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Marijuana smoking and outcomes of infertility treatment with assisted reproductive technologies

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STUDY QUESTION: What is the association of female and male partner marijuana smoking with infertility treatment outcomes with ART?

SUMMARY ANSWER: Women who were marijuana smokers at enrollment had a significantly higher adjusted probability of pregnancy loss during infertility treatment with ART whereas, unexpectedly, there was a suggestion of more favorable treatment outcomes in couples where the man was a marijuana smoker at enrollment.

WHAT IS KNOWN ALREADY: Data on the relation of female and male partner marijuana use with outcomes of infertility treatment is scarce despite increased use and legalization worldwide.

STUDY DESIGN, SIZE, DURATION: We followed 421 women who underwent 730 ART cycles while participating in a prospective cohort (the Environment and Reproductive Health Study) at a fertility center between 2004 and 2017. Among them, 200 women (368 cycles) were part of a couple in which their male partner also enrolled in the study.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Participants self-reported marijuana smoking at baseline. Clinical endpoints were abstracted from electronic medical records. We used generalized linear mixed models with empirical standard errors to evaluate the association of baseline marijuana smoking with ART outcomes adjusting for participants' age, race, BMI, tobacco smoking, coffee and alcohol consumption, and cocaine use. We estimated the adjusted probability of implantation, clinical pregnancy, and live birth per ART cycle, as well as the probability of pregnancy loss among those with a positive B-hCG.

MAIN RESULTS AND THE ROLE OF CHANCE: The 44% of the women and 61% of the men had ever smoked marijuana; 3% and 12% were marijuana smokers at enrollment, respectively. Among 317 women (395 cycles) with a positive B-hCG, those who were marijuana smokers at enrollment ($N = 9$, cycles = 16) had more than double the adjusted probability of pregnancy loss than those who were past marijuana smokers or had never smoked marijuana ($N = 308$, 379 cycles) (54% vs 26%; $P = 0.0003$). This estimate was based on sparse data. However, couples in which the male partner was a marijuana smoker at enrollment ($N = 23$, 41 cycles) had a significantly higher adjusted probability of live birth than couples in which the male partner was a past marijuana smoker or had never smoked marijuana ($N = 177$, 327 cycles) (48% vs 29%; $P = 0.04$), independently of the women's marijuana smoking status. Treatment outcomes of past marijuana smokers, male and female, did not differ significantly from those who had never smoked marijuana.

LIMITATIONS, REASONS FOR CAUTION: Marijuana smoking was self-reported with possible exposure misclassification. Chance findings cannot be excluded due to the small number of exposed cases. The results may not be generalizable to couples from the general population.

WIDER IMPLICATIONS OF THE FINDINGS: Even though marijuana smoking has not been found in past studies to impact the ability to become pregnant among pregnancy planners in the general population, it may increase the risk of pregnancy loss among couples

undergoing infertility treatment. Marijuana smoking by females and males may have opposing effects on outcomes of infertility treatment with ART.

STUDY FUNDING/COMPETING INTEREST(S): The project was financed by grants R01ES009718, P30ES000002, and K99ES026648 from the National Institute of Environmental Health Sciences (NIEHS). None of the authors has any conflicts of interest to declare.

Key words: assisted reproductive technologies / couple / infertility / pregnancy loss / live birth / marijuana

Introduction

One in six couples trying to conceive experience infertility (Louis et al., 2013; Thoma, et al., 2013) and many seek treatment with ART. In the last decade, multiple studies linked fertility to environmental factors and lifestyle choices including exposure to environmental chemicals (Dodge et al., 2015; Minguez-Alarcon et al., 2016), air pollution (Gaskins et al., 2018; Nassan et al., 2018a), diet (Gaskins and Chavarro, 2018; Nassan et al., 2018b), tobacco smoking (Budani et al., 2018), and drug use (Joesoef et al., 1990; Joesoef et al., 1993; du Plessis et al., 2015; Samplaski et al., 2015).

Marijuana is the most widely used illicit drug in the world (UNODC, 2017). In 2016, more than 24 million Americans reported using marijuana (SAMHSA, 2016). Prevalent marijuana use by women and men of reproductive age is of concern given data scarcity on its potential reproductive effects. To date, only three (Klonoff-Cohen et al., 2006; Kasman et al., 2018; Wise et al., 2018) studies have evaluated the relation of marijuana smoking in both partners on fertility. Two studies among pregnancy planners found no evidence that either partner's marijuana use was related to time to pregnancy (Kasman et al., 2018; Wise et al., 2018). Another study (Klonoff-Cohen et al., 2006) among couples undergoing ART, reported that marijuana smoking from both partners was related to lower oocyte yield and fertilization rate but unrelated to pregnancy or live birth rates. These last findings, however, may not be applicable to current practice as more than half of participants underwent gamete or zygote intrafallopian transfer (GIFT/ZIFT) cycles, which currently represent <1% of ART (CDC, 2015). The dearth of literature on the effects on reproduction has been acknowledged by the American College of Obstetricians and Gynecologists (ACOG) (ACOG, 2017). To further study this question using more recent data, we evaluated the relation of marijuana smoking with outcomes of infertility treatment among couples attending the Massachusetts General Hospital (MGH) fertility center. We hypothesized that marijuana smoking in couples would be unrelated to outcomes of infertility treatment.

Materials and Methods

Study design

The Environment and Reproductive Health (EARTH) Study is an ongoing prospective cohort started in 2004 aimed at identifying environmental and lifestyle determinants to fertility among couples presenting to the MGH fertility center, in Boston, Massachusetts (Messerlian et al., 2018). Couples who met the eligibility criteria (18–45 years for women; 18–55 years without vasectomy for men) were invited to participate. Approximately 65% of women and 45% of men approached by study staff enrolled in the study (Messerlian et al., 2018). Joint participation as a couple is encouraged but not required. Of the 850 women who enrolled between 2004 and 2017, 476 women had completed at least one treatment cycle with ART as of December 2017. Of those, 421 (88%) women had answered recreational drug use questions at study enrollment and subsequently underwent 730 ART cycles. There were no statistically significant differences in age, race, education, smoking status, and ART protocol compared between participants who provided data on recreational drug use and those who did not (data not shown). Among these women, 200 (48%) had a non-azoospermic male partner who also enrolled in the study and answered drug use questions. Those 200 couples completed 368 ART cycles between 2005 and 2017 (Supplementary Fig. S1). The Institutional Review Boards of the Harvard T.H. Chan School of Public Health and MGH approved the study. Every participant provided written informed consent.

Assessment of marijuana smoking and covariates

Participants self-reported marijuana smoking at enrollment. Ever marijuana smokers (>2 joints/cigarettes or equivalent amount of marijuana in their lifetime) were also asked to report the average number of joints/cigarettes they smoked per week, age at which they started to smoke marijuana, if they ever quit, last time they smoked marijuana, and the lifetime duration of marijuana smoking. The questionnaire had parallel questions about cocaine use. Participants also self-reported demographic information, data on other lifestyle factors, and medical history.

Assessment of ART outcomes

Trained study staff abstracted the clinical information from the participants' electronic medical records and measured their height and weight at baseline to calculate BMI. Details of participants' clinical management are described elsewhere (Chavarro et al., 2012). Briefly, women underwent a cycle of oral contraceptives for 2–5 weeks to suppress ovulation before their ART cycles, unless contraindicated. On Day 3 of induced menses, women began controlled ovarian stimulation using one of three protocols as clinically indicated: (i) luteal-phase GnRH agonist, (ii) follicular-phase GnRH-agonist/flare, or (iii) follicular-phase GnRH-antagonist. Clinical staff monitored women during stimulation for serum estradiol (E_2), follicle size and counts, and endometrial thickness until 2 days before oocyte retrieval. hCG was administered 35 h before the scheduled oocyte retrieval procedure to induce ovulation. Embryologists classified oocytes as germinal vesicle, metaphase I, metaphase II (MII), or degenerated. Following retrieval, oocytes underwent conventional insemination or ICSI for fertilization, as clinically indicated. Embryologists determined fertilization proportions 17–20 h after insemination as the number of oocytes with two

pro-nuclei divided by the number of mature (MII) oocytes inseminated or injected. Women undergoing cryopreservation-thaw or oocyte donor cycles underwent endometrial preparation prior to transfer. Following embryo transfer, clinical staff assessed clinical outcomes (i.e. implantation, clinical pregnancy, and live birth) identically for fresh, cryo-thaw, and donor-egg recipient cycles. We defined implantation as a serum B-hCG concentration >6m IU/ml, measured ~17 days after oocyte retrieval, clinical pregnancy as the presence of intrauterine gestational sac(s) on transvaginal ultrasonography at 6 weeks gestation, and live birth as the birth of a neonate on or after 24 weeks of gestation. The denominator for the clinical outcomes was the total number of initiated ART cycles. We defined pregnancy loss as positive B-hCG test without a live birth.

Statistical analysis

Participants were categorized according to their baseline marijuana smoking in three different ways: never versus ever marijuana smokers; never, past, or current (at enrollment); and non-current versus current marijuana smokers. We used the Chi-square test and Fisher exact test when appropriate for discrete variables and Kruskal–Wallis test for continuous variables to assess differences in demographic and lifestyle characteristics across marijuana smoking categories. We used multivariable generalized linear mixed models to evaluate the associations between baseline marijuana smoking and ART outcomes, with random intercepts to account for multiple treatment cycles in the same women and empirical (robust) standard errors. We used binomial distribution with logit link function for clinical outcomes (implantation, clinical pregnancy, live birth, and pregnancy loss) and fertilization proportion, normal distribution with identity link for E_2 and endometrial thickness, and Poisson distribution and log link function for total and mature oocyte yields. We accounted for the over-dispersion in the Poisson models by including a scale parameter. We presented the results as population marginal means adjusted for the covariates at their average levels for continuous variables and weighted average level of categorical variable in the model (Searle et al., 1980). We considered the covariates in the model based on the literature and based on the differences between groups in the baseline characteristics. We fitted age-adjusted and multivariable models that included age (years, continuous), BMI (kg/m^2, continuous), race (Caucasian or not), tobacco smoking history (ever vs never), coffee intake (≥5 cup/week vs not), alcohol intake (≥1 day/week), and cocaine use (ever vs never).

We first examined the association between women's marijuana smoking and the clinical outcomes not accounting for men's marijuana smoking or men's covariates among the full cohort of 421 eligible women. Then we considered both partners' marijuana smoking among the 200 enrolled couples by co-adjusting for each partner's marijuana smoking and covariates (as above) of both partners. We further explored the intensity of marijuana smoking, measured in joint-years among all participants and age of start of marijuana smoking among ever marijuana smokers. We calculated joint-years by multiplying the average number of joints of marijuana smoked per day by the number of years the person had smoked. Finally, we cross-classified the couples according to their joint-marijuana smoking as a couple, accounting for both partner's covariates.

We conducted several sensitivity analyses. Specifically, we restricted analyses to the first ART cycle per couple to account for the variable number of cycles per couple, conducted analyses with further adjustment for stimulation protocol, sexually transmitted diseases, education history, and without using the empirical standard errors. All analyses were conducted using the SAS 9.4 (SAS Institute Inc., Cary NC, USA).

Results

Analyses of women's marijuana smoking were based on 421 women who underwent 730 ART cycles (average = 1.7; range: 1–7 cycles/woman). Analyses of men's marijuana smoking and couple co-exposure were based on a subset of 200 couples who underwent 368 ART cycles (average = 1.8; range of 1–7 cycles/couple) (Supplementary Fig. S1). Participants were mostly Caucasian, had college degrees or higher, and had never smoked tobacco (Table I). Mean (SD) age and BMI of women and men was 35.4 (4.0) and 36.6 (5.0) years, and 24.2 (4.3) and 27.2 (4.6) kg/m^2, respectively. Overall, 44% of the women and 61% of the men had ever smoked marijuana, including 12 (3%) women (25 cycles) and 23 (12%) men (41 cycles) who were marijuana smokers at enrollment. Marijuana smoking was positively correlated within couples; 65 couples (33%) had both partners and 60 couples (30%) had neither partners ever smoked marijuana. Marijuana smokers were also more likely to be tobacco smokers and to consume more alcohol and coffee. All but two participants (one woman and one man) who used cocaine had also smoked marijuana (Table I). Women who enrolled as part of a couple had similar characteristics to women who joined alone (Supplementary Table SI).

There were no statistically significant differences in the adjusted probabilities of implantation, clinical pregnancy, or live birth according to women's baseline marijuana smoking status (Table II). However, and despite the small number of women who were marijuana smokers at enrollment and had a positive B-hCG (9 women, 16 cycles), marijuana smokers at enrollment had more than double the adjusted proportion of pregnancy loss than women who were past or never marijuana smokers (54% vs 26%; $P = 0.0003$, Fig. 1). Results were similar after adjustment for joint-years of marijuana smoking. Neither joint-years of marijuana smoking nor age at start of marijuana smoking were statistically significantly related to treatment outcomes (Supplementary Table SII). Results were also similar in the subgroup of women who enrolled as a couple after additional adjustment for male partner's marijuana smoking status and covariates (Supplementary Table SIII).

Couples in which the man was a marijuana smoker at enrollment had higher probabilities of implantation, clinical pregnancy, and live birth after adjusting for women's marijuana smoking status and other potential confounders (Table III). Couples in which the male partner was a marijuana smoker at enrollment had a significantly higher probability of live birth than couples in which the male partner was a never or past marijuana smoker (48% vs 29%; $P = 0.04$), independently of women's marijuana smoking status. Treatment outcomes of couples in which the man had never smoked marijuana closely mirrored those of couples in which the man was a past marijuana smoker (Table III). Intensity of marijuana smoking was statistically significantly unrelated to treatment outcomes (Supplementary Table SIV) and adjustment for intensity of use did not substantially change the results for marijuana use status.

Finally, when couples were jointly stratified according to both partners' marijuana smoking status, the highest adjusted probabilities of live

Table I Demographic and cycle characteristics by marijuana smoking status among women and men participating in the EARTH study.

Baseline characteristics	Marijuana smoking in women ($N = 421$)					Marijuana smoking in men ($N = 200$)				
	All women	Never	Past	At enrollment	*P*-value[1]	All men	Never	Past	At enrollment	*P*-value[1]
Participants, N (%)	421	238 (57)	171 (41)	12 (3)		200	80 (40)	97 (49)	23 (12)	
Cycles, n (%)	730	405 (55)	300 (41)	25 (3)		368	152 (41)	175 (48)	41 (11)	
Age, years	35.4 (4.0)	35.6 (4.1)	35.1 (3.8)	36.8 (1.9)	0.12	36.6 (5.0)	37.1 (5.2)	36.5 (4.9)	34.9 (4.2)	0.21
Caucasian, N (%)	350 (83)	185 (78)	154 (90)	11 (92)	0.003	180 (90)	68 (85)	93 (96)	19 (83)	0.01
BMI, kg/m^2	24.2 (4.3)	24.3 (4.6)	23.9 (3.8)	25.9 (5.0)	0.38	27.2 (4.6)	26.8 (4.0)	27.4 (5.4)	27.7 (3.2)	0.34
Tobacco smoking, N (%)					<0.0001					<0.0001
Never	305 (72)	201 (84)	98 (57)	6 (50)		133 (67)	65 (81)	58 (60)	10 (43)	
Former	106 (25)	35 (15)	68 (40)	3 (25)		56 (28)	12 (15)	36 (37)	8 (35)	
At enrollment	10 (2)	2 (1)	5 (3)	3 (25)		11 (6)	3 (4)	3 (3)	5 (22)	
College degree or higher, N (%)	392 (93)	221 (93)	163 (95)	8 (67)	0.006	168 (84)	69 (86)	82 (85)	17 (74)	0.36
Cocaine use, N (%)	47 (11)	1 (0.4)	42 (25)	4 (33)	<0.0001	39 (20)	1 (1)	28 (29)	10 (43)	<0.0001
Coffee intake ≥5 cup/week, N (%)	198 (47)	97 (41)	94 (55)	7 (58)	0.01	139 (70)	52 (65)	72 (74)	15 (65)	0.37
Alcohol intake ≥1 day/week, N (%)	242 (57)	112 (47)	119 (70)	11 (92)	<0.0001	145 (73)	45 (56)	78 (80)	22 (96)	<0.0001
Moderate to vigorous physical activity, hours/week[2]	4.0 (6.0)	3.6 (4.0)	4.5 (8.2)	4.0 (3.4)	0.55	6.2 (8.0)	7.0 (9.6)	4.9 (4.8)	8.4 (11.1)	0.58
History of Sexually transmitted diseases, N (%)[3]	135 (32)	64 (27)	66 (39)	5 (42)	0.03	17 (9)	6 (8)	7 (7)	4 (17)	0.28
Initial infertility diagnosis/ couple, N (%)										
Male factor[4]	128 (30)	72 (30)	55 (32)	1 (8)	0.26	65 (33)	29 (36)	27 (28)	9 (39)	0.42
Female factor[5]	127 (30)	76 (32)	45 (26)	6 (50)		59 (30)	24 (30)	27 (28)	8 (35)	
Unexplained	166 (39)	90 (38)	71 (42)	5 (42)		76 (38)	27 (34)	43 (44)	6 (26)	
Stimulation protocol, N (%)					0.99					0.34
Luteal phase agonist[6]	292 (69)	163 (68)	120 (70)	9 (75)		145 (73)	64 (80)	64 (66)	17 (74)	
Flare[7]	51 (12)	29 (12)	21 (12)	1 (8)		20 (10)	8 (10)	10 (10)	2 (9)	
Antagonist	48 (11)	28 (12)	19 (11)	1 (8)		21 (11)	4 (5)	14 (14)	3 (13)	
Egg donor or cryo-thaw cycle	30 (7)	18 (8)	11 (6)	1 (8)		14 (7)	4 (5)	9 (9)	1 (4)	

Continued

Table I *Continued*

Baseline characteristics	Marijuana smoking in women ($N = 421$)					Marijuana smoking in men ($N = 200$)				
	All women	Never	Past	At enrollment	*P*-value[1]	All men	Never	Past	At enrollment	*P*-value[1]
Day 3 FSH concentrations, mIU/l	7.4 (2.8)	7.4 (2.4)	7.6 (3.2)	6.6 (1.4)	0.38	7.2 (2.5)	6.9 (2.1)	7.2 (2.8)	7.7 (2.5)	0.38
Average marijuana joints smoked/week[8]		0	0.9 (1.1)	0.7 (0.3)	0.65		0	1.3 (1.8)	1.9 (2.4)	0.09
Duration of marijuana-smoking, years[8]		0	10.5 (5.6)	15.9 (.)[9]	0.30		0	5.8 (6.3)	13.2 (5.3)	0.009
Marijuana joint-year[8]		0	1.3 (1.5)	1.1 (.)[9]	0.55		0	1.6 (3.7)	6.8 (8.8)	0.009
Age of marijuana-smoking start, years[8]		NA	17.8 (3.7)	23.3 (7.3)	0.02		NA	17.7 (2.8)	17.5 (4.1)	0.48
Partner's age, years[10]	36.5 (5.0)	36.8 (5.5)	36.2 (4.3)	36.9 (2.5)	0.92	34.9 (3.8)	34.5 (3.8)	35.5 (3.7)	34.2 (3.7)	0.13
Partner's marijuana smoking at enrollment, N (%)[10]	23 (12)	12 (10)	9 (11)	2 (50)	0.0001	4 (2)	0	2 (2)	2 (9)	<0.0001

N (%) is presented for categorical/binary variables and mean (SD) is presented for continuous variables.
[1]From Chi-square (or Fisher's exact test when appropriate) for discrete variables and Kruskal–Wallis for continuous variables.
[2]Includes weight and aerobic exercise and sports.
[3]Syphilis, gonorrhea, mycoplasma/ureaplasma, chlamydia, trichomonas, herpes, human papilloma virus, lymphogranuloma, group-B strep, or other STDs.
[4]Male factor was defined as having one (or more) of the semen analysis parameters below the lower reference limits of the WHO on two different semen samples collected at least 4 weeks apart.
[5]Female factor was defined as diminished ovarian reserve (DOR), endometriosis, ovulatory, or tubal factors as defined by the Society of Assisted Reproductive Technology (SART) diagnosis of infertility (SART, 2017).
[6]Luteal-phase GnRH-agonist protocol.
[7]Follicular-phase GnRH-agonist/flare protocol.
[8]The numbers presented for the entire cohort are restricted to ever marijuana smokers and comparing past versus marijuana smokers at enrollment.
[9]Only one woman was in this category with non-missing information; therefore, SD could not be estimated.
[10]For women, those values only represent women who were part of participating couples. Abbreviations: EARTH, the Environment and Reproductive Health Study; ART; BMI; FSH, follicle stimulating hormone; STDs, sexually transmitted diseases; mins, minutes.

Table II Marginal covariate-adjusted probabilities of clinical ART outcomes associated with women's marijuana smoking status in the EARTH study ($N = 421$ women, 730 cycles).

		Implantation			Clinical pregnancy			Live birth		
	Total women (N)	Events, n/total cycles, n	Implantation, per 100 cycles initiated		Events, n/total cycles, n	Clinical pregnancy, per 100 cycles initiated		Events, n/total cycles, n	Live birth, per 100 cycles initiated	
Women's marijuana smoking			Age adjusted[1]	MV adjusted[2]		Age adjusted[1]	MV adjusted[2]		Age adjusted[1]	MV adjusted[2]
Never	238	222/405	55.3 (50.2, 60.3)	54.1 (48.6, 59.4)	197/405	48.7 (43.9, 53.7)	48.1 (43.0, 53.3)	156/405	38.6 (33.9, 43.6)	38.3 (33.4, 43.5)
Ever	183	173/325	53.5 (47.8, 59.0)	55.1 (48.9, 61.1)	149/325	45.4 (40.1, 50.8)	46.2 (40.6, 52.0)	129/325	39.4 (34.1, 45.0)	39.5 (33.7, 45.6)
Never	238	222/405	55.3 (50.1, 60.3)	54.0 (48.6, 59.3)	197/405	48.7 (43.9, 53.6)	48.1 (43.0, 53.2)	156/405	38.7 (34.0, 43.6)	38.4 (33.4, 43.6)
Past	171	157/300	52.4 (46.7, 58.1)	54.0 (47.8, 60.1)	136/300	44.7 (39.2, 50.4)	45.5 (39.7, 51.5)	122/300	40.3 (34.6, 46.3)	40.3 (34.2, 46.7)
At enrollment	12	16/25	65.0 (43.6, 81.7)	67.9 (45.9, 84.1)	13/25	53.4 (37.2, 68.9)	54.7 (37.4, 71.0)	7/25	29.6 (18.3, 44.1)	30.6 (18.3, 46.5)
Not at enrollment	409	379/705	54.1 (50.3, 57.8)	54.0 (50.2, 57.7)	333/705	47.1 (43.4, 50.8)	47.0 (43.3, 50.7)	278/705	39.3 (35.7, 43.1)	39.1 (35.5, 42.9)
At enrollment	12	16/25	65.0 (43.5, 81.7)	67.9 (46.0, 84.0)	13/25	53.4 (37.2, 69.0)	55.1 (37.6, 71.5)	7/25	29.6 (18.4, 44.0)	30.3 (18.1, 46.1)

Abbreviations: EARTH, the Environment and Reproductive Health Study; ART; MV, multivariable, n; number of cycles, N; number of women.

[1]Data is presented as covariate-adjusted marginal probabilities with 95% confidence intervals adjusted for women's age.

[2]Data is presented as covariate-adjusted marginal probabilities with 95% confidence intervals adjusted for women's age, BMI, race, tobacco smoking status, coffee intake, alcohol intake, and cocaine use.

All outcomes were analyzed using generalized linear mixed models with random intercepts, binary distribution, and logit link function.

The marginal covariate-adjusted probabilities were used to present the results adjusted for the covariates at their average levels for continuous variables and weighted average level of categorical variable in the model.

Table III Marginal adjusted probabilities of clinical ART outcomes associated with men's marijuana smoking status in the EARTH study ($N = 200$ couples, 368 cycles).

		Implantation			Clinical pregnancy			Live birth		
	Total men (N)	Events, n/total cycles, n	Implantation, per 100 cycles initiated		Events, n/total cycles, n	Clinical pregnancy, per 100 cycles initiated		Events, n/total cycles, n	Live birth, per 100 cycles initiated	
Men's marijuana smoking			Age adjusted[1]	MV adjusted[2]		Age adjusted[1]	MV adjusted[2]		Age adjusted[1]	MV adjusted[2]
Never	80	81/152	54.2 (45.5, 62.7)	56.3 (46.7, 65.5)	67/152	43.1 (34.8, 51.8)	44.4 (35.5, 53.7)	57/152	37.2 (28.4, 46.9)	38.7 (29.4, 49)
Ever	120	122/216	57.0 (49.7, 64.1)	56.8 (48.8, 64.5)	110/216	51.7 (44.7, 58.6)	51.3 (43.9, 58.5)	89/216	42.8 (36.2, 49.6)	41.8 (34.5, 49.5)
Never	80	81/152	59.2 (39.2, 76.5)	57.4 (37.5, 75.2)	67/152	43.6 (30.1, 58.0)	42.2 (28.9, 56.6)	57/152	33.4 (22.1, 47.1)	31.2 (20.0, 45.3)
Past	97	92/175	58.3 (38.5, 75.7)	55.4 (36.6, 72.8)	85/175	49.8 (36.2, 63.5)	47.6 (35.4, 60.0)	67/175	35.8 (24.9, 48.5)	32.9 (23.0, 44.6)
At enrollment	23	30/41	75.5 (54.7, 88.7)	77.2 (57.7, 89.3)	25/41	61.0 (44.0, 75.7)	61.6 (45.5, 75.4)	22/41	52.6 (37.2, 67.6)	52.1 (37.1, 66.8)*
Not at enrollment	177	173/327	61.3 (33.8, 83.1)	56.9 (31.0, 79.5)	152/327	47.6 (30.2, 65.6)	45.1 (30.0, 61.3)	124/327	32.6 (19.8, 48.7)	29.2 (18.0, 43.5)
At enrollment	23	30/41	77.4 (51.8, 91.6)	77.9 (53.5, 91.5)*	25/41	61.5 (42.1, 77.9)	60.1 (42.6, 75.4)	22/41	50.1 (33.9, 66.4)	47.6 (32.4, 63.3)*

Abbreviations: EARTH, the Environment and Reproductive Health Study; ART; MV, multivariable, n; number of cycles, N; number of men.

[1]Data is presented as adjusted marginal probabilities with 95% confidence intervals adjusted for women's marijuana smoking and both men's and women's age.

[2]Data is presented as adjusted marginal probabilities with 95% confidence intervals adjusted for women's marijuana smoking, both men's and women's age, BMI, race, tobacco smoking status, coffee intake, alcohol intake, and cocaine use for both partners. Analysis was done using generalized linear mixed models with random intercepts, binary distribution and logit link function, and empirical standard error. The marginal adjusted probabilities were used to present the results adjusted for the covariates at their average levels for continuous variables and weighted average level of categorical variable in the model. *$P < 0.05$.

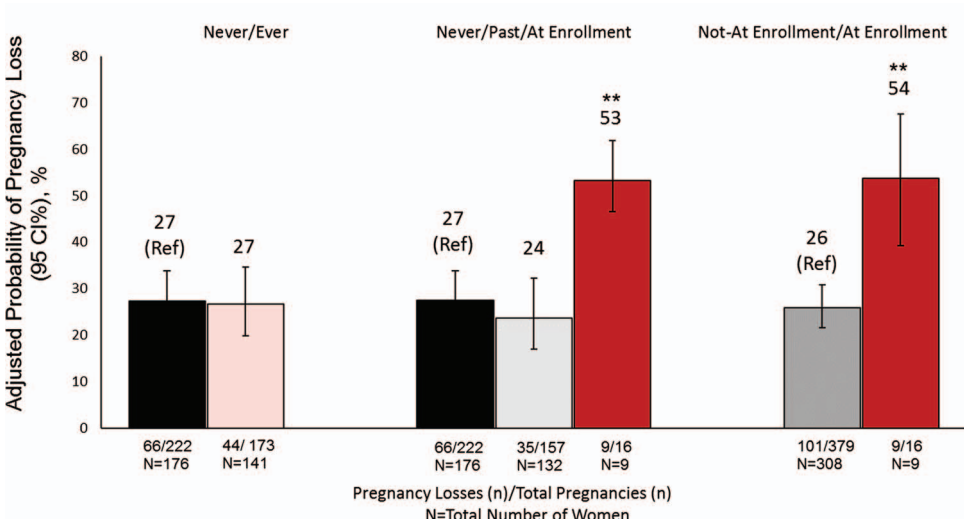

Figure 1 Adjusted probability (95% CI) of pregnancy loss associated with women's marijuana smoking among 317 women who had 395 pregnancies in the EARTH study. Abbreviations: EARTH, the Environment and Reproductive Health Study; N, number of women; n, number of ART cycles. [1]Defined as a positive B-hCG that did not result in live birth. [2]Data is presented as predicted adjusted probabilities with 95% confidence intervals adjusted for women's age, BMI, race, tobacco smoking status, coffee intake, alcohol intake, and cocaine use. Numbers shown below columns represent numbers of pregnancy losses/total number of pregnancies and total number of women (N) across marijuana smoking categories. Analysis was done using generalized linear mixed models with random intercepts, binary distribution and logit link function, and empirical standard error. The marginal covariate-adjusted probabilities were used to present the results adjusted for the covariates at their average levels for continuous variables and weighted average level of categorical variable in the model. $^{**}P$-value < 0.005 compared to never marijuana smokers.

birth were observed in couples where the woman was not a marijuana smoker at enrollment and the man was a marijuana smoker at enrollment which was significantly higher compared to couples where neither partner was a marijuana smoker at enrollment ($P = 0.04$) and compared to couples where both partners were marijuana smokers at enrollment ($P = 0.01$) (Fig. 2). However, estimates for couples with a woman who was a marijuana smoker at enrollment were based on very limited data (four couples, nine cycles).

Marijuana smoking in men or women was not significantly associated with ovarian response to stimulation or fertilization rate (data not shown). All results were consistent when we restricted analyses to the first treatment cycle for each couple and after further adjustment for treatment protocol, history of sexually transmitted diseases, education history, and without empirical standard errors (data not shown).

Discussion

In this prospective study of couples undergoing infertility treatment based at a fertility center, women's marijuana smoking at enrollment was significantly associated with higher risk of pregnancy loss, although very few women were marijuana smokers at enrollment. On the other hand, men's marijuana smoking at enrollment was significantly associated with higher probability of live birth independent of women's marijuana smoking. Intensity of marijuana in men or women was not associated with these outcomes. Moreover, past and never marijuana smokers had similar success rates. While the results should be interpreted with caution given the low frequency of marijuana smoking at enrollment among women, they suggest that marijuana smoking among women may be related to worse infertility treatment outcomes. They also highlight the importance of simultaneously considering lifestyle factors of both partners when evaluating risk factors for couple-based outcomes.

We did not observe statistically significant differences in the adjusted probability of biochemical or clinical pregnancy according to women's marijuana smoking status. This finding is in agreement with the three previous studies (Klonoff-Cohen et al., 2006; Kasman et al., 2018; Wise et al., 2018) that have addressed this question. Klonoff-Cohen et al. (2006) examined the association between marijuana use and outcomes of infertility treatment with ART among 221 couples enrolled in California between 1993 and 1997. Similar to our findings, this study (Klonoff-Cohen et al., 2006) found no significant association of women's marijuana smoking with clinical pregnancy and live birth; however, estimates for non-statistically significant associations were not reported in this study making it difficult to make a full comparison between studies including a comparison of the magnitude of associations. Our findings are also consistent with the two studies among pregnancy planners attempting conception without medical assistance (Kasman et al., 2018; Wise et al., 2018) that reported no significant association between women's marijuana use and time to pregnancy. However, these three studies (Klonoff-Cohen et al., 2006; Kasman et al., 2018; Wise et al., 2018) did not assess pregnancy loss. Data on marijuana use and pregnancy loss is equally scarce. A meta-analysis (Conner et al., 2016) summarizing the results of two previous studies (Wilcox et al., 1990; Kline et al., 1991) evaluating the association of maternal marijuana use and spontaneous abortion concluded that maternal use of marijuana was not associated with spontaneous abortion. It should be noted that most of the pregnancy losses in the meta-analyses were clinical

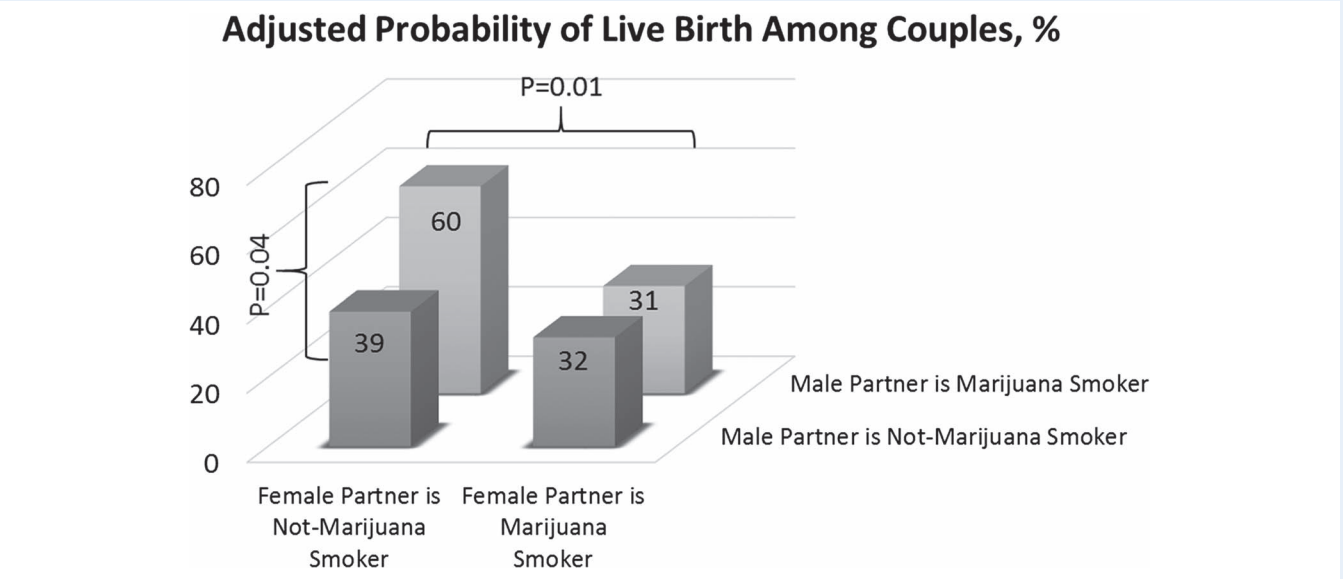

Figure 2 Adjusted probability of clinical ART outcomes associated with joint male and female partners' marijuana smoking at enrollment among 200 couples (368 cycles) in the EARTH study. Abbreviations: EARTH, the Environment and Reproductive Health Study. Couples with not at enrollment marijuana smoker woman and not at enrollment marijuana smoker man were 175 couples and 324 cycles. Couples with not at enrollment marijuana smoker woman and marijuana smoker at enrollment man were 21 couples and 35 cycles. Couples with marijuana smoker woman at enrollment and not at enrollment marijuana smoker man were 2 couples and 3 cycles. Couples with marijuana smoker woman at enrollment and marijuana smoker man at enrollment were 2 couples and 6 cycles. Data is presented as covariate-adjusted marginal means adjusted for both men's and women's age, BMI, race, tobacco smoking status, coffee intake, alcohol intake, and cocaine use. Analysis was done using generalized linear mixed models with random intercepts, binary distribution and logit link function, and empirical standard error. The marginal covariate-adjusted probabilities were used to present the results adjusted for the covariates at their average levels for continuous variables and weighted average level of categorical variable in the model. ∗Indicates <0.05 compared to the couples with not at enrollment marijuana smoker woman and marijuana smoker man at enrollment.

losses, whereas 49 (45%) of the 110 losses in our study were losses of biochemical pregnancies. Hence, results may not be directly comparable. However, these results are supported by experimental studies. In female rodent and primate models, Delta 9 tetrahydrocannabinol (THC)—marijuana's active component—was associated with reduced gonadotropin concentrations (by suppressing of LH pulsatile secretion) (Chakravarty et al., 1975; Besch et al., 1977; Dalterio et al., 1983). In addition, in female monkeys, administration of marijuana in early pregnancy led to pregnancy loss that was associated with a rapid decline in chorionic gonadotropin and a subsequent fall in progesterone concentrations to non-detectable levels (Asch and Smith, 1986). Furthermore, endocannabinoid disruption led to high nitric oxide (NO) production, as an inflammation and sepsis marker and a free radical, that was associated with septic abortion in female animals (Vercelli et al., 2009; Aisemberg et al., 2010). Given the increased use and legalization of marijuana in the United States and the scarcity of data regarding the reproductive effects of marijuana smoking, additional studies that include a greater proportion of marijuana smokers at enrollment are warranted.

We found that couples where the male partner was a marijuana smoker at enrollment had a higher adjusted probability of live birth. These findings stand in contrast not only to our hypothesis but to the results of the three previous studies (Klonoff-Cohen et al., 2006; Kasman et al., 2018; Wise et al., 2018) and to findings of a rodent model that also finds no effect of chronic exposure of male mice to THC on outcomes of IVF (Lopez-Cardona et al., 2018). These apparent discrepancies should be carefully examined. As previously mentioned, Klonoff-Cohen et al. (2006) did not report relationships that were not statistically significant, including the association between male partner marijuana smoking and adjusted probability of clinical pregnancy or live birth. Therefore, it is not possible to determine whether the nominal differences between the two studies are due to true differences related to study population characteristics (e.g. more frequent marijuana use and high frequency of GIFT/ZIFT cycles in the Klonoff-Cohen study), approaches to data analysis (e.g. co-adjustment of marijuana smoking status of both partners and consideration of other lifestyle factors including use of other drugs in this study but not in Klonoff-Cohen's), or are due to differences in statistical power resulting from differences in sample size. While unexpected, positive health effects of marijuana have been reported. Of greatest relevance, we have reported that men in this study who had ever smoked marijuana had significantly higher sperm concentration (62.7 (95% CI: 56.0, 70.3) million/ml) than men who had never smoked marijuana (45.4 (95% CI: 38.6, 53.3) million/ml) after adjusting for potential confounders ($P = 0.0003$). There were no significant differences in sperm concentration between at enrollment (59.5 (95% CI: 47.3, 74.8) million/ml) and past marijuana smokers (63.5 (95% CI: 56.1, 72.0) million/ml; $P = 0.60$) (Nassan et al., 2019). Others also reported non-deleterious relations with other health outcomes. For example, marijuana use has been previously related to improved pulmonary function (Pletcher et al., 2012; Papatheodorou et al., 2016), lower fasting insulin concentrations, improved insulin resistance, smaller waist circumference, and lower

diabetes prevalence (Rajavashisth et al., 2012; Penner et al., 2013). Nevertheless, given the preponderance of evidence, our findings may be better interpreted as lack of evidence for a deleterious effect rather than as evidence of a positive effect of male partner marijuana smoking on outcomes of infertility treatment. Furthermore, we have previously observed in this same study population that men's exposure to certain environmental chemicals (Dodge et al., 2015; Carignan et al., 2018) and nutritional factors (e.g. meat intake) (Xia et al., 2015) can influence outcomes of ART (independent of their female partner); therefore, it is not implausible that marijuana smoking among men could impact these same endpoints.

Although we adjusted for tobacco smoking as an ever versus never variable, the study population consisted mostly of women who never smoked (72%) and men who never smoked (67%). Most of those who reported smoking were past smokers with only 10 (2%) women out of 421 and 11 (6%) men out of 200 men were current smokers at baseline. In addition, only 3 (25%) out of the 12 women who were marijuana smokers at enrollment were also tobacco smokers at enrollment. Similarly, for men, only 5 men (22%) out of the 23 men who were marijuana smokers at enrollment were tobacco smokers at enrollment. Of note, we have previously reported the association between tobacco smoking and outcomes of ART in this population (Vanegas et al., 2017). In our previous report, we found that female partner tobacco smoking was associated to a higher rate of failure during ART, but most of the failures were cycle cancellations prior to oocyte retrieval (e.g. cancellation due to poor response) and to a lesser extent chemical losses. Moreover, we did not observe clear relations of male partner smoking with ART outcomes. The low frequency of smoking and of concurrent use of tobacco and marijuana smoking, along with the divergent pattern of association for tobacco and marijuana smoking in the same study is further evidence that the results for marijuana smoking reported here are unlikely to be explained by residual confounding due to tobacco smoking.

The limitations of the study must be considered when interpreting the results. First, residual confounding cannot be ruled out since marijuana use may be correlated with other lifestyle factors that we did not measure, including use of other drugs and other risk-seeking behaviors. However, we controlled for many potential confounders, including both partners' smoking, coffee and alcohol consumption, and cocaine use. Second, there may be misclassification in self-reported marijuana use especially given the legal status (illegal during most of the study), social stigma, and potential effects on care delivery in this particular group. However, self-report of marijuana is highly correlated with cannabinoid levels in blood and urine (Fried, 1980; Greenland et al., 1982). Another limitation is that few women reported being marijuana smokers at enrollment, which limited the statistical power. Therefore, we cannot exclude the possibility that our results are a chance finding. Moreover, we assessed marijuana smoking at enrollment only. However, the percentage of the women who reported marijuana smoking at baseline in our study was similar to the percentage reported previously for women who reported marijuana smoking month before, week before, and day before the IVF procedure (Klonoff-Cohen et al., 2006) and close to rates of marijuana use among pregnant women in the general population (Brown et al., 2017). This potential exposure misclassification is expected to lead to non-differential misclassification relative to study outcomes and result in attenuation of associations. In addition, we did not have information about forms of marijuana use other than smoking. Lastly, generalizability to couples trying to conceive without medical assistance may be limited as the most important findings relate to an outcome that would not normally be observed outside the setting of ART. However, early pregnancy losses, while often time are unrecognized in spontaneous conceptions, do occur and would likely be identified as prolonged time to pregnancy. Strengths of our study include its prospective design with multiple cycles per couple and complete follow-up of all treatment cycles. We also had information on both partners' use of marijuana and related lifestyle factors that permitted simultaneously co-adjustment for a wide range of potential confounders for both partners.

In conclusion, we found that marijuana smoking at enrollment among women in couples undergoing infertility treatment was associated with a higher probability of pregnancy loss. However, marijuana smoking at enrollment in men was associated with higher live birth rates. Importantly, success rates for couples with female and male past marijuana smokers were comparable to those of never marijuana smokers. Given the scarcity of data on the reproductive effects of marijuana smoking, despite its increased use and legalization, additional research to clarify the role of marijuana use on human reproduction and on the offspring's health is urgently needed.

Supplementary data

Supplementary data are available at *Human Reproduction* online.

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Authors' roles

All the authors of this manuscript have made substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data for the work, and have contributed drafting the work or revising it critically for important intellectual content, and have approved the final version to be published, and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of Interest

The authors report no conflict of interest.

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