Women's alcohol consumption and cumulative incidence of live birth following in vitro fertilization

L. E. Dodge^{1,2} · S. A. Missmer^{3,4,5} · K. L. Thornton^{2,6} · M. R. Hacker^{1,2,4}

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Abstract

Objective The objective of this study was to determine the effect of alcohol consumption on outcomes among women undergoing in vitro fertilization (IVF).

Design This study is a retrospective cohort study.

Setting This study was performed in a private academically affiliated IVF center.

Patients Patients included women presenting for their first IVF cycle from July 2004 through October 2012.

Intervention Women completed self-administered questionnaires before their first IVF cycle, which included report of usual alcohol consumption. Women were categorized as non-drinkers, social drinkers, or daily drinkers, as well as by the number of drinks consumed per week. Competing risks

analysis was used to calculate the cumulative incidence of live birth after 6 cycles stratified by alcohol consumption.

Main outcome measures Main outcome measures included spontaneous abortion, clinical pregnancy, and live birth following IVF.

Results There were 591 (27.7%) non-drinkers, 1466 (68.7%) social drinkers, and 77 (3.6%) daily drinkers (total $n = 2134$). In the first cycle, compared to non-drinkers, daily drinkers had a twofold increased risk of spontaneous abortion (adjusted risk ratio [aRR] 2.2; 95% confidence interval [CI] 1.1–4.5) among all cycle starts, and while their risk of live birth was 30% lower (aRR 0.7; 95% CI 0.4–1.3), the sample size was small, and it was not significantly lower. By the end of 6 cycles, social drinkers and daily drinkers did not differ from non-drinkers in their cumulative incidence of live birth (56.1, 50.6, and 52.1%, respectively; both $P \geq 0.28$).

Conclusion There was a trend towards lower risk of live birth among daily drinkers. Daily drinkers had an increased risk of spontaneous abortion in the first cycle, but the number of daily drinkers was small.

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✉ M. R. Hacker
mhacker@bidmc.harvard.edu

¹ Department of Obstetrics and Gynecology, Beth Israel Deaconess Medical Center, 330 Brookline Ave., KS 3, Boston, MA 02215, USA

² Department of Obstetrics, Gynecology and Reproductive Biology, Harvard Medical School, 25 Shattuck St, Boston, MA 02115, USA

³ Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital and Harvard Medical School, 221 Longwood Ave, Boston, MA 02115, USA

⁴ Department of Epidemiology, Harvard T.H. Chan School of Public Health, 667 Huntington Ave, Boston, MA 02115, USA

⁵ Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115, USA

⁶ Boston IVF, 130 Second Ave, Waltham, MA 02451, USA

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Introduction

While the adverse effects of alcohol consumption during pregnancy on obstetric and fetal health have long been recognized [1], less is known regarding the effects of alcohol consumption on fertility. Among women conceiving spontaneously, alcohol has been linked to increased time to pregnancy [2], decreased probability of conception [3], decreased implantation rate [4], increased risk of spontaneous abortion [4], and increased risk of fetal death [5]. Links also have been found

with anovulation, luteal phase dysfunction, and abnormal blastocyst development [5]. Among men, a meta-analysis of 57 studies found links between alcohol consumption, teratozoospermia, and oligozoospermia [6]. Alcohol has also been linked to sperm morphology and sperm motility [7].

To date, two studies have examined the effects of alcohol use among women undergoing in vitro fertilization (IVF). A study by Klonoff-Cohen and colleagues reported that alcohol drinkers had a decreased, though not significantly so, chance of pregnancy, and that with each drink per day, the number of oocytes retrieved decreased by 13% [8]. They also examined alcohol use among male partners and found the strongest associations with pregnancy and spontaneous abortion for consumption closest to the time when the semen sample was collected [8]. A later study by Rossi et al. found that among women who had at least four drinks per week, the odds of having a live birth decreased by 16% compared to women who consumed fewer than four drinks per week [9]. Among couples in which both partners consumed more than four drinks per week, the odds decreased by 21% compared to those who consumed fewer than four drinks per week [9].

Given the high cost and invasive nature of IVF, it is important to identify modifiable factors that influence IVF success. Given that the two prior studies used total weekly alcohol consumption, the aim of the present study was to examine the effect of alcohol consumption using a measure that also accounts for pattern of consumption (i.e., non-drinker, social drinker, daily drinker) among a large cohort of women undergoing infertility treatment with IVF.

Materials and methods

Study population

We performed a retrospective cohort study of all patients who were ≥ 18 years of age at the start of their first fresh-embryo, non-donor IVF cycle from January 2009 through December 2013 at our center. Subsequent frozen-embryo transfer cycles were included and were considered to be distinct cycles. Up to 6 cycles were included for all eligible women.

Women completed a self-administered questionnaire online prior to beginning their first IVF cycle. This questionnaire was completed for clinical purposes and included questions regarding alcohol consumption and demographic characteristics. Women were asked to classify themselves as non-drinkers, social drinkers, or daily drinkers. Self-reported social drinkers were asked to report the number of drinks they consumed per week, and self-reported daily drinkers were asked to report the number of drinks they consumed per day, which was multiplied by 7 to obtain the number of drinks consumed per week. Cycle characteristics, including cycle day 3 level of follicle stimulating hormone, use of intracytoplasmic sperm

injection and/or assisted hatching, number of oocytes retrieved, and number of embryos frozen and transferred, and pregnancy outcomes were obtained from the electronic medical record. Intrauterine pregnancy was confirmed by rising β -human chorionic gonadotropin and fetal heartbeat seen on early ultrasound performed at approximately 6–7 weeks of gestational age. Spontaneous abortion was defined as any intrauterine pregnancy that did not end in induced abortion or delivery of a live or stillborn fetus. The institutional review board at Beth Israel Deaconess Medical Center approved this study (#2015P-000047).

IVF protocols

Patients underwent IVF treatment protocols for ovarian stimulation, monitoring, and oocyte retrieval as described previously [10]. Both assisted hatching and intracytoplasmic sperm injection were performed when indicated clinically. Embryos were transferred in numbers consistent with national guidelines [11]. Luteal-phase support was provided until 8 weeks of gestation [10]. For patients undergoing frozen-embryo transfer, exogenous estradiol with or without a GnRH agonist was administered as described previously [12]. After the endometrial lining was noted to be ≥ 7 mm on transvaginal ultrasound, luteal-phase support was initiated either 4 days prior to a day-3 embryo transfer or 6 days prior to a blastocyst transfer and continued until 10 weeks of gestation.

Statistical analysis

Descriptive data are presented as the mean $\pm$ standard deviation (SD) or the count and proportion; these were compared with a Student's *t* test or chi-square test, as appropriate. We used Poisson regression with robust variance estimates to calculate the risk ratio (RR) and 95% confidence interval (CI) for the outcomes following the first IVF cycle. A competing risk regression model was used to compute the cumulative incidence function to estimate the cumulative incidence and 95% CI of the first live birth during the study period, with IVF cycle number as the time metric [13]. Each woman could experience one of the following three possible outcomes: (1) achieving a live birth, (2) completing six IVF cycles without achieving a live birth, or (3) not returning to care before either of the first two outcomes occurred; this last group included women who pursued oocyte donation and/or gestational carrier, those who transferred care to another center, those who had a spontaneous pregnancy, and those who discontinued care altogether. Not returning to care was considered to be a competing risk in the analysis. This method of competing risk analysis is a more conservative approach to cumulative live birth rates than the Kaplan-Meier method, in which women who do not return to care are censored at the time of their last IVF cycle. In this case, where all of the censored observations are women who do not return to care, the competing risk approach is mathematically equivalent to the “conservative”

estimates that have been published previously [12, 14]. The cumulative incidence of live birth was calculated for the full cohort and for non-drinkers, social drinkers, and daily drinkers.

Additionally, in order to compare our results with those previously published in the literature, we also classified women as having <4 or ≥ 4 drinks per week. The Pepe-Mori test was used to compare the stratified estimates [15]. Further, we examined drinks per week as a continuous variable. Due to its biological relevance, age was included in all adjusted models. Additional variables that could influence alcohol consumption and live birth were considered as potential confounders, including the cycle characteristics mentioned above and body mass index, cigarette smoking (i.e., never smoker, former smoker, or current smoker), and caffeine use (i.e., non-user or user), and those with an appreciable effect on the risk ratio were retained in the model. All tests were two-sided, and P values <0.05 were considered statistically significant. All statistical analyses were conducted with SAS 9.4 (SAS Institute, Cary, NC) and Stata12 (StataCorp, College Station, TX).

Results

A total of 2134 women underwent 5028 cycles. Of these women, 27.7% reported themselves to be non-drinkers, 68.7% reported themselves to be social drinkers, and 3.6% reported themselves to be daily drinkers. Among the social drinkers, 77.9% reported consuming <4 drinks per week. Among the daily drinkers, 68.4% reported consuming one drink per day, and 31.6% reported consuming two drinks per day. With regards to the number of drinks consumed per week, 81.7% of all women reported consuming <4 drinks per week, and 18.3% of women reported consuming ≥ 4 drinks per week. The women's mean age was 35.7 ± 4.8 years, and their mean body mass index was 25.8 ± 5.8 kg/m². Characteristics at the start of the first IVF cycle are shown in Table 1.

Social drinkers did not differ from non-drinkers in any clinical characteristics at the first cycle, including the number of embryos cryopreserved or the number of embryos transferred (both $P \geq 0.39$). Daily drinkers had fewer oocytes retrieved than non-drinkers (9.5 ± 5.4 vs. 11.8 ± 8.4 ; $P = 0.002$),

Table 1 Participant characteristics at the first cycle

Characteristic	Non-drinkers <i>n</i> = 591	Social drinkers <i>n</i> = 1466	Daily drinkers <i>n</i> = 77
Age (years)	35.5 $\pm$ 5.2	35.7 $\pm$ 4.6	37.2 $\pm$ 4.5
BMI (kg/m ²)	26.3 $\pm$ 6.1	25.7 $\pm$ 5.7	25.0 $\pm$ 4.3
Underweight (<18.5)	18 (3.3)	26 (1.9)	0 (0.0)
Normal weight (18.5–<25)	257 (47.1)	742 (54.5)	38 (55.9)
Overweight (25–<30)	152 (27.8)	373 (27.4)	22 (32.4)
Obese (≥ 30)	119 (21.8)	220 (16.2)	8 (11.8)
Gravidity			
0	297 (50.3)	837 (57.1)	45 (58.4)
1	141 (23.9)	321 (21.9)	16 (20.8)
2+	153 (25.9)	308 (21.0)	16 (20.8)
Parity			
0	423 (71.6)	1177 (80.3)	61 (79.2)
1	122 (20.6)	226 (15.4)	14 (18.2)
2+	46 (7.8)	63 (4.3)	2 (2.6)
Cycle day 3 FSH	7.3 $\pm$ 2.8	7.6 $\pm$ 3.3	8.3 $\pm$ 4.3
Infertility diagnosis ^a			
Male factor	150 (25.4)	354 (24.2)	23 (29.9)
Diminished ovarian reserve	52 (8.8)	183 (12.5)	14 (18.2)
Tubal factor	56 (9.5)	97 (6.6)	6 (7.8)
Ovarian dysfunction	40 (6.8)	89 (6.1)	4 (5.2)
Endometriosis	26 (4.4)	60 (4.1)	5 (6.5)
Uterine factor	11 (1.9)	27 (1.8)	2 (2.6)
Unexplained	212 (35.9)	540 (36.8)	22 (28.6)

Data are presented as mean $\pm$ standard deviation or count (proportion)

BMI body mass index, FSH follicle stimulating hormone

^a Multiple diagnoses may be reported

but they did not differ significantly with respect to the other clinical characteristics measured (Table 2).

With regards to the outcomes of the first cycle (Table 3), the incidence of clinical pregnancy per cycle start did not differ between non-drinkers and social drinkers (33.7 vs. 31.1%, $P = 0.26$) or between non-drinkers and daily drinkers (33.7 vs. 31.2%, $P = 0.66$); results for clinical pregnancy per transfer were similar. While spontaneous abortion did not differ per cycle start or per transfer between non-drinkers and social drinkers (both $P \geq 0.73$), compared to non-drinkers, daily drinkers experienced more than twice as many spontaneous abortions both per cycle start (13.0 vs. 5.3%, $P = 0.02$) and per transfer (16.1 vs. 6.3%, $P = 0.02$). While the incidence of live birth was lower among daily drinkers (18.2% per cycle start and 22.6% per transfer) compared to non-drinkers (28.1% per cycle start and 33.9% per transfer), this difference was only borderline significant (both $P = 0.07$). There were no differences in the incidence of live birth between non-drinkers and social drinkers (both $P \geq 0.21$).

After adjusting for age, the number of oocytes retrieved, and the number of embryos transferred, there were no significant differences in the risk of clinical pregnancy, spontaneous abortion, or live birth in the first cycle between non-drinkers and social drinkers (all $P \geq 0.60$) (Table 4). When comparing non-drinkers and daily drinkers, however, daily drinkers had a more than twofold increased risk of spontaneous abortion (adjusted RR [aRR] 2.21; 95% CI 1.08–4.53), which seemed to drive a lower, though not significantly so, risk of live birth in this group (aRR 0.73; 95% CI 0.42–1.27).

With regards to the cumulative incidence of live birth (Supplemental Table 1), among all women, 54.8% (95% CI 52.7–57.0) achieved a live birth by the end of 6 cycles. Daily drinkers consistently had the lowest cumulative incidence of live birth after each cycle. The difference between daily drinkers and non-drinkers was more marked in the earlier cycles (18.2 and 28.1%, respectively, in cycle 1) and was nearly equivalent by cycles 4 (48.1 and 49.6%, respectively) and 5 (50.6 and 51.3%, respectively). While non-drinkers had higher cumulative incidences of live birth than social drinkers after cycles 1 and 2, they had lower cumulative incidences of live birth after cycles 4, 5, and 6. The cumulative live birth curve for non-drinkers did not significantly differ from that of social drinkers ($P = 0.59$) or daily drinkers ($P = 0.28$) (Fig. 1).

Finally, when we classified alcohol consumption by <4 or ≥ 4 drinks per week, we found no difference in the risk of live birth after the first cycle between women who consumed <4 and those who consumed ≥ 4 drinks per week (aRR 1.01; 95% CI 0.80–1.28); there was no difference in the cumulative incidence of live birth by the end of 6 cycles (54.4 and 56.1%, respectively; $P = 0.98$). However, there was an increased, though not significantly so, risk of spontaneous abortion among women consuming ≥ 4 drinks per week compared to those consuming <4 (aRR 1.45; 95% CI 0.93–2.26). There were non-significant risks of spontaneous abortion (aRR 0.97; 95% CI 0.86–1.11) and live birth with each additional drink per week (aRR 1.06; 95% CI 0.999–1.11).

Table 2 Clinical characteristics of the first cycle

Characteristic	Non-drinkers <i>n</i> = 591	Social drinkers <i>n</i> = 1466	<i>P</i> ^a	Daily drinkers <i>n</i> = 77	<i>P</i> ^b
Manipulation					
ICSI ^c	211 (35.7)	518 (35.3)	0.87	26 (33.8)	0.74
Assisted hatching ^c	32 (5.4)	73 (5.0)	0.69	7 (9.1)	0.19
Total gonadotropins (IU) ^c	3117 ± 1820	3136 ± 1807	0.84	3202 ± 1925	0.71
Peak estradiol (pg/mL) ^c	2011 ± 1458	2119 ± 1481	0.15	1981 ± 1278	0.87
Oocytes retrieved ^c	11.8 ± 8.4	12.1 ± 8.1	0.52	9.5 ± 5.3	0.001
Embryos cryopreserved ^c			0.40		0.46
0	308 (57.0)	699 (53.7)		43 (58.9)	
1–3	127 (23.5)	324 (24.9)		20 (27.4)	
≥4	105 (19.4)	280 (21.5)		10 (13.7)	
Embryos transferred ^c	1.8 ± 1.0	1.8 ± 1.0	0.90	1.9 ± 1.2	0.54

Data are presented as mean standard deviation or *n* (%)

ICSI intracytoplasmic sperm injection

^a *P* compares non-drinkers to social drinkers

^b *P* compares non-drinkers to daily drinkers

^c Calculated only among fresh cycles

Table 3 Outcomes of the first IVF cycle stratified by drinking status

Characteristic	Non-drinkers <i>n</i> = 591	Social drinkers <i>n</i> = 1466	<i>P</i> ^a	Daily drinkers <i>n</i> = 77	<i>P</i> ^b
Fresh cycle	591 (100.0)	1466 (100.0)	–	77 (100.0)	–
Cancellation	39 (6.6)	111 (7.6)	0.44	4 (5.2)	0.81
Oocyte retrieval	552 (93.4)	1355 (92.4)	0.44	73 (94.8)	0.81
Embryo transfer ^c	490 (88.8)	1163 (85.8)	0.09	62 (84.9)	0.34
Implantation rate ^d	0.63 ± 0.34	0.65 ± 0.36	0.49	0.56 ± 0.41	0.37
Outcomes per cycle start					
Clinical pregnancy	199 (33.7)	456 (31.1)	0.26	24 (31.2)	0.66
Spontaneous abortion	31 (5.3)	79 (5.4)	0.90	10 (13.0)	0.02
Termination	2 (0.3)	1 (0.1)	0.20	0 (0.0)	1.00
Live birth	166 (28.1)	372 (25.4)	0.21	14 (18.2)	0.07
Stillbirth	1 (0.2)	1 (0.1)	0.49	0 (0.0)	1.00
Unknown	0 (0.0)	4 (0.3)	0.58	0 (0.0)	–
Outcomes per transfer					
Clinical pregnancy	199 (40.6)	456 (39.2)	0.59	24 (38.7)	0.77
Spontaneous abortion	31 (6.3)	79 (6.8)	0.73	10 (16.1)	0.02
Live birth	166 (33.9)	372 (32.0)	0.45	14 (22.6)	0.07

Data are presented as mean standard deviation or *n* (%)

^a *P* compares non-drinkers to social drinkers

^b *P* compares non-drinkers to daily drinkers

^c Denominator is the number of cycles that were not canceled prior to oocyte retrieval

^d Calculated as the number of fetal heartbeats divided by the number of transferred embryos among cycles with an embryo transfer

Discussion

Findings

The incidence of clinical pregnancy and live birth after the first cycle did not differ by alcohol consumption among women undergoing IVF. However, after adjusting for covariates, daily drinkers were found to have a twofold increased risk of spontaneous abortion in the first IVF cycle. While this increased risk may be meaningful for clinical outcomes, it should be noted that few women reported being daily drinkers; thus, this estimate may be unstable due to small sample size. Prior research has found no effect of pre-

pregnancy alcohol consumption on the risk of spontaneous abortion in populations without infertility [16–20], and one study in the infertility population also found no effect [9].

The cumulative incidence of live birth after 6 cycles did not differ between the groups, though daily drinkers showed lower cumulative incidences of live birth after the first 3 cycles. This finding is consistent with a non-significantly lower incidence of live birth in the first cycle as observed by Klonoff-Cohen et al. [8], though this previous study did not examine live birth in subsequent cycles. Unlike the study by Rossi et al., we did not find an effect of alcohol consumption on IVF outcomes after multiple cycles among women who consumed at least four drinks per week [9]. However, women in

Table 4 Risk ratios of pregnancy outcomes in the first cycle start using modified Poisson regression with robust variance

Outcome	<i>Social drinker vs. non-drinker</i>		<i>Daily drinker vs. non-drinker</i>	
	Unadjusted RR (95% CI)	Adjusted ^a RR (95% CI)	Unadjusted RR (95% CI)	Adjusted ^a RR (95% CI)
Clinical pregnancy	0.92 (0.78–1.1)	0.94 (0.79–1.1)	0.93 (0.61–1.4)	1.00 (0.65–1.5)
Spontaneous abortion	1.02 (0.68–1.6)	1.1 (0.73–1.8)	2.5 (1.2–5.1)	2.3 (1.04–5.1)
Live birth	0.90 (0.75–1.1)	0.92 (0.77–1.1)	0.65 (0.38–1.1)	0.72 (0.42–1.2)

RR risk ratio, CI confidence interval

^a Clinical pregnancy and live birth models are adjusted for age; spontaneous abortion models are adjusted for age and body mass index, and *n* = 1975 due to missing values of body mass index

Fig. 1 Cumulative incidence curves for live birth stratified by drinking status

the prior study reported consuming higher levels of alcohol than women in the current study, suggesting that these groups may not be entirely comparable.

Anecdotally, fertility patients are interested in recommendations for alcohol consumption while pursuing treatment. While there is some evidence that couples decrease their alcohol consumption as they approach treatment [8], there are no explicit professional society recommendations regarding patients' alcohol consumption. A patient booklet from the American Society of Reproductive Medicine notes that "alcohol...may be harmful," but offers no other information for patients [21]. Thus, it is important to define the effect of alcohol consumption on IVF outcomes in order to accurately counsel patients about their best chances for success with IVF treatment.

Strengths and limitations

Alcohol consumption was categorized at the initiation of IVF treatment and not during the IVF cycle(s). This measure may reflect a woman's long-term alcohol consumption habits, though the extent to which the women in this study changed their behavior in the time leading up to infertility treatment is unknown. Further, women may change their behaviors over time while undergoing IVF treatment, particularly if they have failed cycles. This may show regression to the mean as daily drinkers and social drinkers become non-drinkers with the accumulation of failed cycles. The relevant exposure window for alcohol consumption in women and outcomes of IVF remains unclear. As such, this use of an alcohol consumption measure from a single time point is a weakness of the present study, and the extent of this weakness depends on the extent to which this measure represents the relevant exposure window. Additionally, while self-report has shown to be a valid measure of alcohol consumption [22], the alcohol measure may suffer from misclassification if women under-reported their

consumption due to social desirability bias. This misclassification would be expected to be similar regardless of the woman's cycle outcome and thus would be expected to attenuate any true effect of alcohol consumption on the cumulative incidence of live birth following IVF. Further, the type of alcohol (i.e., beer, wine, spirits) was not assessed, which is important because the volume of alcohol varies by type, and the type of alcohol consumed may be correlated with other patient factors such as age or body mass index. Finally, we are unable to calculate a response rate to the clinical questionnaire because the denominator of women who were asked to complete it is unknown. However, there is no reason to believe that women who completed the questionnaire had different alcohol consumption from those who did not complete the questionnaire. Among women who completed the questionnaire, only 1% skipped the alcohol questions. Because this study made use of an existing clinical assessment, we were unable to modify the alcohol questions to address our hypotheses in greater detail; future studies should consider using a prospective survey to obtain additional information on alcohol consumption.

This study benefits from its use of a two-part question quantifying alcohol exposure. While prior studies have focused solely on weekly alcohol consumption, they have not assessed any measure of patterns of alcohol consumption (i.e., non-drinker, social drinker, daily drinker), which may be more easily assessed in the clinical setting and may be more biologically relevant. Our study first asked women to categorize themselves as non-drinkers, social drinkers, or daily drinkers, which provides information regarding the pattern of alcohol consumption in addition to the number of drinks consumed per week. While it is possible for both a social drinker and a daily drinker to consume seven drinks per week, it may be more likely that the social drinker is having more drinks on fewer occasions, while the daily drinker may be more likely to be having fewer drinks at any one time but consuming alcohol on a more regular basis. Because the extent to which various patterns of alcohol consumption affect IVF outcomes is unknown, this multi-pronged analysis is a strength of this study. Future studies with larger sample sizes should determine whether there are differences between self-reported social drinkers and self-reported daily drinkers who consume a similar number of drinks per week.

Conclusion

In summary, alcohol consumption was not associated with the cumulative incidence of live birth in up to 6 cycles of IVF, though daily drinkers did experience lower cumulative incidence of live birth after the first 3 cycles, which may be clinically significant. Daily drinkers were at twofold increased risk of spontaneous abortion after the first cycle compared to

non-drinkers. Future work should include both women and men and focus on identifying the relevant exposure window for alcohol consumption prior to pregnancy, as well as the relevant exposure pattern.

Compliance with ethical standards The institutional review board at Beth Israel Deaconess Medical Center approved this study (#2015P-000047).

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