OBSTETRICS

Miscarriage among women in the United States Women's Interagency HIV Study, 1994–2017

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BACKGROUND: Relatively little is known about the frequency and factors associated with miscarriage among women living with HIV.

OBJECTIVE: The objective of the study was to evaluate factors associated with miscarriage among women enrolled in the Women's Interagency HIV Study.

STUDY DESIGN: We conducted an analysis of longitudinal data collected from Oct. 1, 1994, to Sept. 30, 2017. Women who attended at least 2 Women's Interagency HIV Study visits and reported pregnancy during follow-up were included. Miscarriage was defined as spontaneous loss of pregnancy before 20 weeks of gestation based on self-report assessed at biannual visits. We modeled the association between demographic, behavioral, and clinical covariates and miscarriage (vs live birth) for women overall and stratified by HIV status using mixed-model logistic regression.

RESULTS: Similar proportions of women living with and without HIV experienced miscarriage (37% and 39%, respectively, $P = .638$). In adjusted analyses, smoking tobacco (adjusted odds ratio, 2.0), alcohol use (adjusted odds ratio, 4.0), and marijuana use (adjusted odds ratio, 2.0) were associated with miscarriage. Among women living with HIV, low HIV viral load (<4 log10 copies/mL) (adjusted odds ratio, 0.5) and protease inhibitor (adjusted odds ratio, 0.4) vs the nonuse of combination antiretroviral therapy use were protective against miscarriage.

CONCLUSION: We did not find an increased odds of miscarriage among women living with HIV compared with uninfected women; however, poorly controlled HIV infection was associated with increased miscarriage risk. Higher miscarriage risk among women exposed to tobacco, alcohol, and marijuana highlight potentially modifiable behaviors. Given previous concern about antiretroviral therapy and adverse pregnancy outcomes, the novel protective association between protease inhibitors compared with non–combination antiretroviral therapy and miscarriage in this study is reassuring.

Key words: antiretroviral treatment, HIV, marijuana, miscarriage, Women's Interagency HIV Study

In the current combined antiretroviral treatment (cART) era, pregnancy rates have increased among US women with HIV and are comparable with women without HIV.[1] Miscarriage occurs in an estimated 10–20% of US women.[2–4] However, relatively little is known about the frequency and factors associated with miscarriage among women living with HIV (WLHIV).

Among the few cART-era analyses, data are conflicting as to whether women with HIV experience an increased risk miscarriage; 3 studies from Africa reported an increased risk,[5–7] while one from the United States did not.[8] Most studies have focused on outcomes of low birthweight, preterm birth, neonatal intensive care unit admission, and neonatal morbidity,[9–22] with fewer and more contradictory studies, mostly from sub-Saharan Africa, focused on miscarriage.[5–8,23–26]

Previous analyses from the Women's Interagency HIV Study (WIHS), the largest ongoing multicenter prospective cohort study of HIV among women in the United States, have explored factors associated with miscarriage. In the 1994–2002 WIHS cohort, Massad et al[8] found that miscarriage rates were similar for WLHIV and women without HIV and that in WLHIV, miscarriage was associated with prior miscarriage, marijuana use, and non–antiretroviral treatment (ART) use. That analysis did not consider the role of potential correlates including alcohol, frequency of marijuana use, sexually transmitted infections (STIs), specific cART regimens, or women without HIV.[8]

In the 1994–2012 WIHS cohort, Cates et al[25] found that HIV viral load during pregnancy predicted pregnancy loss, while Westreich et al[26] found cigarette smoking was associated with pregnancy loss in the 1994–2014 WIHS cohort.

Neither of these studies reported on factors associated with miscarriage outside viral load and smoking, respectively. To provide a more comprehensive and contemporary evaluation, we assessed the frequency and factors associated with miscarriage in both women living with and without HIV enrolled in the WIHS.

Materials and Methods

Cohort

We analyzed data collected between Oct. 1, 1994, and Sept. 30, 2017, from women enrolled in the WIHS.[27] This cohort is comprised of women living with and without HIV recruited from 10 US sites. In 1994, enrollment began at 6 sites (Bronx, NY; Brooklyn, NY; Chicago, IL; Washington DC; Los Angeles, CA; and San Francisco, CA), and those sites

Cite this article as: Wall KM, Haddad LB, Mehta CC, et al. Miscarriage among women in the United States Women's Interagency HIV Study, 1994–2017. Am J Obstet Gynecol 2019;221:347.e1-13.

0002-9378

https://doi.org/10.1016/j.ajog.2019.05.034

AJOG at a Glance

Why was this study conducted?

To provide a more comprehensive and contemporary evaluation of miscarriage, we assessed the frequency and factors associated with miscarriage in both women living with and without HIV enrolled in the Women's Interagency HIV Study.

Key findings

HIV status was not associated with miscarriage risk. Poorly controlled HIV infection and tobacco, alcohol, and marijuana use were associated with an increased miscarriage risk, while protease inhibitors were protective compared with a noncombination antiretroviral treatment.

What does this add to what is known?

Our study adds several years of analytic follow-up to previous analyses, confirms previous findings related to HIV status and miscarriage, and identifies new findings related to alcohol use, marijuana use frequency, and the protective effect of protease inhibitors.

reenrolled during 2001–2002 and 2011–2012.

The cohort was expanded in 2013–2015 to include 4 additional sites to represent the southern United States (Atlanta, GA; Chapel Hill, NC; Miami, FL; and Birmingham, AL/Jackson, MS). Enrollees were frequency matched on demographics and risk factors for acquiring HIV including drug use and number of sexual partners.[27,28] Medical and laboratory examinations (including CD4 T-cell count and HIV viral load) as well as detailed interviews (collecting data including cART use, obstetric and gynecological history, and medication use) are conducted longitudinally at semiannual visits by trained interviewers.

Ethics

Each WIHS site and the data center provided institutional review board approval prior to study enrollment. Enrollees provided written informed consent. All data used in this analysis were deidentified.

Outcome definition

Women who attended at least 2 WIHS visits and self-reported a pregnancy during longitudinal follow-up were included in this analysis. Because prenatal care, delivery, and other obstetrical services were received outside the study, pregnancy outcomes and dates were self-reported. Interviewers were trained to assess pregnancy and pregnancy outcome information from women by asking at every visit: "since your last study visit, how many times have you been pregnant?" and, for those responding with a non-zero number, "what was the outcome of the pregnancy?"

Pregnancy outcomes were explained to help reduce misclassification error. Miscarriage was defined as spontaneous loss of a pregnancy before 20 weeks of gestation. Other pregnancy outcomes included stillbirth, defined as a child born dead after 20 weeks of gestation; live birth, defined as a child born alive; ectopic pregnancy, defined as any pregnancy outside the uterus; and abortion, defined as any pregnancy terminated through an elective procedure.

In total, 755 women reported 1487 pregnancies with known outcomes. We excluded pregnancies that ended in stillbirths (n = 11, 0.7% of total pregnancies ending in stillbirth; n = 5 women with only stillbirths) or ectopic pregnancies (n = 47, 3% of total pregnancies ending in ectopic pregnancy; n = 16 women with only ectopic pregnancies).

We also excluded pregnancies without information in the visit prior to an outcome (n = 64, 4% of total pregnancies; n = 29 women) and those pregnancies that ended in abortion (n = 454, 31% of total pregnancies ending in abortion; n = 121 women with only abortion outcomes). We excluded women in the 2011–2012 wave (n = 11) and southern sites (n = 25) because of small numbers (comprising 44 pregnancies). In primary analyses, we compared women reporting miscarriage with the referent group of women reporting live births. In sensitivity analyses, the referent group also included abortions.

Covariates of interest

Baseline covariates of interest measured at enrollment included the following: race/ethnicity, income, marital status, education, employment status, insurance status, WIHS site and enrollment wave, number of lifetime male sexual partners (categorized based on the distribution of the continuous variable and meaningful groupings), parity, prior miscarriage, and year of cART initiation for women with HIV.

Because of the small number of self-reported prior STI events (<6 cases were recorded for each STI and none were individually associated with the outcome of interest), a composite variable for any prior STIs included gonorrhea, trichomonas, genital herpes, genital warts, syphilis, and chlamydia.

Time-varying covariates occur in the visit prior to the outcome of interest (and thus occur either during pregnancy or just prior to conception). Time-varying covariates of interest included the following: age group; alcoholic drinks per week (dichotomized as abstainers vs drinkers); marijuana use (dichotomized as yes/no) and frequency coded as none, less than weekly, 1–6 times a week, and at least daily); current cigarette smoking; any health-related issues (including stroke, cancer, myocardial infarction, high blood pressure pulmonary embolism, diabetes); year of pregnancy; any new STI diagnosis (including gonorrhea, trichomonas, genital herpes, genital warts, syphilis, and chlamydia); yeast infection; bacterial vaginosis infection; and having a loop electrosurgical excision procedure.

Time-varying HIV-specific covariates of interest included the following: HIV viral load (dichotomized as ≥ 4 $\log_{10}$ copies/mL of plasma vs <4 $\log_{10}$ copies/mL of plasma for comparability with other WIHS analyses); CD4+ T-cell count (dichotomized as <350 cells/μL vs

TABLE 1
Baseline characteristics stratified by HIV status and miscarriage, WIHS 1994–2017

	All women (N = 548)					Women living with HIV (N = 322)					Women without HIV (N = 226)				
	Miscarriage (n = 207, 38%)		Live birth (n = 341, 66%)			Miscarriage (n = 119, 37%)		Live birth (n = 203, 63%)			Miscarriage (n = 88, 39%)		Live birth (n = 138, 61%)		
Variables	n	%	n	%	*P* value	n	%	n	%	*P* value	n	%	n	%	*P* value
Race/ethnicity															
White/other	22	11	48	14	.193	9	8	29	14	.140	13	15	19	14	.494
African American	130	63	188	55		79	66	117	58		51	58	71	51	
Hispanic	55	27	105	31		31	26	57	28		24	27	48	35	
Income per year															
≤$12,000	108	55	184	56	.951	62	54	109	56	.726	46	55	75	56	.539
$12,000–24,000	47	24	75	23		27	24	51	26		20	24	24	18	
>$24,000	43	22	70	21		25	22	36	18		18	21	34	26	
Marital status															
Legally/common-law married	28	14	67	20	.082	17	14	42	21	.117	11	13	25	18	.525
Unmarried but living with partner	36	17	70	21		21	18	47	23		15	17	23	17	
Single/widowed	142	69	204	60		80	68	114	56		62	70	90	65	
Education	125	61	200	59	.668	72	61	115	57	.499	53	61	85	62	.866
High school or higher	81	39	140	41		47	39	88	43		34	39	52	38	
Employed															
No	147	71	237	70	.708	90	76	150	74	.730	57	65	87	63	.792
Yes	60	29	104	30		29	24	53	26		31	35	51	37	
Insurance															
No	48	23	108	32	.035	18	15	51	25	.041	30	34	57	42	.241
Yes	157	77	231	68		99	85	152	75		58	66	79	58	
Site group															
New York	105	51	130	38	.038	62	52	76	37	.071	43	49	54	39	.281
District of Columbia	27	13	53	16		15	13	38	19		12	14	15	11	
California	53	26	111	33		27	23	61	30		26	30	50	36	
Chicago	22	11	47	14		15	13	28	14		7	8	19	14	

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(continued)

TABLE 1
Baseline characteristics stratified by HIV status and miscarriage, WIHS 1994–2017 *(continued)*

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Variables	n	%	n	%	*P* value	n	%	n	%	*P* value	n	%	n	%	*P* value
WIHS enrollment wave															
Original cohort (1994–1995)	106	51	149	44	.087	69	58	98	48	.701	37	42	51	37	.444
2001–2002 recruitment	101	49	192	56		50	42	105	52		51	58	87	63	
Number of lifetime male partners															
0–4	43	21	103	31	.013	24	21	73	37	.001	19	22	30	22	.978
5–24	94	46	155	46		51	44	86	43		43	49	69	50	
≥25	67	33	78	23		41	35	39	20		26	30	39	28	
Parity															
0	62	30	89	26	.313	27	23	48	24	.530	35	40	41	30	.268
1–2	84	41	161	47		51	43	97	48		33	38	64	46	
≥3	61	29	91	27		41	34	58	29		20	23	33	24	
Prior miscarriage															
No	130	63	237	70	.106	71	60	149	73	0.011	59	67	88	64	.614
Yes	77	37	104	30		48	40	54	27		29	33	50	36	
Prior STI[a]															
No	82	40	137	40	.853	39	33	78	39	0.279	43	49	59	43	.368
Yes	125	60	202	60		80	67	123	61		45	51	79	57	
Year of cART initiation															
1995–1999	61	54	143	55	0.576	61	54	98	51	.092					
2000–2003	32	29	72	28		32	29	61	32						
2004–2008	15	13	28	11		15	13	21	11						
2009–	4	4	18	7		4	4	11	6						

P values are 2 tailed.
cART, combination highly active antiretroviral therapy; *STI*, sexually transmitted infection; *WIHS*, Women's Interagency HIV Study.

[a] Includes gonorrhea, trichomonas, genital herpes, genital warts, syphilis, and chlamydia.

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TABLE 2
Time-varying characteristics stratified by HIV status and miscarriage, WIHS 1994–2017

	All women (N = 848)					Women living with HIV (N = 468)					Women without HIV (N = 380)				
	Mis-carriage (n = 250, 29%)		Live birth (n = 598, 71%)			Mis-carriage (n = 140, 30%)		Live birth (n = 328, 70%)			Mis-carriage (n = 110, 29%)		Live birth (n = 270, 71%)		
Variables (previous visit)	n	%	n	%	*P* value	n	%	n	%	*P* value	n	%	n	%	*P* value
Age group															
<25	63	25	97	16	.011	29	21	38	12	.062	34	31	59	22	.138
25–30	50	20	155	26		29	21	90	27		21	19	65	24	
30–35	65	26	189	32		41	29	105	32		24	22	84	31	
>35	72	29	157	26		41	29	95	29		31	28	62	23	
Alcohol use															
Abstain	118	49	450	81	< .0001	76	56	263	84	< .0001	42	40	187	77	< .0001
Drinkers	123	51	108	19		60	44	51	16		63	60	57	23	
Alcohol use frequency															
Abstain	118	49	450	81	< .0001	76	56	263	84	< .0001	42	40	187	77	< .0001
0–7	101	42	89	16		46	34	45	14		55	52	44	18	
>7	22	9	19	3		14	10	6	2		8	8	13	5	
Marijuana use															
No	171	70	492	88	< .0001	105	77	288	91	< .0001	66	62	204	83	< .0001
Yes	72	30	68	12		32	23	27	9		40	38	41	17	
Marijuana use frequency															
None	171	71	492	88	< .0001	105	77	288	91	.001	66	64	204	84	.001
Less than weekly	15	6	24	4		6	4	11	3		9	9	13	5	
1–6 times per week	22	9	16	3		12	9	7	2		10	10	9	4	
At least daily	32	13	27	5		14	10	9	3		18	17	18	7	
Cigarette smoking															
No	120	49	401	72	< .0001	65	47	231	73	< .0001	55	52	170	69	.003
Yes	123	51	159	28		72	53	84	27		51	48	75	31	

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(continued)

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Time-varying characteristics stratified by HIV status and miscarriage, WIHS 1994–2017 *(continued)*

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Variables (previous visit)	n	%	n	%	*P* value	n	%	n	%	*P* value	n	%	n	%	*P* value
Health related[a]															
No	193	77	477	80	.414	108	77	256	78	.829	85	77	221	82	.334
Yes	57	23	121	20		32	23	72	22		25	23	49	18	
Pregnancy year															
1994–1997	50	20	86	14	.066	36	26	49	15	.023	14	13	37	14	.655
1998–2001	46	18	85	14		29	21	57	18		17	16	28	10	
2002–2005	74	30	215	36		39	28	124	38		35	32	91	34	
≥2006	79	32	208	35		36	26	95	29		43	39	113	42	
Any STI diagnosis[b]															
No	211	86	493	88	.564	114	83	265	84	.688	97	92	228	93	.608
Yes	33	14	67	12		24	17	50	16		9	8	17	7	
Yeast infection															
No	200	82	434	78	.120	111	81	237	75	.177	89	84	197	80	.509
Yes	43	18	126	23		26	19	78	25		17	16	48	20	
BV infection															
No	186	80	356	85	.134	97	73	192	81	.066	89	90	164	90	.873
Yes	46	20	63	15		36	27	44	19		10	10	19	10	
LEEP procedure															
No	248	99	596	100	.389	138	99	327	100	.208	110	100	269	100	n/a
Yes	2	1	2	0		2	1	1	0		0	0	1	0	
HIV viral load															
≥4 $\log_{10}$ copies/ mL						45	33	43	14	< .0001					
<4 $\log_{10}$ copies/ mL						90	67	266	86						

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(continued)

TABLE 2
Time-varying characteristics stratified by HIV status and miscarriage, WIHS 1994–2017 *(continued)*

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Variables (previous visit)	n	%	n	%	*P* value	n	%	n	%	*P* value	n	%	n	%	*P* value
CD4 count <500 cells/μL															
No						57	43	127	41	.759					
Yes						77	57	183	59						
cART regimen															
II, NRTI, NNRTI						23	17	71	22	< .0001					
PI						28	20	128	40						
No cART						87	63	121	38						
AIDS-defining illness															
No						98	70	247	75	.235					
Yes						42	30	81	25						

n is given over all study intervals. *P* values are 2 tailed.

BV, bacterial vaginosis; *cART*, combination highly active antiretroviral therapy; *II*, integrase inhibitor; *LEEP*, loop electrosurgical excision procedure; *NNRTI*, non–nucleoside reverse transcriptase inhibitors; *NRTI*, nucleoside reverse transcriptase inhibitors; *PI*, protease inhibitor; *STI*, sexually transmitted infection; *WIHS*, Women's Interagency HIV Study.

[a] Includes stroke, cancer, myocardial infarction, high blood pressure, pulmonary embolism, and diabetes; [b] Includes gonorrhea, trichomonas, herpes-2, genital warts, syphilis, and chlamydia.

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≥350 cells/μL); ART regimen (categorized as follows: (1) cART-containing protease inhibitor (PI)–based regimen with nucleoside reverse transcriptase inhibitors (NRTI), (PI-based cART); (2) cART-containing integrase inhibitors and/or non–NNRTI-based regimens (non-PI cART) with NRTIs; and (3) no cART including NRTI therapy alone or no ART); and ever having an AIDS-defining illness.

Analysis methods

We describe the frequencies of baseline categorical covariates using counts and percentages stratified by the primary outcome of interest (miscarriage vs live birth), with differences by miscarriage status quantified by χ^2 or Fisher exact tests, as appropriate. Frequencies for time-varying variables were calculated over all longitudinal visits. Descriptive analyses were calculated overall and stratified by HIV status.

To account for multiple pregnancy outcomes per woman, we modeled associations between covariates and miscarriage (vs live birth) for women overall and stratified by HIV status using mixed logistic regression models with a random intercept and an unstructured covariance matrix. Model-based point estimates (adjusted odds ratios) and 95% confidence intervals are reported.

Covariates significant in bivariate analyses at $P < .05$ within a given strata (overall, living with or without HIV) were included in the corresponding multivariate models after assessing for multicollinearity. We decided a priori to include HIV status as a covariate in the model for women overall. Possible 2-way interactions between marijuana use and cigarette smoking, marijuana use and drinking, and drinking and cigarette smoking were explored. In sensitivity analyses, models included both live births and abortion in the referent group. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Miscarriage outcomes

Among the 548 women included in the primary analysis, 207 (38%) experienced a miscarriage during follow-up and 341

TABLE 3
Baseline and time-varying factors associated with miscarriage in all women, WIHS 1994-2017

Factors	Level	aOR	95% CI	*P* value
HIV status	HIV positive (ref: HIV-)	1.23	0.84–1.79	.280
Insurance (baseline)	Yes (ref: No)	1.11	0.72–1.71	.628
Site group	New York (ref: California)	1.84	1.18–2.86	.007
	District of Columbia (ref: California)	1.09	0.58–2.04	.789
	Chicago (ref: California)	0.80	0.41–1.56	.502
Number male partners	5–24 (ref: 0–4)	0.99	0.63–1.55	.962
	≥25 (ref: 0–4)	1.21	0.72–2.03	.471
Age group (previous visit)	25–30 (ref: <25)	0.48	0.28–0.82	.007
	30–35 (ref: <25)	0.56	0.34–0.92	.022
	>35 (ref: >25)	0.63	0.38–1.05	.078
Alcohol use (previous visit)	Drinkers (ref: abstainers)	3.97	2.71–5.81	< .0001
Marijuana use (previous visit)	Yes (ref: No)	1.68	1.06–2.67	.029
Cigarette smoking (previous visit)	Yes (ref: No)	1.98	1.35–2.91	.001

Mixed models with random intercept and unstructured covariance matrix. *P* values are 2 tailed.

aOR, adjusted odds ratio; *CI*, confidence interval; *ref*, reference; *WIHS*, Women's Interagency HIV Study.

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(68%) experienced only live birth. Among 226 women without HIV, 88 (39%) ever experienced a miscarriage and 138 (61%) experienced only live birth. Among 322 WLHIV, 119 (37%) ever experienced a miscarriage and 203 (63%) experienced only live birth. There was no significant difference in the proportion of women ever having a miscarriage between WLHIV vs women without HIV (37% vs 39%, respectively, $P = .638$).

Baseline descriptive findings (Table 1)

The majority of women were African American (58%), earned ≤$12,000 USD per year (55%), had less than a high school education (60%), were unemployed (70%), and had between 1 and 2 children (45%) upon entry into the WIHS. Among all women, those experiencing a miscarriage were more likely ($P < .05$) to be insured, be recruited from the New York WIHS sites, and have a higher number of lifetime male sex partners. Among WLHIV, those experiencing a miscarriage were more likely ($P < .05$) to be insured, have a higher number of male sex partners, and have had a prior miscarriage. No differences were observed between baseline covariates and miscarriage in women without HIV.

Time-varying descriptive findings (Table 2)

In the visit prior to pregnancy outcomes of interest, the majority of women were older than 30 years (57%), did not use alcohol (71%) or marijuana (83%), did not smoke (65%), and had no STI diagnosis (88%). Among all women, those experiencing a miscarriage were more likely ($P < .05$) to be alcohol drinkers, marijuana users, and cigarette smokers. WLHIV experiencing a miscarriage were also more likely ($P < .05$) to have experienced a pregnancy before 1998, have a higher viral load, and not be taking cART.

Adjusted model: all women (Table 3)

Factors associated ($P < .05$) with miscarriage (vs live birth) included the following: being enrolled in the New York WIHS sites vs California sites, drinking alcohol, using marijuana in the previous visit, and cigarette smoking. Older age was protective for miscarriage. HIV status was not associated with miscarriage ($P = .280$). None of the 2-way interactions between marijuana use and cigarette smoking, marijuana use and drinking, and drinking and cigarette smoking were significant. In sensitivity analyses when elective abortions were included in the referent group, we found similarly adjusted findings (data not tabled).

Adjusted model: WLHIV (Table 4)

Factors associated ($P < .05$) with miscarriage (vs live birth) included the following: having insurance, drinking alcohol, and smoking cigarettes. Lower log HIV viral load (<4 log10 copies/mL) and using a PI regimen (vs no cART) were protective for miscarriage. Women with HIV viral load <4 log10 copies/mL experienced similar miscarriage proportions compared with women without HIV (data not tabled). None of the 2-way interactions between marijuana use and cigarette smoking, marijuana use and drinking, and drinking and cigarette smoking were significant. In sensitivity analyses when abortion was included in the referent group, we found similarly adjusted findings.

TABLE 4
Baseline and time-varying factors associated with miscarriage in women living with HIV, WIHS 1994–2017

Variable	Level	aOR	95% CI	*P* value
Insurance (baseline)	Yes (ref: no)	2.30	1.12– 4.72	.024
Number of male partners	5–24 (ref: 0-4)	1.05	0.55–1.99	.885
	≥25 (ref: 0-4)	1.02	0.49–2.14	.955
Prior miscarriage	Yes (ref: no)	1.25	0.73–2.14	.412
Alcohol use (previous visit)	Drinkers (ref: abstainers)	2.96	1.71–5.12	< .001
Marijuana use (previous visit)	Yes (ref: no)	1.58	0.75–3.32	.226
Cigarette smoking (previous visit)	Yes (ref: no)	2.20	1.26–3.85	.006
Pregnancy year	1998–2001 (ref: 1994–1997)	1.02	0.45–2.34	.961
	2002–2005 (ref: 1994–1997)	0.80	0.37–1.75	.576
	≥2006 (ref: 1994–1997)	1.30	0.56–3.05	.540
HIV viral load <4 $\log_{10}$ copies/mL (previous visit)	Yes (ref: no)	0.45	0.24–0.84	.013
ART regimen	cART-containing II, NRTI, NNRTI (ref: no cART)	0.69	0.34–1.40	.302
	cART containing PI (ref: no cART)	0.40	0.21–0.79	.008

Mixed models with random intercept and unstructured covariance matrix. *P* values are 2 tailed.
aOR, adjusted odds ratio; *cART*, combination highly active antiretroviral therapy; *CI*, confidence interval; *NNRTI*, non–nucleoside reverse transcriptase inhibitors; *NRTI*, nucleoside reverse transcriptase inhibitors; *PI*, protease inhibitor; *ref*, reference; *WIHS*, Women's Interagency HIV Study.
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Adjusted model: women without HIV (Table 5)

Factors associated ($P < .05$) with miscarriage (vs live birth) included the following: drinking alcohol and smoking cigarettes. None of the 2-way interactions between marijuana use and cigarette smoking, marijuana use and drinking, and drinking and cigarette smoking were significant. In sensitivity analyses when abortion was included in the referent group, we found similarly adjusted findings, although marijuana use became statistically significant (adjusted odds ratio [aOR], 1.71; 95% confidence interval, 1.02–2.86, $P = .041$).

Marijuana frequencies (Figure)

In addition to dichotomized marijuana use (yes/no), frequency of marijuana use was also significant in bivariate analyses. Among all women, only the highest category of marijuana use (at least daily) reached statistical significance ($P = 032$) compared with either no marijuana use or none/less than weekly marijuana use. Similar findings were observed for women living with and without HIV, although the adjusted point estimates for frequency of marijuana use did not reach statistical significance after stratifying by HIV status.

Comment

Principal Findings

In this longitudinal study, a similar proportion of women living with and without HIV reported miscarriage (37% and 39%, respectively; $P = .638$). These proportions are similar to previous (1994–2002) WIHS analyses, which observed 41% of women living with and 34% of women living without HIV reporting miscarriage (among women reporting either a miscarriage or live birth).[8]

These proportions are considerably higher than the general population in which miscarriage occurs in an estimated 10–20% of US women,[2–4] which was not surprising, given that women in the WIHS are on average of lower socioeconomic status, report more substance use, and have more genital infections relative to the general population, all of which have been associated with miscarriage in other studies.[21,29–34]

Our study adds several years of follow-up to confirm previous WIHS findings including no association between miscarriage and HIV status,[8] a positive association between miscarriage and higher HIV viral load,[25] and an effect for cigarette use that is stronger among women living with vs without HIV.[26] We also identified new factors associated with miscarriage: alcohol use, marijuana use frequency, and a protective effect for PI vs non-cART use. Interestingly, a history of miscarriage was not associated with miscarriage.

Results

Alcohol use was associated with miscarriage in this analysis. Heavy alcohol use in pregnancy has been related to negative birth outcomes, including miscarriage, and the amount and pattern of drinking likely influences these outcomes.[29–31] Although we did not have sufficient sample size to evaluate moderate and heavy drinking, a systematic review reported that low to moderate drinking is not associated with negative birth outcomes including miscarriage.[35] However, given that low to moderate alcohol

TABLE 5
Baseline and time-varying factors associated with miscarriage in women without HIV, WIHS 1994–2017

Variable	Level	aOR	95% CI	*P* value
Alcohol use (previous visit)	Drinkers (ref: abstainers)	4.16	2.38–7.28	< .0001
Marijuana use (previous visit)	Yes (ref: no)	1.82	0.97–3.43	.062[a]
Cigarette smoking (previous visit)	Yes (ref: no)	1.77	1.01–3.10	.047

Mixed models with random intercept and unstructured covariance matrix. *P* values are 2 tailed.
aOR, adjusted odds ratio; *CI*, confidence interval; *ref*, reference; *WIHS*, Women's Interagency HIV Study.

[a] Point estimate is significant in sensitivity analyses including abortion in reference group (aOR, 1.71; 95% CI, 1.02–2.86, P = .041).

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consumption has not been shown to be definitively safe during pregnancy, US medical societies and the Centers for Disease Control and Prevention recommend alcohol avoidance when trying to conceive or during pregnancy/breastfeeding.[36]

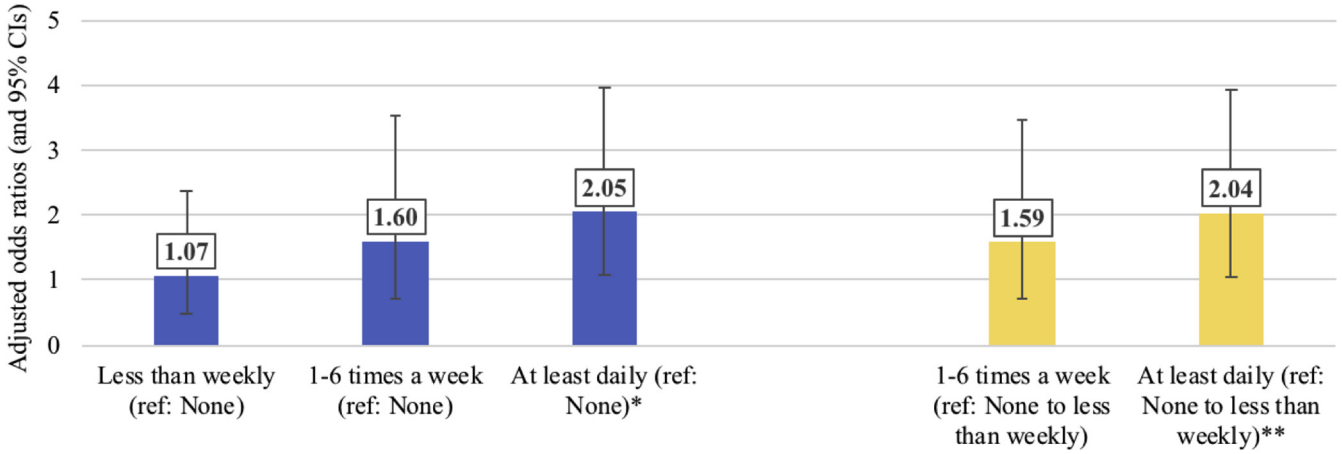
In a previous (1994–2002) WIHS analysis by Massad et al,[8] marijuana use in 2 visits prior to pregnancy in women with HIV was associated with miscarriage (aOR, 6.6 compared with women with no or inconsistent use), but findings for women without HIV were not explored, nor was the effect of frequency of marijuana use for women living with and without HIV.

In the present analysis, we found that any marijuana use was associated with miscarriage overall, with a trend for increasing marijuana use. Although publications have demonstrated a potential biological mechanism for the effect of marijuana on miscarriage (primarily related to the harmful effect of delta-9-tetrahydrocannabinol, the main psychoactive in marijuana that crosses the placental barrier),[37–39] several studies failed to show an association between marijuana use and miscarriage.

Earlier (1987–2002) longitudinal studies of prenatal marijuana exposure in women without HIV found no association between marijuana use during pregnancy and miscarriage.[10,40–43] However, contemporary marijuana products have higher levels of delta-9-tetrahydrocannabinol than in the 1980s–1990s.[44] As access to marijuana increases through legalization and stigmatization diminishes, women may be more likely to accurately disclose their marijuana use, and thus, future studies may be more accurate. Given conflicting literature on marijuana use and adverse birth outcomes including miscarriage, low birthweight, preterm birth, and neonatal morbidity,[9–15,21,40–43,45] professional societies recommend women discontinue marijuana during pregnancy, while breastfeeding, or when attempting to conceive.[46]

In a previous WIHS analysis, ART at the visit prior to pregnancy appeared protective against miscarriage (aOR, 0.37).[8] Here we explored specific cART regimens and found that PI-containing regimens vs no cART were significantly protective for miscarriage, while other cART regimens may also be protective (although their association did not reach statistical significance). While data are conflicting, some studies show cART to be associated with adverse pregnancy outcomes including preterm delivery and low birthweight.[16–18]

FIGURE 1
Adjusted associations between marijuana use frequency and miscarriage, WIHS, 1994–2017



Adjusted association between marijuana use, frequency categories, and miscarriage, WIHS, 1994–2017. Odds ratios are adjusted for the same covariates as the primary analyses. Asterisk indicates *P* = .0320 comparing items at least daily vs none. Double asteriska indicate *P* = .0324 comparting items at least daily vs none to less than weekly.

CI, confidence interval; *WIHS*, Women's Interagency HIV Study.

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A review of studies published between 1980 and 2017 compared women receiving tenofovir vs nontenofovir cART regimens during pregnancy and found no increased miscarriage risk,[47] and a study of zidovudine vs nonzidovudine cART regimens found a protective effect for miscarriage.[48] Meanwhile, PIs may lower progesterone levels,[49] possibly leading to adverse pregnancy outcomes including miscarriage,[50] preterm birth,[19] and lower birthweight.[20]

History of miscarriage was not associated with miscarriage in our adjusted models. This finding contradicts Massad et al[8] in which miscarriage was significantly associated with prior miscarriage in women with HIV (aOR, 1.94). This difference may be related to our inclusion of an additional 15 years of study data and control for influential covariates such as alcohol and cART. Importantly, we are not differentiating between 1−2 vs recurrent prior miscarriage (3 or more), the latter being much less common and likely reflective of underlying factors that may increase miscarriage risk.

Research implications

The protective association with PIs persists when controlling for viral load, indicating that possible mechanism of protection is not conferred by viral suppression. This mechanism warrants further exploration.

Clinical implications

Alcohol consumption and marijuana use are potentially modifiable behaviors that providers can counsel on to have an impact on the miscarriage risk. The finding that PIs appeared significantly protective for miscarriage importantly adds to PI safety data.

Strengths and limitations

Several limitations warrant discussion. First, miscarriage in the WIHS is self-reported. The risk of miscarriage is highest in the first several weeks of pregnancy[51] when women and their providers may not diagnose early pregnancy.[52,53] This could contribute to ascertainment bias. Additionally, use of marijuana, alcohol, tobacco use, and STI could be differentially reported by the outcome of interest, with women experiencing miscarriage perhaps less likely to report exposure. However, self-reported data in other WIHS studies has been strongly correlated with clinical outcomes.

We did not have sufficient numbers to explore the role of individual STIs or levels of drinking. We also did not have measures of time-varying intimate partner violence, which may be associated with miscarriage. Future analyses could consider the role of various measures of smoking frequency and different time-varying combinations of ART regimens. Although rare, it is possible that a proportion of miscarriages could include early ectopic pregnancies. Although we excluded the 2011−2012 wave and southern because of small numbers, when combined with the analysis cohort, findings did not meaningfully change. As the southern cohort accrues more women, future analyses will be able to draw conclusions from this group. Finally, our results are most generalizable to US urban women living with and without HIV who are primarily older and African American.

Conclusions

The WIHS is one of the largest and longest-running cohorts of women living with and without HIV in the world and is well validated with standardized data collection procedures and highly trained staff. Our study adds several years of analytic follow-up to confirm previous findings and identify new findings related to alcohol use, marijuana use frequency, and the protective effect of PIs. These findings highlight additional potentially modifiable behaviors addressable via interventions that could reduce miscarriage risk. ■

Acknowledgment

Data in this manuscript were collected by the Women's Interagency HIV Study (WIHS). WIHS (principal investigators) include the following: University of Alabama at Birmingham-Mississippi WIHS (Mirjam-Colette Kempf and Deborah Konkle-Parker), grant U01-AI-103401; Atlanta WIHS (Ighovwerha Ofotokun, Anandi, Sheth, and Gina Wingood), grant U01-AI-103408; Bronx WIHS (Kathryn Anastos and Anjali Sharma), grant U01-AI-035004; Brooklyn WIHS (Deborah Gustafson and Tracey Wilson), grant U01-AI-031834; Chicago WIHS (Mardge Cohen and Audrey French), grant U01-AI-034993; metropolitan Washington WIHS (Seble Kassaye and Daniel Merenstein), grant U01-AI-034994; Miami WIHS (Maria Alcaide, Margaret Fischl, and Deborah Jones), grant U01-AI-103397; University of North Carolina WIHS (Adaora Adimora), grant U01-AI-103390; Connie Wofsy Women's HIV Study, northern California (Bradley Aouizerat and Phyllis Tien), grant U01-AI-034989; WIHS Data Management and Analysis Center (Stephen Gange and Elizabeth Golub), grant U01-AI-042590; and southern California WIHS (Joel Milam), grant U01-HD-032632 (WIHS I−WIHS IV).

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Received Feb. 12, 2019; revised May 13, 2019; accepted May 21, 2019.

The views expressed herein are those of the authors and do not represent the official views of the National Institutes of Health.

The Women's Interagency HIV Study is supported primarily by the National Institute of Allergy and Infectious Diseases with additional co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, the National Cancer Institute, the National Institute on Drug Abuse, and the National Institute on Mental Health. Targeted supplemental funding for specific projects is also provided by the National Institute of Dental and Craniofacial Research, the National Institute on Alcohol Abuse and Alcoholism, the National Institute on Deafness and Other Communication Disorders, and the National Institutes of Health Office of Research on Women's Health. Women's Interagency HIV Study data collection is also supported by grant UL1-TR000004 (University of California, San Francisco, Clinical and Translational Science Award), grant UL1-TR000454 (Atlanta Clinical and Translational Science Award), grant P30-AI-050410 (University of North Carolina Centers for AIDS Research), and grant P30-AI-027767 (University of Alabama at Birmingham Centers for AIDS Research. Dr Dionne-Odom's effort is supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (grant 1K23HD090993), Dr Haddad's effort is supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (grant 1K23HD078153-01A1), and Dr Wall's effort is supported by the National Institute on Mental Health (grant K01MH107320).

The authors report no conflicts of interest.

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