Predictors of pregnancy and live birth after insemination in couples with unexplained or male-factor infertility

Hao Huang, M.P.H.,[a] Karl R. Hansen, M.D.,[b] Pamela Factor-Litvak, Ph.D.,[c] Sandra A. Carson, M.D.,[d] David S. Guzick, M.D.,[e] Nanette Santoro, M.D.,[f] Michael P. Diamond, M.D.,[g] Esther Eisenberg, M.D., MPH,[h,i] and Heping Zhang, Ph.D.,[a] for the National Institute of Child Health and Human Development Cooperative Reproductive Medicine Network

[a] Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Connecticut; [b] Section of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma; [c] Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, New York; [d] Division of Reproductive Endocrinology and Infertility, Women and Infants Hospital of Rhode Island, Providence, Rhode Island; [e] University of Florida Health Science Center, Gainesville, Florida; [f] Department of Obstetrics and Gynecology, University of Colorado School of Medicine, Anschutz Medical Campus, Aurora, Colorado; [g] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Wayne State University, Detroit, Michigan; [h] Division of reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, Vanderbilt University Medical Center, Nashville, Tennessee, and [i] Reproductive Medicine Network Reproductive Sciences Branch/Center for Population Research, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland

Objective: To identify risk factors for pregnancy outcomes in couples treated with intracervical or intrauterine insemination, with or without superovulation for unexplained or male-factor infertility.
Design: Secondary analysis of data from a randomized superovulation and intrauterine insemination trial.
Setting: Academic medical centers.
Intervention(s): Treatment continued for four cycles unless pregnancy was achieved.
Patient(s): Out of 932 couples randomized to four treatment groups, 664 couples who had completed the lifestyle questionnaires were assessed for occurrence of pregnancy and live birth.
Main Outcome Measure(s): Pregnancy and live birth.
Result(s): The pregnancy and live birth rates were significantly higher in couples in which the female partners reported that they had consumed coffee or tea in the past or drank alcoholic beverages in the past (past users) compared with those who had never consumed coffee, tea, or alcoholic beverages. Past users also had significantly higher pregnancy and live birth rates than those currently consuming coffee or tea or alcoholic beverages. Demographic, occupational exposure, and other lifestyle factors were not significant.
Conclusion(s): Couples in which the female partners drank coffee, tea, or alcoholic beverages in the past had higher pregnancy and live birth rates compared with never or current users. When discontinuing these habits, they might have made other lifestyle changes to improve the pregnancy outcome. (Fertil Steril® 2012;97:959–67. ©2012 by American Society for Reproductive Medicine.)
Key Words: Infertility, lifestyle, pregnancy, live birth, insemination, superovulation

Infertility, defined as the inability to conceive after 12 months of unprotected intercourse, is a major public health problem affecting up to 15% of all couples (1, 2). Lifestyle factors, including smoking, caffeine use, alcoholic beverage drinking, and obesity, have been associated with subfertility and an increase in early pregnancy loss in some investigations (3–9). A variety of occupational exposures have also been linked to impaired natural fertility (10, 11). However, the effect of lifestyle factors and occupational exposures on natural fertility is not consistent from study to study (10, 12). In addition, many studies have been too small to detect an effect or have relied on retrospective information, which is subject to recall bias (13–16).

Multiple studies have investigated the impact of lifestyle factors on outcomes of in vitro fertilization (IVF). Both tobacco use and high body mass index (BMI) have been associated with a negative effect on IVF pregnancy rates (17, 18). Additionally, alcohol use has been associated with a reduction in IVF pregnancy rate (19). The relationship between caffeine use and IVF outcomes is less clear; however, a decrease in good-quality embryos has been reported in high caffeine users compared with moderate users (20).

Little is known regarding the relationship between lifestyle factors and

Received October 17, 2011; revised January 1, 2012; accepted January 3, 2012; published online January 21, 2012.
H.H. has nothing to disclose. K.R.H. has nothing to disclose. P.F.-L. has nothing to disclose. S.A.C. has nothing to disclose. D.S.G. has nothing to disclose. N.S. has nothing to disclose. M.P.D. has nothing to disclose. E.E. has nothing to disclose. H.Z. has nothing to disclose.
Supported by National Institutes of Health (NIH)/ National Institute of Child Health and Human Development (NICHD) grants HD55925 and U10 HD39005. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NICHD or NIH.
Reprint requests: Heping Zhang, Ph.D., 60 College Street, New Haven, CT 06520-8034 (E-mail: heping.zhang@yale.edu).

Fertility and Sterility® Vol. 97, No. 4, April 2012 0015-0282/$36.00

doi:10.1016/j.fertnstert.2012.01.090

pregnancy outcomes after less-aggressive infertility treatments, such as controlled ovarian stimulation (COS), intrauterine insemination (IUI), or a combination of both. Given that many couples undergo such treatment cycles to achieve a pregnancy, a better understanding of the relationship between lifestyle factors and outcomes is important to appropriately counsel patients.

To address these questions, we examined the relationship between lifestyle factors, occupational exposures and treatment outcomes in a large multicenter randomized clinical trial (21) evaluating the effectiveness of different treatments (intracervical insemination [ICI], COS with ICI, natural-cycle IUI, and COS with IUI) for unexplained infertility.

SUBJECTS AND METHODS

Study Design

From 1991 to 1997, 932 infertile couples with unexplained infertility were recruited from university-based infertility and gynecology clinics (21, 22). The couples were randomly assigned to receive ICI, IUI, COS-ICI, or COS-IUI. Treatment continued for four cycles unless pregnancy was achieved. Inclusion criteria consisted of $\geq$12 months of infertility, a detailed fertility evaluation with normal results, and the presence of motile sperm on semen analysis for male partners. Exclusion criteria included previous infertility treatment, a history of chemotherapy or radiation therapy, previous surgery (tubal surgery, myomectomy, ovarian cystectomy, or unilateral oophorectomy for women; vasovasostomy or varicocelectomy within 6 months before study, or pelvic-node dissection for men), or a medical condition related to infertility. The primary outcome studied was the establishment of pregnancy. Pregnancy was determined by an increase in the serum β-hCG concentration between luteal days 15 and 17 (21). Live birth was also recorded for the study and was defined as the delivery of a viable infant. Pregnancy loss included miscarriage, abortion, stillbirth, and nonviable infant. The Institutional Review Board at each center approved the protocol, and each of the couples gave written informed consent.

Lifestyle Factors and Occupational Exposure Assessment

Enrolled subjects completed extensive self-report questionnaires before undergoing treatment. The influence of subjects' baseline characteristics, lifestyle habits, and occupational exposures of the female partner on pregnancy outcome was evaluated. We selected the following 25 putative risk factors from a long list of variables: treatment group, age, BMI, race, education, pregnancy history, infertility length, history of smoking, coffee, tea, soda, and alcohol use, use of marijuana and cocaine, and exposure to solvents, lead, paint, pesticide, metal fumes, anesthetic gases, chemotherapeutic drugs, excess heat, vibration, and radiation during the preceding month. For smoking, "never" refers to those who had never smoked regularly or had smoked less than one cigarette per day; "current" refers to those who smoked regularly, at least one cigarette per day, within the past month; "past" refers to those who had smoked regularly, at least one cigarette per day more than 1 month before. For coffee or tea drinking, "never" refers to those who had never drunk or drank less than one 8-ounce cup of coffee or tea per week; "current" refers to those who drank at least one cup of coffee or tea per week within the past month; "past" refers to those who had drunk at least one cup of coffee or tea per week more than 1 month before. For alcoholic beverage (including beer, wine, and liquor) drinking, "never" refers to those who had never drunk or drank less than one alcoholic beverage per week; "current" refers to those who drank at least one alcoholic beverage per week within the past month; "past" refers to those who had drunk at least one alcoholic beverage per week more than 1 month before. One glass of beer equals 12 ounces; one glass of wine equals 4 ounces; one shot of liquor equals 1 ounce. The putative risk factors were selected by a combination of our knowledge and intuition. Our approach was not entirely hypothesis driven, allowing us flexibility in using the collected data; we limited the number to 25 to avoid being overly exploratory.

Data Analysis

The study sample in this analysis was used in a previous analysis looking at the efficacy of superovulation and IUI in the treatment of infertility (21). Of the 932 infertile couples recruited for that study, 268 (29%) did not complete the lifestyle or occupational exposure questionnaire. Those subjects were excluded from the present analysis, leaving 664 couples. All data management and analyses were performed using SAS (v 9.1; SAS Institute).

Baseline characteristics of the couples were compared among different treatment groups. Next, bivariate analyses were performed to determine the association between pregnancy outcome and the different factors based on a priori hypotheses. For live birth analysis, the live birth rate was the ratio of the total number of patients who delivered a live birth to the total number of patients in the groups, regardless of their pregnancy status. Pearson chi-square test was used for categoric data. Multivariable logistic regression analyses were then performed by applying the backward and stepwise procedures on the predictors introduced above (P values $<.1$ to enter and $<.05$ to stay), leading to the same final model. When the final model was obtained, the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were computed with respect to the corresponding reference groups. We further performed an analysis on a subset of the data by including only the couples who underwent IUI (IUI and COS-IUI groups), to evaluate whether the results were changed. A two-tailed P value of $<.05$ was considered to be statistically significant. The reported P values were not adjusted for multiple comparisons.

RESULTS

Baseline Characteristics

The baseline characteristics of the 664 couples included in the following analysis are listed in Table 1. They are similar to those reported previously for the entire cohort (21).

TABLE 1

Baseline characteristics of 664 subjects.

Characteristic	ICI (n = 170)	IUI (n = 171)	COS-ICI (n = 159)	COS-IUI (n = 164)	*P* value[a]
Age (y), mean ± SD					
Women	32 ± 4	32 ± 4	32 ± 4	32 ± 4	.743
Men	35 ± 5	34 ± 4	34 ± 5	35 ± 5	.711
BMI (kg/m^2), mean ± SD (women)	24 ± 5	23 ± 4	23 ± 4	23 ± 4	.669
Bachelor's degree (%)					
Women	32	38	43	44	.089
Men	36	33	36	42	.406
White race (%)					
Women	88	88	88	89	.968
Men	88	88	89	89	.924
Nulliparous (women) (%)	62	62	60	58	.838
Duration of infertility (mo), mean ± SD	44 ± 33	45 ± 32	42 ± 30	40 ± 24	.466

Note: BMI = body mass index; COS-ICI = controlled ovarian stimulation and intracervical insemination; COS-IUI = controlled ovarian stimulation and intrauterine insemination; ICI = intracervical insemination; IUI = intrauterine insemination.
[a] The chi-square test was used for categoric variables, and the F statistic from an analysis of variance was used for continuous variables.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

Among the 664 remaining couples, there were 170 subjects in the ICI group, 171 in the natural-cycle IUI group, 159 in the COS-ICI group, and 164 in the COS-IUI group. There were no statistically significant differences in the baseline characteristics among the four treatment groups (Table 1). In addition, there was no significant difference in pregnancy rate or live birth rate between the patients included in the current analysis and those excluded (Supplemental Table 1, available online at www.fertstert.org). Therefore, not completing lifestyle or occupational exposure questionnaire seemed to have occurred randomly in terms of the baseline characteristics, treatment assignments, and the primary outcomes, and the patients in the present study remained representative of the population and selection bias was not apparent.

Bivariate Analyses

The association between the individual factors and pregnancy outcome is presented in Table 2. Besides the different treatment effects, as also reported in the previous study (21), women who reported that they had consumed coffee, tea, or alcoholic beverages in the past (>1 month) had significantly higher rates of pregnancy and live birth compared with never users (Table 2). For the subjects who drank coffee, tea, or alcoholic beverages in the past, the duration since they stopped drinking is presented in Supplemental Table 2 (available online at www.fertstert.org). There was no significant association between pregnancy or live birth and the duration since the subjects stopped drinking coffee or tea (Supplemental Table 2), nor between pregnancy or live birth and the length of years the subjects drank coffee, tea, or alcoholic beverages in the past (data not shown; $P>.1$). There was a significantly negative association between pregnancy or live birth and the duration since the subjects stopped drinking alcoholic beverage beer and liquor, but not wine (Supplemental Table 2). The amount of coffee, tea, or alcoholic beverages consumed by the subjects is shown in Supplemental Table 2. There was no significant association between pregnancy or live birth rate and the amount of coffee or tea or alcoholic beverages consumed by the subjects before the subjects stopped drinking coffee or tea or alcoholic beverages (Supplemental Table 2). In addition, for subjects who drank coffee, tea or alcoholic beverage in the past, there was no significant difference in the pregnancy rate and live birth rate between those who stopped drinking coffee, tea, or alcoholic beverages because they were trying to conceive and those who stopped drinking coffee, tea, or alcoholic beverages for other reasons (Supplemental Table 3, available online at www.fertstert.org).

No significant association was found between pregnancy and live birth rates and other factors evaluated, including age, BMI (range: 15–44 kg/m^2), race, education, female infertility duration, smoking, and all occupational exposures (Table 2). For smoking, the current smokers had smoked regularly, at least one cigarette a day, for 12.4 ± 4.8 years (n = 78); the past smokers had smoked regularly, at least one cigarette a day, for 6.8 ± 4.7 years (n = 126), with a duration of 79.8 ± 60.5 months since they stopping smoking, and before they stopped smoking regularly, they smoked 11.8 ± 8.7 cigarette a day. Although these variables were not significant, we assessed whether they might confound the significant associations reported above and found that they had little effect.

The pregnancy loss rate was not significantly different between the subjects in terms of their smoking, coffee or tea drinking, alcoholic beverage drinking, cocaine trying, or marijuana trying status or different occupational exposure history (data not shown).

Multivariable Analyses

The results of the multivariable analyses with pregnant versus not pregnant or live birth versus non live birth status as the outcome are presented in Table 3. After backward selection, variables for women of coffee, tea, and alcohol drinking were included the final model (variable for exposure to pesticide was also included when the outcome was pregnancy). In particular, women who drank coffee, tea, or alcoholic

TABLE 2

Bivariate analyses of risk factors for pregnancy outcome (pregnant vs. non pregnant; live birth vs. non live birth).

Characteristic	n	Pregnancy rate per couple, %	*P* value	Live birth rate per couple, %[a]	*P* value
Treatment					
ICI	170	8.2	<.001	5.9	<.001
IUI	171	17.5		15.2	
COS-ICI	159	21.4		16.4	
COS-IUI	164	34.2		23.2	
Sociodemographics					
Women age (y)					
20–29	169	21.9	.734	18.3	.379
30–34	306	19.0		13.7	
35–40	189	20.6		14.3	
Men age (y)					
20–29	95	23.2	.696	17.9	.666
30–39	508	19.9		14.8	
40–55	61	18.0		13.1	
Women race					
White	601	19.6	.316	14.6	.806
Black	19	36.8		21.1	
Asian	32	21.9		18.8	
Other	12	16.7		16.7	
Men race					
White	606	19.0	.105	14.4	.431
Black	18	38.9		22.2	
Asian	30	30.0		23.3	
Other	10	30.0		20.0	
Women BMI (kg/m^2)					
<25	450	19.1	.318	14.4	.620
25–30	95	23.2		17.9	
>30	53	28.3		18.9	
Women educational level					
High school	108	18.5	.430	12.0	.626
College	469	19.6		15.6	
Postcollege	87	25.3		16.1	
Men educational level					
High school	113	19.5	.974	15.0	.940
College	431	20.4		15.3	
Postcollege	120	20.0		14.2	
Infertility risk factors (women)					
Pregnant history					
No	403	17.9	.065	14.1	.412
Yes	261	23.8		16.5	
Infertility length (mo)					
12–23	149	26.2	.100	18.1	.459
24–35	166	19.9		15.1	
≥36	349	17.8		13.8	
Lifestyle risk factors (women)					
Smoking					
Never	455	19.1	.567	13.9	.391
Current	80	23.8		16.3	
Past (>1 mo)	129	21.7		18.6	
Coffee or tea drinking					
Never	74	16.2	.008	13.5	.007
Current	545	19.3		13.9	
Past (>1 mo)	45	37.8		31.1	
Soda drinking					
Never	70	28.6	.296	20.0	.536
Current	543	19.3		14.2	
Past (>1 mo)	50	18.0		18.0	
Alcoholic drinking					
Never	260	16.9	.008	13.1	<.001
Current	274	18.3		11.7	
Past (>1 mo)	128	30.5		25.8	
Marijuana trying					
No	311	19.9	.825	13.5	.532
Yes	342	20.5		16.4	
Unknown	11	18.2		18.2	

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

TABLE 2

Continued.

Characteristic	n	Pregnancy rate per couple, %	*P* value	Live birth rate per couple, %[a]	*P* value
Cocaine trying					
No	524	19.7	.857	13.9	.396
Yes	131	22.1		19.1	
Unknown	9	22.2		22.2	
Occupational exposures (women)					
Solvents					
No	513	21.3	.460	16.0	.564
Yes	91	18.7		13.2	
Unknown	60	13.3		10.0	
Lead					
No	604	20.9	.426	15.2	.743
Yes	8	25.0		25.0	
Unknown	52	11.5		11.5	
Paint					
No	517	20.3	.457	15.1	.309
Yes	129	21.7		17.1	
Unknown	18	5.5		0.0	
Pesticide					
No	539	21.7	.095	16.1	.167
Yes	88	17.1		13.6	
Unknown	37	5.4		2.7	
Metal fumes					
No	625	20.3	.853	15.2	.932
Yes	8	25.0		12.5	
Unknown	31	16.1		12.9	
Anesthetic gases					
No	610	21.0	.204	15.9	.199
Yes	39	15.4		7.7	
Unknown	15	0.0		0.0	
Chemotherapy drugs					
No	639	20.5	.563	15.2	.704
Yes	9	22.2		22.2	
Unknown	16	6.3		6.3	
Excess heat					
No	613	20.6	.418	15.7	.404
Yes	40	20.0		10.0	
Unknown	11	0.0		0.0	
Vibration					
No	627	20.9	.304	15.6	.321
Yes	21	9.5		9.5	
Unknown	16	6.3		0.0	
Radiation					
No	591	20.3	.495	15.4	.539
Yes	50	24.0		16.0	
Unknown	23	8.7		4.3	
Video display terminal					
No	171	21.6	.623	15.8	.768
Yes	487	19.9		15.0	
Unknown	6	0.0		0.0	
Electromagnetic field					
No	512	20.3	.055	15.4	.101
Yes	39	33.3		23.1	
Unknown	113	15.0		10.6	

Note: Abbreviations as in Table 1.

[a] Live birth rate was calculated as the ratio of the total number of patients who delivered a live birth to the total number of patients in the groups, regardless of their pregnancy status.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

beverages in the past, but not current users, had a higher rate of pregnancy and live birth compared with never users. Also compared with current users, women who reported that they had consumed coffee, tea, or alcoholic beverages in the past had significantly higher rates of pregnancy (aOR 3.3, 95% CI 1.6–6.7 [$P<.001$] for tea or coffee drinking; aOR 1.7, 95% CI 1.1–2.9 [$P=.035$] for alcoholic beverage drinking) and live birth (aOR 3.3, 95% CI 1.6–6.8 [$P=.002$] for tea or coffee drinking; aOR 2.3, 95% CI 1.3–4.0 [$P=.004$] for alcoholic beverage drinking).

Subgroup Analyses

When we repeated the main data analyses including only the couples who underwent IUI treatments (IUI and COS-IUI

TABLE 3

Multivariable logistic regression analyses of risk factors for pregnancy outcome (pregnant vs. not pregnant, live birth vs. non live birth).

Characteristic	OR for pregnancy	95% CI	*P* value	OR for live birth	95% CI	*P* value
Treatment						
ICI	Reference			Reference		
IUI	2.5	1.3–5.0	<.001	3.0	1.4–6.4	.006
COS-ICI	3.3	1.7–6.6	.009	3.4	1.6–7.5	.002
COS-IUI	6.6	3.4–12.7	<.001	5.1	2.4–10.9	<.001
Women coffee or tea drinking						
Never	Reference			Reference		
Current	1.2	0.6–2.4	.608	1.0	0.5–2.0	.898
Past (>1 mo)	4.0	1.6–10.2	.004	3.1	1.2–8.1	.023
Women alcoholic drinking						
Never	Reference			Reference		
Current	1.2	0.7–1.9	.508	0.9	0.5–1.5	.715
Past (>1 mo)	1.9	1.1–3.2	.017	2.1	1.2–3.7	.007
Women exposure to pesticide						
No	Reference					
Yes	0.6	0.3–1.1	.103			
Unknown	0.2	0.1–0.9	.033			

Note: Only variables having a significant association with pregnancy are included in the final model and used for the calculation for the odds ratio from the logistic regression (using backward selection). CI = confidence interval; OR = odds ratio; other abbreviations as in Table 1.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

groups), similar results were again obtained: Past use of coffee, tea, or alcohol was associated with significantly greater pregnancy and live birth rates compared with never or current users (Table 4). No significant association was identified between pregnancy or live birth rates and self-reported exposure to pesticide.

Coffee or tea drinking and smoking may interact with each other (3, 12, 23, 24). Therefore, we also stratified our analyses according to female partner's smoking history. In couples in which the woman had never smoked regularly, past alcoholic beverage drinking was still significantly associated with pregnancy and live birth rate, but past coffee or tea drinking had no significant association with pregnancy outcomes (Supplemental Table 4, available online at www.fertstert.org). In smokers (including both current and past smokers), however, coffee or tea drinking was significantly associated with pregnancy outcomes (Supplemental Table 4).

DISCUSSION

In this investigation, we have examined the relationship between lifestyle factors/occupational exposures and pregnancy outcomes resulting from treatments for unexplained infertility in a large prospective multicenter trial. Supplemental Table 5 (available online at www.fertstert.org) provides a summary of our findings. Given the high prevalence of exposure to these factors in modern society, it is imperative to have a better understanding of the relationship between these factors and outcomes to better counsel women regarding lifestyle modifications that may improve the chances of conception while undergoing treatment. Of the lifestyle

TABLE 4

Bivariate analysis of risk factors for pregnancy outcome (pregnant vs. not pregnant; live birth vs. non live birth) among couples in the IUI groups (n = 335).

Characteristic	n	Pregnancy rate per couple, %	*P* value	Live birth rate per couple, %	*P* value
Women coffee or tea drinking					
Never	36	13.9	<.001	8.3	<.001
Current	277	24.6		17.7	
Past (>1 mo)	22	59.1		54.6	
Women alcoholic drinking					
Never	128	20.3	.006	15.6	<.001
Current	138	23.2		13.8	
Past (>1 mo)	68	39.7		35.3	
Women exposure to pesticide					
No	264	27.7	.259	20.8	.285
Yes	49	22.5		16.3	
Unknown	22	9.1		4.6	

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

factors and exposures evaluated in this investigation, only coffee, tea, or alcohol use was significantly associated with pregnancy and live birth outcomes. Specifically, past users of coffee, tea, or alcohol had significantly higher chances of conception and live-birth compared with never and current users. Other factors that have been related to impaired natural fertility in earlier investigations, such as smoking, high BMI, illicit drug use, and exposure to environmental toxins (25–28), were not significantly associated with the outcomes of fertility treatments. These findings were consistent in both the bivariate and the logistic regression analyses.

Any relationship between illicit drug use and pregnancy outcomes would have been difficult to ascertain in this investigation, because the variables related to illicit drug use ("women marijuana trying" and "women cocaine trying") only captured any use of marijuana and cocaine rather than specified current or past use or the use of any other substance. Moreover, because both of these drugs are illegal, actual use may be underreported. Regarding age, we found that the live birth rates were lower in the 30–40-year-old women compared with women in the 20–29-year-old group (13.9% vs. 18.3%, respectively; $P=.167$; Table 2). One explanation for the lack of significant difference in pregnancy or live birth rates among different age groups is that this is a preselected group of women with "unexplained" infertility. It is possible that the younger women have subclinical reduced ovarian reserve or some other unmeasured variables that make them similar to the older women in resulting in infertility; thus, the younger women show results similar to the older women regarding pregnancy and delivery (29).

The effect of alcohol use on natural fertility in women has not been clearly established. In a prospective study of 7,393 women, Eggert et al. (30) identified an increased risk of infertility (relative risk 1.6; 95% CI 1.1–2.3) in high consumers of alcohol ($\geq$2 drinks per day) compared with moderate consumers. Conversely, other investigations have not identified a significant relationship between alcohol use in women and fecundability (3–5), but have shown an increase in first-trimester pregnancy loss (8). Within the context of infertility treatments such as COS-IUI, we are unaware of earlier studies investigating the relationship between alcohol use and outcomes; however, consumption of at least four drinks per week was associated with a decrease in the IVF live birth rate in one investigation (19).

As with alcohol use, we are unaware of earlier investigations evaluating the effect of coffee or tea drinking on outcomes after infertility treatments such as COS-IUI. Given that both coffee and tea contain significant amounts of caffeine, it seems to be likely that the relevant exposure is caffeine. We identified no significant relationship between soda drinking and either pregnancy or live birth rates; however, soda contains significantly less caffeine than either coffee or tea. High caffeine use (>5–7 cups per day) has been associated with decreased natural fertility in some investigations (3, 31), an effect which may be dose related (32). However, others have failed to identify a significant relationship (4). It has been shown in some studies that moderate to heavy caffeine use increased the rate of pregnancy loss (33, 34). One may hypothesize that higher pregnancy and live birth rates observed in past users of coffee or tea may be due to higher pregnancy loss rates in current users. However, this is not supported by our data. In fact, the pregnancy loss rate in the past users was the highest among the three groups (past: 6.7%; current: 5.4%; never: 2.7%).

Given that previous investigations have generally shown a negative effect of female smoking and obesity on the time to spontaneous conception (25, 26) and outcomes after IVF treatment (17, 18), we were surprised that no significant relationship was identified between these variables and either pregnancy or live birth rates. Consistent with our findings, Farhi et al. (35) did not identify significant differences in pregnancy rate between smokers and nonsmokers (16.3% and 15.8%, respectively) in a retrospective review of 885 couples undergoing COS-IUI, although a higher dose of gonadotropins was required in smokers. Similarly, a retrospective review of the outcomes of 333 ovulatory women undergoing COS-IUI identified no significant difference in cycle fecundity among different BMI groups ranging from underweight to obese (36). It is possible that the observation of impaired natural fertility in obese women is partially related to ovulatory dysfunction.

Our observation of increased pregnancy and live birth rates in past users of coffee, tea, or alcohol relative to current and never users requires further evaluation and validation. Although we did not have prior knowledge for this finding or an external dataset with which to validate it, there are reasons to believe its validity. If these exposures had long-lasting negative effects on conception, one would expect to observe a similar negative impact on outcomes in both current and past users compared with never users. Alternatively, if exposure to these factors resulted in only short-term effects, then one would expect past and never users to have similar pregnancy rates, both of which would be superior to current users. However, neither of these outcomes was observed. It is possible that women who discontinue drinking coffee, tea, or alcohol in anticipation of attempting conception possess characteristics that are associated with positive health outcomes, such as an internal locus of control (i.e., a belief that their ability to conceive can be self-managed and controlled), because it is generally considered that consumption of caffeine containing beverages and alcohol are not healthy habits before conception. Perhaps women who have recently discontinued the use of coffee, tea, or alcohol in an attempt to improve their chances of achieving a pregnancy are also making other lifestyle changes that were not measured or not fully adjusted for in the present investigation. Because the discontinuation of coffee or tea or alcohol increase both the pregnancy and live birth rate, the possible undetected positive lifestyle changes along with the discontinuation of these habits may have beneficial effects on both pregnancy and live birth (37). One of the factors is smoking status. Smoking has been shown to increase or decrease the effect of coffee or tea drinking on pregnancy outcome (23, 24). The lack of effect of coffee or tea drinking on pregnancy outcome among patients who never smoked in this study suggests that smoking and coffee or tea drinking have an interacting relationship with conception and live birth rates. Another possibility is that never users of coffee, tea, or alcohol are simply different in their ability to conceive at baseline than are current and past users. In other words, if exposure to these factors causes a temporary and reversible negative impact on fecundability, then one would expect past users to experience higher pregnancy rates than current users. Never users who would have been susceptible to the negative effects of coffee, tea, or alcohol could have already achieved a pregnancy before enrollment. Therefore, the remaining never users have different underlying etiologies for their infertility. Earlier studies have investigated the relationship between social class status and pregnancy outcome, and lower level of social class may have a lower pregnancy rate and higher rate of adverse birth outcome (38, 39). The lack of significant association between coffee, tea, or alcoholic beverage drinking and male or female education level (data not shown), one of the main social class factors, suggests that baseline social class status may not be a potential explanation for the differences in pregnancy and live birth rate observed in this study. Regardless of the mechanism, the magnitude of the effects observed in this investigation (aORs 4.0 for past users of coffee or tea, 1.9 for past users of alcohol) is considerable. Therefore, further prospective investigations are needed to confirm and extend the finding of improved pregnancy and live birth rates after recent discontinuation of alcohol, coffee, and tea.

Limitations of the present investigation should be noted. First, all data regarding lifestyle factors were self-reported, and it is possible that subjects may have underreported exposures. This may be particularly true regarding smoking and alcohol use behaviors. Second, the association between greater pregnancy and live birth rates noted in past users of coffee, tea, and alcohol compared with current and never users does not necessarily imply a causal relationship between these factors and outcomes. The data do not contain information to infer this causal relationship.

In summary, in a large prospective multicenter trial investigating the effectiveness of treatments for unexplained infertility, we identified past use of alcohol, coffee, or tea as being significantly associated with increased odds of conception and live birth. Other lifestyle factors and exposures, including smoking, BMI, ever use of illicit drug, and exposure to environmental toxins, were not significantly related to outcomes. Additional prospective investigations are necessary to confirm the finding of improved fecundity after recent discontinuation of alcohol, coffee, and tea.

Acknowledgments: The authors thank Christos Coutifaris and Richard Legro for their encouragement and comments.

REFERENCES

1. Mosher WD, Pratt WF. Fecundity and infertility in the United States: incidence and trends [editorial]. Fertil Steril 1991;56:192–3.
2. Berkowitz King R, Davis J. Introduction: health disparities in infertility. Fertil Steril 2006;85:842–3.
3. Florack EI, Zielhuis GA, Rolland R. Cigarette smoking, alcohol consumption, and caffeine intake and fecundability. Prev Med 1994;23:175–80.
4. Curtis KM, Savitz DA, Arbuckle TE. Effects of cigarette smoking, caffeine consumption, and alcohol intake on fecundability. Am J Epidemiol 1997; 146:32–41.
5. Olsen J, Bolumar F, Boldsen J, Bisanti L, European Study Group on Infertility and Subfertility. Does moderate alcohol intake reduce fecundability? A European multi-center study on infertility and subfecundity. Alcohol Clin Exp Res 1997;21:206–12.
6. Adelusi B, al-Twaijiri MH, al-Meshari A, Kangave D, al-Nuaim LA, Younnus B. Correlation of smoking and coffee drinking with sperm progressive motility in infertile males. Afr J Med Med Sci 1998;27:47–50.
7. Zhu Q, Meisinger J, Emanuele NV, Emanuele MA, LaPaglia N, van Thiel DH. Ethanol exposure enhances apoptosis within the testes. Alcohol Clin Exp Res 2000;24:1550–6.
8. Henriksen TB, Hjollund NH, Jensen TK, Bonde JP, Andersson AM, Kolstad H, et al. Alcohol consumption at the time of conception and spontaneous abortion. Am J Epidemiol 2004;160:661–7.
9. Robbins WA, Elashoff DA, Xun L, Jia J, Li N, Wu G, et al. Effect of lifestyle exposures on sperm aneuploidy. Cytogenet Genome Res 2005; 111:371–7.
10. Younglai EV, Holloway AC, Foster WG. Environmental and occupational factors affecting fertility and IVF success. Hum Reprod Update 2005;11: 43–57.
11. Winker R, Rüdiger HW. Reproductive toxicology in occupational settings: an update. Int Arch Occup Environ Health 2006;79:1–10.
12. Leviton A, Cowan L. A review of the literature relating caffeine consumption by women to their risk of reproductive hazards. Food Chem Toxicol 2002; 40:1271–310.
13. Lahdetie J. Occupation and exposure related studies on human sperm. J Occup Environ Med 1995;37:922–30.
14. Bonde JP, Giwercman A, Ernst E. Identifying environmental risk to male reproductive function by occupational sperm studies: logistics and design options. Occup Environ Med 1996;53:511–9.
15. Bigelow PL, Jarrell J, Young MR, Keefe TJ, Love EJ. Association of semen quality and occupational factors: comparison of case-control analysis and analysis of continuous variables. Fertil Steril 1998;69:11–8.
16. Cohn BA, Overstreet JW, Fogel RJ, Brazil CK, Baird DD, Cirillo PM. Epidemiologic studies of human semen quality: considerations for study design. Am J Epidemiol 2002;155:664–71.
17. Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach R, SART Writing Group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011;26: 245–52.
18. Klonoff-Cohen H, Natarajan L, Marrs R, Yee B. Effects of female and male smoking on success rates of IVF and gamete intra-fallopian transfer. Hum Reprod 2001;16:1382–90.
19. Rossi BV, Berry KF, Hornstein MD, Cramer DW, Ehrlich S, Missmer SA. Effect of alcohol consumption on in vitro fertilization. Obstet Gynecol 2011;117: 136–42.
20. Al-Saleh I, El-Doush I, Grisellhi B, Coskun S. The effect of caffeine consumption on the success rate of pregnancy as well various performance parameters of in-vitro fertilization treatment. Med Sci Monit 2010;16:598–605.
21. Guzick DS, Carson SA, Coutifaris C, Overstreet JW, Factor-Litvak P, Steinkampf MP, et al. Efficacy of superovulation and intrauterine insemination in the treatment of infertility. N Engl J Med 1999;340:177–83.
22. Guzick DS, Overstreet JS, Factor-Litvak P, Brazil CK, Nakajima ST, Coutifaris C, et al, National Cooperative Reproductive Medicine Network. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.
23. Olsen J. Cigarette smoking, tea and coffee drinking, and subfecundity. Am J Epidemiol 1991;133:734–9.
24. Jensen TK, Henriksen TB, Hjollund NH, Scheike T, Kolstad H, Giwercman A, et al. Caffeine intake and fecundability: a follow-up study among 430 Danish couples planning their first pregnancy. Reprod Toxicol 1998;12:289–95.
25. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod 1998;13:1502–5.
26. Hassan MA, Killick SR. Negative lifestyle is associated with a significant reduction in fecundity. Fertil Steril 2004;81:384–92.
27. Mueller BA, Daling JR, Weiss NS, Moore DE. Recreational drug use and the risk of primary infertility. Epidemiology 1990;1:195–200.

28. Hruska K, Furth P, Seifer D, Sharara FI, Flaws JA. Environmental factors in infertility. Clin Obstet Gynecol 2000;43:821–9.
29. Randolph JF, Ginsburg KA, Leach RE, Blacker CM, Moghissi KS, Diamond MP, Reame NE. Elevated early follicular gonadotropin levels in women with unexplained infertility do not provide evidence for disordered gonadotropin-releasing hormone secretion as assessed by luteinizing hormone pulse characteristics. Fertil Steril 2003;80:320–7.
30. Eggert J, Theobald H, Engfeldt P. Effects of alcohol consumption on female fertility during an 18-year period. Fertil Steril 2004;81:379–83.
31. Bolumar F, Olsen J, Rebagilato M, Bisanti L. Caffeine intake and delayed conception: a European multicenter study on infertility and subfecundity. Am J Epidemiol 1997;145:324–34.
32. Wilcox A, Weinberg C, Baird D. Caffeinated beverages and decreased fertility. Lancet 1988;332:1453–6.
33. Infante-Rivard C, Fernandez A, Gauthier R, David M, Rivard GE. Fetal loss associated with caffeine intake before and during pregnancy. JAMA 1993; 270:2940–3.
34. Peck JD, Leviton A, Cowan LD. A review of the epidemiologic evidence concerning the reproductive health effects of caffeine consumption: a 2000–2009 update. Food Chem Toxicol 2010;48:2549–76.
35. Farhi J, Orvieto R. Influence of smoking on outcome of COH and IUI in subfertile couples. J Assist Reprod Genet 2009;26:421–4.
36. Dodson WC, Kunselman AR, Legro RS. Association of obesity with treatment outcomes in ovulatory infertile women undergoing superovulation and intrauterine insemination. Fertil Steril 2006;86:642–6.
37. Anderson K, Nisenblat V, Norman R. Lifestyle factors in people seeking infertility treatment—a review. Aust N Z J Obstet Gynaecol 2010;50: 8–20.
38. Villalbí JR, Salvador J, Cano-Serral G, Rodríguez-Sanz MC, Borrell C. Maternal smoking, social class and outcomes of pregnancy. Paediatr Perinat Epidemiol 2007;21:441–7.
39. Blumenshine P, Egerter S, Barclay CJ, Cubbin C, Braveman PA. Socioeconomic disparities in adverse birth outcomes: a systematic review. Am J Prev Med 2010;39:263–72.

SUPPLEMENTAL TABLE 1

Pregnancy and live birth rates in the patients included in the analysis (n = 664) and those not included (n = 268).

Group	n	Pregnancy rate per couple, %	*P* value	Live birth rate per couple, %	*P* value
Patients included	664	20.0	.788	15.1	.350
Patients not included	268	19.4		12.7	

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

SUPPLEMENTAL TABLE 2

Association between pregnancy or live birth and duration since the subject stopping drinking or the amount drunk before stopping coffee or tea or alcoholic beverages.

Characteristic	Reg. coffee	Decaf. coffee	Reg. tea	Decaf. tea	Beer	Wine	Liquor
Duration since stopped drinking (mo)	37.4 ± 58.9	10.9 ± 42.3	36.3 ± 51.6	9.5 ± 39.0	39.4 ± 47.6	27.9 ± 41.5	35.8 ± 45.2
Estimated coefficient (β) and P value for pregnancy and duration	$\beta = 0.011$; $P = .181$[a]	$\beta = 0.022$; $P = .579$	$\beta = -0.001$; $P = .894$	$\beta = 0.022$; $P = .482$	$\beta = -0.015$; $P = .030$	$\beta = -0.008$; $P = .26$	$\beta = -0.017$; $P = .025$
Estimated coefficient and P value for live birth and duration	$\beta = 0.013$; $P = .118$	$\beta = 0.025$; $P = .573$	$\beta = -0.002$; $P = .781$	$\beta = 0.025$; $P = .471$	$\beta = -0.017$; $P = .028$	$\beta = -0.012$; $P = .45$	$\beta = -0.023$; $P = .019$
Coffee, tea, and alcoholic beverage amount drunk per day before stopping (cups, glasses, shots)[b]	1.3 ± 1.3	0.4 ± 0.6	1.1 ± 1.3	0.4 ± 0.8	0.8 ± 1.3	0.4 ± 0.5	0.5 ± 0.7
Estimated coefficient and P value for pregnancy and amount	$\beta = 0.505$; $P = .149$	$\beta = -0.646$; $P = .460$	$\beta = -0.283$; $P = .454$	$\beta = -4.782$; $P = .165$	$\beta = -0.375$; $P = .214$	$\beta = 0.074$; $P = .877$	$\beta = 0.201$; $P = .577$
Estimated coefficient and P value for live birth and amount	$\beta = 0.694$; $P = .069$	$\beta = -0.421$; $P = .626$	$\beta = -0.189$; $P = .611$	$\beta = -4.005$; $P = .217$	$\beta = -0.332$; $P = .260$	$\beta = 0.067$; $P = .891$	$\beta = 0.312$; $P = .393$

[a] Logistic regression was used to calculate the estimated coefficient and *P* value.
[b] The unit for coffee or tea drinking is a cup, for beer and wine it is a glass, and for liquor a shot. One cup of coffee or tea equals 8 ounces; one glass of beer equals 12 ounces; one glass of wine equals 4 ounces; one shot of liquor equals 1 ounce.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

SUPPLEMENTAL TABLE 3

Pregnancy and live birth rates among subjects who drank coffee or tea or alcoholic beverages in the past.

Characteristic	n	Pregnancy rate, %	Live birth rate, %
Stopped drinking coffee or tea because of trying to conceive	12	33.3	25.0
Stopped drinking coffee or tea not because of trying to conceive	33	39.4	33.3
P value		.998	.725
Stopped drinking alcoholic beverages because of trying to conceive	39	38.5	35.9
Stopped drinking alcoholic beverages not because of trying to conceive	89	27.0	21.4
P value		.193	.083

Note: Chi-square or Fisher exact test was used to determine *P* values.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

SUPPLEMENTAL TABLE 4

Bivariate analysis of risk factors for pregnancy outcome (pregnant vs. non pregnant; live birth vs. non live birth) among nonsmokers (n = 455) and smokers (including current and past smokers; n = 209).

Characteristic	n	Pregnancy rate per couple, %	*P* value	Live birth rate per couple, %	*P* value
Nonsmokers					
Women coffee or tea drinking					
Never	63	14.3	.164	12.7	.537
Current	363	19.0		13.5	
Past (>1 mo)	29	31.0		20.7	
Women alcoholic drinking					
Never	216	14.4	.002	10.2	.003
Current	166	19.3		13.3	
Past (>1 mo)	73	32.9		26.0	
Women exposure to pesticide					
No	368	21.5	.074	15.8	.111
Yes	62	9.7		6.5	
Unknown	25	8.0		4.0	
Smokers					
Women coffee or tea drinking					
Never	11	27.3	.020	18.2	.002
Current	182	19.8		14.8	
Past (>1 mo)	16	50.0		50.0	

Huang. Lifestyle and pregnancy. Fertil Steril 2012.

SUPPLEMENTAL TABLE 5

Summary of the association between pregnancy or live birth rates and different factors included in the study.

Variable	Pregnancy rate	Live birth rate
Women age	None	None
Men age	None	None
Women race	None	None
Men race	None	None
Women BMI	None	None
Women education	None	None
Men education	None	None
Women pregnancy history	None	None
Women infertility length	None	None
Women smoking	None	None
Women coffee or tea drinking[a]	None	None
Current	None	None
Past	+	+
Duration since stopped drinking	None	None
Amount drunk before stopping drinking	None	None
Stopped drinking because of trying to conceive	None	None
Women alcoholic beverage drinking	None	None
Current	None	None
Past	+	+
Duration since stopped drinking	−	−
Stopped drinking because of trying to conceive	None	None
Amount drunk before stopping drinking	None	None
Women marijuana trying	None	None
Women cocaine trying	None	None
Women occupational exposures	None	None

Note: None indicates no significant association; "+" indicates positive significant association; and "−" indicates negative significant association.
[a] For coffee, tea, and alcohol drinking, current and past drinkers were compared with those who never drank; the results for duration since stopped drinking, amount drunk before stopping drinking, and stopped drinking because of trying to conceive were for subjects who drank coffee, tea, or alcohol in the past.

Huang. Lifestyle and pregnancy. Fertil Steril 2012.