Effects of Caffeine Consumption by Women and Men on the Outcome of *In Vitro* Fertilization

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Objective: The objective of this study was to estimate the association between caffeine consumption and *in vitro* fertilization (IVF) outcomes.

Methods: A total of 2474 couples were prospectively enrolled prior to undergoing their first cycle of IVF, contributing a total of 4716 IVF cycles. Discrete survival analysis adjusting for observed confounders was applied to quantify the relation between caffeine consumption and livebirth. Secondary outcomes of interest were oocyte retrieval, peak estradiol level, implantation rate, and fertilization rate.

Results: Overall, caffeine consumption by women was not significantly associated with livebirth ($p_{\text{trend}}=0.74$). Compared with women who do not drink caffeine, the likelihood of livebirth was not significantly different for women who drank low (>0 –800 mg/week; odds ratio [OR]=1.00, 95% confidence interval [CI]=0.83–1.21), moderate (>800 –1400 mg/week; OR=0.89, 95% CI=0.71–1.12), or high levels of caffeine (>1400 mg/week; OR=1.07, 95% CI=0.85–1.34). Greater caffeine intake by women was associated with a significantly lower peak estradiol level ($p_{\text{trend}}=0.03$), but was not associated with the number of oocytes retrieved ($p_{\text{trend}}=0.75$), fertilization rate ($p_{\text{trend}}=0.10$), or implantation rate ($p_{\text{trend}}=0.23$). There was no significant association between caffeine intake by men and livebirth ($p_{\text{trend}}=0.27$), fertilization ($p_{\text{trend}}=0.72$), or implantation ($p_{\text{trend}}=0.24$). The individual effects of consumption of coffee, tea, or soda by women or men were not related to livebirth.

Conclusion: Caffeine consumption by women or men was not associated with IVF outcomes.

Introduction

CAFFEINE IS A STIMULANT found in many foods and medications that are consumed by more than 75% of pregnant women.¹ Several studies have examined the association between caffeine consumption and fertility in women, but the results have been conflicting. Wilcox *et al.* in 1988 were the first to report that women who consumed more than the equivalent of one cup of coffee per day were less likely to become pregnant than women who drank less.² However, two subsequent studies found no evidence of an adverse effect of caffeine on time to conceive/fertility.^{3,4} Specific to assisted reproduction technology (ART) outcomes, a single study suggested a detrimental effect of caffeine consumption on livebirth with *in vitro* fertilization (IVF) or GIFT in 221 couples.⁵

The effects of caffeine consumption on ART outcomes, therefore, remain unclear. Caffeine use is a modifiable dietary

factor about which clinicians can counsel their patients attempting to conceive if evidence suggests a detrimental impact. This study aimed to examine the association between caffeine consumption and IVF outcomes in a large, prospective cohort comprised of 2474 couples who underwent a total of 4716 IVF cycles.

Materials and Methods

Approval for the study was obtained from the Brigham and Women's Hospital's Institutional Review Board.

Study population and data collection

The data for these analyses were collected from couples undergoing treatment for infertility from 1994 to 2003 at three IVF clinics in the greater Boston area as part of a collaborative

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prospective cohort study. The original study population included 2687 couples undergoing assisted reproductive treatment (ART) for up to six cycles. Those whose treatment included the use of donor gametes were ineligible. Non-IVF cycles (such as GIFT or cryo-embryo transfer cycles) were excluded from this analysis. After additionally excluding women with previous IVF history, no IVF cycles, and missing exposure or cycle outcome information, the analytic dataset consisted of information from 2474 couples who contributed 4716 cycles.

The primary aim of this cohort study was to identify predictors of IVF outcomes, with caffeine use being one of the characteristics evaluated *a priori*. Couples consented to review of their medical records and completed a self-administered questionnaire (one for women and one for men) prior to starting infertility treatment. All survey information was obtained prior to starting the first IVF cycle and thus prior to knowledge of the IVF cycle outcomes. Sixty-five percent of couples agreed to participate in the study. The study questionnaire included questions about medical, environmental, and lifestyle factors.

Age, gravidity, parity, and alcohol, tobacco, and caffeine use were self-reported. Ever smokers were defined as women or men who smoked more than 100 cigarettes during their lifetime. Current smokers were those still smoking cigarettes at the time the questionnaire was completed. Body mass index (BMI, kilograms per meter²) was calculated based on self-reported height and weight. Information on the couple's infertility history and ART cycle-specific data were abstracted from medical records, including day 3 follicle stimulating hormone and serum estradiol (E2) levels, gonadotropin dose, number of oocytes retrieved, and number of embryos transferred. Through repeat abstraction and database review, we quantified that <1% of data were observed to have an entry error, and this very low proportion did not vary across time.

Dietary exposures of interest were included in the questionnaire *a priori*, and these included caffeine consumption. Questions focused on beverage-based caffeine exposures and included caffeinated coffee and caffeinated tea, decaffeinated coffee and decaffeinated tea, and caffeinated soft drinks. Participants were asked about the type (i.e., coffee, tea, soda) of caffeinated beverages they drink, how often they drink (none, weekly, daily), and how much they drink (i.e., the number of cups or cans per week). Total caffeine intake was estimated by assigning 100 mg caffeine per cup of coffee, 50 mg per cup of tea, and 40 mg per can of soft drink based on the estimates by Wilcox *et al.*²

Statistical analysis

To account for correlation between cycles contributed by the same couple and to accommodate for highly tied failure times, discrete survival analysis was used by fitting an unconditional logistic regression model with cycle number as a nominal categorical covariate and adjusting for observed confounders to quantify the relation between caffeine consumption and the odds of livebirth.⁶ In primary analyses of the relation with livebirth, crude and multivariable odds ratios (ORs) and 95% confidence intervals (CIs) are presented.

Mixed models were used to analyze the effect of caffeine on peak estradiol level; other secondary analyses looking at number of oocytes retrieved, fertilization rate, and implanta-

tion rate used the method of generalized estimating equations with a Poisson distribution and log link. Fertilization and implantation analyses were offset by number of oocytes inseminated and number of embryos transferred, respectively. In all analyses, women or men who reported no caffeine consumption were the referent group.

Multivariable models were adjusted for variables that were found to confound the crude relations. We considered all variables as potential confounders of the association of caffeine consumption with IVF outcomes if addition of that variable to the model changed the OR by 10% or more.⁷ If a factor was identified as a confounder of any estimated effect, it was kept in all models. Age, BMI, clinical site, primary diagnosis, tobacco, alcohol, and year of the IVF cycle were identified as confounders and kept in all models. Gravidity, parity, ethnicity, years of schooling, and vitamin intake were all analyzed and not found to be confounders. Gonadotropin dose and number of embryos transferred were also analyzed and not found to affect the primary results; thus, they were not included in the final analysis.

The total amounts (mg) of caffeine consumed per week by women and men separately were analyzed first as continuous predictors, and then, if linear relationships did not exist, as quintiled categorical predictors with cutpoints based on the observed distribution among caffeine consumers. The women were grouped into four categories: 0, >0–800 (>0–8 cups of coffee/week), >800–1400 (>8–14 cups of coffee/week), and >1400 mg/week (>14 cups of coffee/week). The men were grouped into four categories: 0, >0–1400 (>0–14 cups of coffee/week), >1400–2100 (>14–21 cups of coffee/week), and >2100 mg/week (>21 cups of coffee/week). Individual associations between coffee, tea, and soda consumption and IVF outcomes were also included in the analysis.

Tests for linear trend across continuous variables and ordinal categorical variables (assigning each woman or man to the median of the exposure category) were calculated using the two-sided Wald test. All analyses were performed using SAS[®], version 9.2.

Results

The demographics within each caffeine strata of the 2474 couples are presented in Table 1. Female partners had a median age of 35 years at cycle start (SD=4.3; range=20–49 years). The median male age was 36 years (SD=5.6; range=20–69). The median number of IVF attempts was 2 and the maximum was 6.

Twenty-one percent of the women reported that they did not drink any caffeine; 40% reported they drank >0–800 mg/week, 18% drank >800–1400 mg/week, and 21% of the women reported that they drank >1400 mg/week. Of the men, 8% reported that they did not drink any caffeine, 51% reported they drank >0–1400 mg/week, 20% drank >1400–2100 mg/week, and 21% of the men reported they drank >2100 mg/week.

Female caffeine intake and livebirth

A linear trend was not observed across female caffeine consumption and livebirth before or after adjusting for confounders (*p*-value, test for linear trend=0.08, *p*-value, test for linear trend=0.74, respectively; Table 2). The unadjusted ORs suggested that moderate levels (>800–1400 mg/week)

TABLE 1. PATIENT CHARACTERISTICS OVERALL AND BY CAFFEINE CATEGORY AMONG 2474 COUPLES UNDERGOING *IN VITRO* FERTILIZATION

	Overall	No caffeine	>0–800 mg/week	>800–1400 mg/week	>1400 mg/week
Female	(n = 2474)	(n = 527)	(n = 987)	(n = 448)	(n = 512)
Age at first cycle (years)	35.0 (20.0, 49.0)	35.0 (20.0, 45.0)	35.0 (23.0, 46.0)	35.0 (20.0, 46.0)	36.0 (22.0, 49.0)
Body mass index (kg/m ²)	22.6 (15.7, 52.3)	22.4 (15.8, 50.6)	22.6 (16.3, 48.7)	22.6 (15.7, 52.3)	23.1 (16.3, 45.8)
Smoking status					
Never	1602 (64.8%)	381 (72.3%)	704 (71.3%)	276 (61.6%)	241 (47.1%)
Former	715 (28.9%)	131 (24.9%)	236 (23.9%)	140 (31.3%)	208 (40.6%)
Current	157 (6.3%)	15 (2.8%)	47 (4.8%)	32 (7.1%)	63 (12.3%)
Smoking (cigarettes/week), among users	10.0 (1.0, 60.0)	10.0 (1.0, 40.0)	10.0 (1.0, 60.0)	10.0 (1.0, 50.0)	10.0 (1.0, 50.0)
Alcohol (drinks/week), among users	4.0 (1.0, 28.0)	3.0 (1.0, 21.0)	3.0 (1.0, 21.0)	4.0 (1.0, 28.0)	4.0 (1.0, 22.0)
IVF attempts	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)	2.0 (1.0, 6.0)
Gravidity	1.0 (0.0, 13.0)	1.0 (0.0, 11.0)	0.0 (0.0, 7.0)	0.0 (0.0, 7.0)	1.0 (0.0, 13.0)
Parity	0.0 (0.0, 5.0)	0.0 (0.0, 4.0)	0.0 (0.0, 3.0)	0.0 (0.0, 3.0)	0.0 (0.0, 5.0)

	Overall	No caffeine	>0–1400 mg/week	>1400–2100 mg/week	>2100 mg/week
Male	(n = 2474)	(n = 202)	(n = 1260)	(n = 491)	(n = 521)
Age at first cycle (years)	36.0 (20.0, 69.0)	37.0 (20.0, 69.0)	36.0 (22.0, 65.0)	36.0 (27.0, 58.0)	37.0 (24.0, 67.0)
Body mass index (kg/m ²)	26.2 (13.4, 50.0)	25.1 (17.2, 36.9)	26.2 (16.9, 45.3)	26.1 (13.4, 46.5)	26.5 (14.8, 50.0)
Smoking status					
Never	1678 (67.8%)	158 (78.2%)	950 (75.4%)	303 (61.7%)	267 (51.2%)
Former	549 (22.2%)	34 (16.8%)	216 (17.1%)	132 (26.9%)	167 (32.1%)
Current	247 (10.0%)	10 (5.0%)	94 (7.5%)	56 (11.4%)	87 (16.7%)
Smoking (cigarettes/week), among users	13.5 (1.0, 60.0)	10.0 (1.0, 50.0)	10.0 (1.0, 60.0)	12.0 (1.0, 50.0)	20.0 (1.0, 60.0)
Alcohol (drinks/week), among users	4.0 (1.0, 84.0)	2.0 (1.0, 34.0)	4.0 (1.0, 84.0)	5.0 (1.0, 49.0)	6.0 (1.0, 45.0)

Statistics displayed are median (min, max) for continuous variables and *n* (%) for categorical variables.
IVF, *in vitro* fertilization.

TABLE 2. ASSOCIATIONS BETWEEN CAFFEINE CONSUMPTION AND LIVEBIRTH AMONG 2474 COUPLES UNDERGOING *IN VITRO* FERTILIZATION

	No. of cycles with livebirth	No. of cycles without livebirth	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Female				
No caffeine	253	734	1.00 (referent)	1.00 (referent)
>0–800 mg/week	477	1395	0.99 (0.83, 1.18)	1.00 (0.83, 1.21)
>800–1400 mg/week	191	700	0.80 (0.64, 0.99)	0.89 (0.71, 1.12)
>1400 mg/week	226	740	0.88 (0.72, 1.09)	1.07 (0.85, 1.34)
<i>p</i> -value, test for linear trend			0.08	0.74
Male				
No caffeine	96	281	1.00 (referent)	1.00 (referent)
>0–1400 mg/week	617	1769	1.02 (0.80, 1.31)	1.03 (0.80, 1.34)
>1400–2100 mg/week	215	722	0.88 (0.66, 1.16)	0.96 (0.72, 1.29)
>2100 mg/week	219	797	0.81 (0.62, 1.07)	0.93 (0.70, 1.24)
<i>p</i> -value, test for linear trend			0.007	0.27
Couple				
Female ≤800 mg/week and male ≤140 mg/week	499	1359	1.00 (referent)	1.00 (referent)
Only female >800 mg/week	214	691	0.85 (0.71, 1.02)	0.97 (0.80, 1.18)
Only male >1400 mg/week	231	770	0.83 (0.69, 0.99)	0.91 (0.76, 1.10)
Female >800 mg/week and male >140 mg/week	203	749	0.74 (0.62, 0.90)	0.91 (0.75, 1.11)

Odds ratio (OR) and 95% confidence interval (CI) are from discrete survival analysis (Cox proportional odds model). Adjusted models included female age (<35, 35–37, 38–40, >40 years), body mass index (<19, 19–24.9, 25–29.9, ≥30 kg/m²), clinic site (1, 2, 3), study enrollment period (1994–1998 vs. 1999–2003), female tobacco use (0, 1–6, 7–60 cigarettes/week), female alcohol use (0, >0–38, >38 g/week), and primary infertility diagnosis. *p*-values, tests for linear trend, are calculated from the Wald statistic and are two-sided.

of caffeine consumption may be associated with decreased likelihood of livebirth compared with no caffeine consumption (OR=0.80, 95% CI=0.64–0.99). However, the association was attenuated after adjustment for confounders. Compared with women who do not drink caffeine, the likelihood of livebirth was not significantly different for women who drank low (>0–800 mg/week; OR=1.00, 95% CI=0.83–1.21), moderate (>800–1400 mg/week; OR=0.89, 95% CI=0.71–1.12), or high levels of caffeine (>1400 mg/week; OR=1.07, 95% CI=0.85–1.34).

In addition, a linear trend was not observed across coffee consumption (p -value, test for linear trend=0.95), tea consumption (p -value, test for linear trend=0.99), or soda consumption (p -value, test for linear trend=0.68) (data not shown). Compared with women who do not drink any coffee, the likelihood of livebirth was not significantly different for women who drank coffee weekly (OR=0.93, 95% CI=0.74–1.17) or daily (OR=1.00, 95% CI=0.85–1.16). The likelihood of livebirth was also not significantly different for women who drank tea weekly (OR=0.94, 95% CI=0.78–1.13) or daily (OR=1.02, 95% CI=0.83–1.26), compared with women who do not drink any tea. Compared with women who do not drink any soda, the likelihood of livebirth was not significantly different for women who drank soda weekly (OR=0.98, 95% CI=0.84–1.16) or daily (OR=0.96, 95% CI=0.78–1.18).

Male caffeine intake and livebirth

Before adjusting for confounders, a linear trend was observed across male caffeine consumption and odds of livebirth (p -value, test for linear trend <0.01; Table 2). However, after adjusting for confounders, the association was attenuated (p =0.27) such that, compared with men who do not drink caffeine, the likelihood of livebirth for men who drank low (>0–1400 mg/week; OR=1.03, 95% CI=0.80–1.34), moderate (>1400–2100 mg/week; OR=0.97, 95% CI=0.72–1.29), or high levels of caffeine (>2100 mg/week; OR=0.93, 95% CI=0.70–1.24) were lower in odds but not statistically different.

An adjusted linear trend was also not observed across coffee consumption (p =0.20), tea consumption (p =0.70), or soda consumption (p =0.58) (data not shown). Compared with men who do not drink any coffee, the likelihood of livebirth was suggestively lower but not significantly different for men who drank coffee weekly (OR=0.93, 95% CI=0.74–1.17) or daily (OR=0.90, 95% CI=0.77–1.05).

Couple caffeine intake and livebirth

Further analyses examined the potentially synergistic effect of caffeine consumption within the couple. Caffeine consumption was separated into four categories (the woman consumed $\leq$ 800 mg/week and the man consumed $\leq$ 1400 mg/week [referent]; only the woman consumed $\leq$ 800 mg/week; only the man consumed $\leq$ 1400 mg/week; the woman consumed >800 mg/week and the man consumed >1400 mg/week). Again, unadjusted ORs suggest that caffeine consumption as a couple may be associated with decreased likelihood of livebirth (Table 2). However, the association was attenuated after adjusting for confounders. Compared with couples wherein the woman consumed $\leq$ 800 mg/week and the man consumed $\leq$ 1400 mg/week, the likelihood of livebirth if the woman con-

sumed >800 mg/week and the man consumed >1400 mg/week was 9% lower (95% CI=0.75–1.12).

Caffeine intake and other reproductive outcomes

Evaluating intermediate cycle outcomes, caffeine intake by women was associated with peak estradiol level, but did not affect the number of oocytes retrieved, fertilization rate, or implantation rate (Table 3). The adjusted model showed an attenuated association between increased caffeine intake and decreased peak estradiol level, but the adjusted test for trend was significant (p_{trend} =0.03). Despite observing lower estradiol levels in women with moderate-to-high caffeine intake, the number of oocytes retrieved did not differ by caffeine category. Results from analyses examining fertilization rate and implantation rate were also null for females and males.

Discussion

This prospective study of couples undergoing IVF found that caffeine consumption by women was not significantly associated with livebirth, after adjusting for age, BMI, site, primary diagnosis, tobacco, alcohol, and year of the IVF cycle. Caffeine intake by women was associated with peak estradiol level, but not with the number of oocytes retrieved, fertilization rate, or implantation rate. The individual effects of consumption of coffee, tea, and soda by women or men were not related to livebirth. Our analyses also did not suggest any significant association between caffeine intake by men and livebirth, fertilization rate, and implantation rate.

A prospective cohort study by Klonoff-Cohen *et al.*⁵ examined the relation between caffeine intake and ART outcomes among 221 couples undergoing IVF or GIFT. They observed that woman's usual caffeine intake of >2–50 or >50 mg/day, compared with intake of 0–2 mg/day, increased the odds of not having a livebirth by 3.1 (95% CI=1.1, 9.7) and 3.9 (95% CI=1.3, 11.6) times, respectively. They did not observe a significant relation with other cycle outcomes. This study included greater detail of caffeine consumption, having measured self-reports of usual intake—as did our study—and also intake during the week of the initial clinical visit, the week before the cycle start, and during the first week of the cycle. The caffeine consumption reported in the study by Klonoff-Cohen *et al.*, if converted to consumption per week (as was our unit of measurement), is considerably lower than that reported in our study population, with their highest category being equivalent to only >350 mg/week. Thus, their highest intake patients would fall into the lowest intake category reported by our patients. In addition, although multiple cycles from a couple were included (36% contributed >1 cycle), the statistical analyses included multivariable linear and unconditional logistic regression models—both of which have an assumption of independence of observations and therefore do not appropriately account for the correlation between cycles contributed by the same couple.

The results have been mixed from previous studies examining the effects of caffeine on fertility without ART. Several studies^{2,8–10} have reported that caffeine intake may reduce the risk of conceiving, whereas others^{3,11–13} (Alderete 1995) have reported that there is no association between caffeine intake and pregnancy. There may be several biologic reasons for caffeine to affect conception. Caffeine may affect endogenous levels of hormones via changes in ovarian function or

TABLE 3. ASSOCIATION BETWEEN CAFFEINE INTAKE AND OTHER REPRODUCTIVE OUTCOMES AMONG 2472 COUPLES UNDERGOING *IN VITRO* FERTILIZATION

	No. of cycles	Unadjusted	Adjusted
<i>Female</i>		<i>Unadjusted mean difference (p-value)</i>	<i>Adjusted mean difference (p-value)</i>
Peak estradiol level ^a			
No caffeine	958	(Referent)	(Referent)
>0–800 mg/week	1808	–14.6 (0.77)	–29.9 (0.52)
>800–1400 mg/week	872	–151.8 (<.01)	–94.7 (0.06)
>1400 mg/week	949	–189.6 (<.001)	–100.9 (0.09)
test for linear trend		<.0001	0.03
		<i>Unadjusted RR (95% CI)</i>	<i>Adjusted RR (95% CI)</i>
Number of oocytes retrieved ^b			
No caffeine	905	1.00 (referent)	1.00 (referent)
>0–800 mg/week	1747	1.03 (0.97–1.09)	1.02 (0.96–1.08)
>800–1400 mg/week	810	0.97 (0.90–1.05)	1.00 (0.93–1.07)
>1400 mg/week	898	0.98 (0.91–1.05)	1.00 (0.93–1.07)
test for linear trend		0.21	0.75
Fertilization rate ^c			
No caffeine	897	1.00 (referent)	1.00 (referent)
>0–800 mg/week	1741	0.97 (0.93–1.01)	0.98 (0.94–1.02)
>800–1400 mg/week	802	0.96 (0.91–1.01)	0.98 (0.93–1.03)
>1400 mg/week	894	0.93 (0.89–0.98)	0.95 (0.91–1.00)
test for linear trend		0.01	.10
Implantation rate ^c			
No caffeine	774	1.00 (referent)	1.00 (referent)
>0–800 mg/week	1487	0.99 (0.85–1.15)	0.99 (0.85–1.15)
>800–1400 mg/week	680	0.91 (0.76–1.10)	1.02 (0.85–1.22)
>1400 mg/week	771	0.93 (0.78–1.12)	1.10 (0.91–1.32)
test for linear trend		0.32	0.23
<i>Male</i>		<i>Unadjusted RR (95% CI)</i>	<i>Adjusted RR (95% CI)</i>
Fertilization rate ^c			
No caffeine	338	1.00 (referent)	1.00 (referent)
>0–1400 mg/week	2203	1.01 (0.95–1.07)	1.02 (0.97–1.08)
>1400–2100 mg/week	868	0.97 (0.91–1.04)	0.99 (0.93–1.05)
>2100 mg/week	925	1.00 (0.93–1.06)	1.01 (0.95–1.08)
test for linear trend		0.38	0.72
Implantation rate ^c			
No caffeine	294	1.00 (referent)	1.00 (referent)
>0–1400 mg/week	1886	1.01 (0.81–1.27)	1.04 (0.84–1.29)
>1400–2100 mg/week	731	0.90 (0.70–1.15)	0.97 (0.76–1.23)
>2100 mg/week	801	0.84 (0.66–1.08)	0.94 (0.74–1.2)
test for linear trend		0.01	0.24

Adjusted models included female age (<35, 35–37, 38–40, >40 years), BMI (<19, 19–24.9, 25–29.9, ≥30 kg/m²), site, study enrollment period (1994–1998 vs. 1999–2003), female tobacco use (0, 1–6, 7–60 cigarettes/week), female alcohol use (0, >0–38, >38 grams/week), and primary infertility diagnosis.

^aMean differences and *p*-values are from a linear mixed model.

^bRisk ratio (RR) and 95% CI are from generalized estimating equations using a Poisson distribution and a log link.

^cIncidence rate ratio (RR) and 95% CI are from generalized estimating equations using a Poisson distribution, log link, and an offset term.

alterations in hormone metabolism.¹³ In addition, caffeine consumption has been associated with increased levels of early follicular phase E₂,¹³ although this is the opposite direction of association from what we observed in our study population. A study by Caan *et al.*⁴ suggested a significant association between tea consumption and increased fertility in the earlier cycles of a woman's attempt at conception. An explanation for the positive tea association is that a chemical component of tea rather than caffeine may be responsible for increase in fertility.⁴ Studies have demonstrated that the polyphenolic compounds found in tea have the ability to inhibit chromosomal aberrations, which could increase fertility by decreasing the number of nonviable embryos.^{4,15}

There are limitations of the present study that need to be considered when interpreting the presented results. The exact amount of caffeine in caffeinated beverages is difficult to quantify. Although patients reported the number of cups or cans of caffeinated beverages that they drink, the exact amount of milligrams of caffeine in a cup depends on the mix of the brew, how it is prepared, and the size of the cup.⁴ The questionnaire also did not ask questions about decaffeinated soda, cocoa, chocolate, or caffeinated medications and supplements. Given the prospective design that couples report their caffeine intake prior to cycle start, misclassification cannot be influenced by recall bias and therefore would be nondifferential with respect to outcome, thus driving associations to-

ward the null. However, sources of caffeine that were not included on the questionnaire may bias the results if they were more likely to be consumed by those who ultimately had a successful or failed cycle. For example, chocolate consumption was not queried. Total caffeine intake would be differentially biased if chocolate represents a larger proportion of caffeine intake among those who ultimately had a livebirth relative to those who did not.

Another limitation is that there may be inaccuracies in the self-reporting of caffeine consumption. However, patients completed the survey and reported their caffeine history before the start of the IVF cycle, and therefore, recall bias is eliminated and additionally any differential bias should be negated, given that the patients did not know the outcome of their treatment.

Last, caffeine consumption is a lifestyle factor that may be correlated with several other factors that may confound the relation with livebirth. The analysis in this study was designed to address some of these factors by adjusting for BMI and use of alcohol and tobacco. However, there likely are residual confounders for which we could not account, such as diet and occupational stress.

Despite these limitations, this large, prospective study demonstrates that caffeine intake by women and men does not appear to be associated with IVF outcomes. The upper bounds of the CI suggest that even if a detrimental effect exists, it is likely small in magnitude. As with all studies, findings should be replicated before making any definitive clinical recommendation.

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