieving a live birth in women undergoing treatment with IUI compared with women who abstained from having coffee. This is not the first time that coffee consumption has been linked to better fertility or markers thereof. For example, caffeine has been linked to lower circulating levels of total and free testosterone, a lower frequency of sporadic anovulation, and a lower risk of infertility due to anovulation among healthy women (see references 9 and 21 in reference 4). These apparent benefits on ovulation could be an explanation for the divergent relations in IUI versus ART in this study.

So, where does this study leave us? First, it provides additional evidence that coffee is not deleterious to fertility. The findings among women undergoing IUI, however, pose an intriguing question. Is it possible that, despite much malignment, coffee is actually good for fertility? Obviously, answering this question will require further research that, like the study by Lyngsø et al., is sufficiently large and assesses coffee intake before conception to avoid key methodologic problems such as those that cloud the interpretation of studies on the relation between coffee and pregnancy loss. Taking advantage of diverging cultural expectations around coffee and pregnancy may also prove advantageous in future research addressing this highly relevant topic.

Disclosure: Having grown up in Colombia, I cannot remember a day in my life in which I have not had coffee and suspect I was introduced to coffee drinking around the same time I was introduced to solid foods. I currently drink ~6 cups of coffee per day.

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