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RESEARCH ARTICLE

Administration of antineoplastic drugs and fecundity in female nurses

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Abstract

Background: We examined the association between the administration of antineoplastic drugs (AD) and fecundity among female nurses.

Methods: AD administration and use of exposure controls (EC) such as gloves, gowns, and needleless systems were self-reported at baseline among 2649 participants of the Nurses' Health Study 3, who were actively attempting pregnancy. Every 6 months thereafter, the nurses reported the current duration of their pregnancy attempt. Multivariable accelerated failure time models were used to estimate time ratios (TR) and 95% confidence intervals (CI) adjusted for age, race, body mass index, smoking, marital status, hours of work, and other occupational risk factors.

Results: Mean (standard deviation) age and BMI at baseline were 30.7 years (4.7) and 26.0 kg/m^2 (6.4). Forty-one percent of nurses reported ever administering AD; 30% only in the past and 11% currently. The former administration of AD (TR = 1.02, 95% CI, 0.93-1.12) was unrelated to the ongoing duration of pregnancy attempt. Among nurses currently administering AD, those who had administered AD for 6 years and above had a 27% (95% CI, 6%-53%) longer duration of pregnancy attempt than nurses who never handled ADs in unadjusted analyses. This difference disappeared in multivariable analyses (TR = 1.01, 95% CI, 0.85-1.21). 93% (n = 270) of the nurses currently administering ADs reported consistent use of EC. These nurses had a similar median duration of pregnancy attempt to those who never handled AD (TR = 1.00, 95% CI, 0.87-1.15).

Conclusions: Administration of ADs did not appear to have an impact on fecundity in a cohort of nurses planning for pregnancy with a high prevalence of consistent ECs. Our results may not be generalizable to women who are less compliant with PPE use or with less availability to ECs. Therefore, it is possible that we did not observe an association between occupational exposure to AD and reduced fecundity because of lower exposure due to the more prevalent use of effective ECs.

KEYWORDS

antineoplastic drugs, nurses, Nurses' Health Study, occupational exposure, pregnancy, protective equipment, reproductive health, time to pregnancy

1 | INTRODUCTION

Antineoplastic drugs (ADs) are highly toxic agents with known and well-documented reproductive toxicity for patients receiving them as treatment.[1] Most workplaces where ADs are handled are contaminated with ADs and numerous studies have demonstrated worker exposure to these drugs.[2-5] Healthcare workers could be exposed to ADs by preparing or administering ADs; working in areas where ADs are used through contaminated work surfaces, drug vials, containers, clothing, or medical equipment; and in the patient excreta and other secretions such as urine, feces, and sweat.[6] Healthcare workers with chronic, long-term exposure to low levels of ADs appear to have an increased risk of adverse reproductive outcomes.[6] Furthermore, there are no established occupational exposure limits for ADs and it is not possible to establish low-risk exposure levels for ADs because the carcinogenic, mutagenic, and reproductive toxic effects are not dependent on a minimum dosage.[7] Therefore, nurses of reproductive age, who administer these drugs could be, specifically, at risk because of the documented reproductive toxicity of these drugs.

Previous studies on occupational exposure to ADs have reported associations with fetal loss, spontaneous abortion, and malformations in the offspring.[6] Particularly, the association with fecundity as measured by time to pregnancy is understudied. To our knowledge, there is only one study[8] that investigated the association between occupational exposure to ADs and time to pregnancy. Fransman et al.[8] reported that Dutch nurses who were highly exposed to ADs had a longer duration of pregnancy attempt than the nurses with no exposure. Because this study investigated reproductive outcomes collected retrospectively up to 7 years after the pregnancy attempt, they could not exclude the possibility that the differential recall of time to pregnancy might explain their findings.

To further evaluate the potential reproductive effects of occupational exposure to ADs, we evaluated the association between administration of ADs and fecundity as measured by time to pregnancy among female nurses in a large cohort study. We also aimed to assess whether duration, frequency, the physical form of ADs, and exposure control (EC) use modify this association. We hypothesized that unprotected administration of ADs would be related to a longer time to pregnancy among nurses.

2 | METHODS

2.1 | Study population

The Nurses' Health Study 3 (NHS3) is an ongoing, Internet-based prospective cohort study of nurses in the United States and Canada which started recruitment in 2010.[9] Female nurses (registered nurses, licensed practical/vocational nurses or nursing students) born on or after 1 January 1965 were eligible to participate. As of 15 October 2017, 44 077 female nurses had joined the study. Every 6 months, questionnaires are sent to participants to update information on lifestyle and medical characteristics. The response rate for the first follow-up questionnaire is 71%; for women who have completed two questionnaires or more, the response rates range between 78% and 88%. Nurses were excluded from this analysis if they reported being postmenopausal ($n = 825$), not employed outside the home during the last year on their baseline questionnaire ($n = 7493$), and not trying to get pregnant on any subsequent questionnaire ($n = 31\,469$) (Figure S1). From the 2659 nurses who met these criteria, we excluded those who failed to report the duration of their ongoing pregnancy attempt ($n = 6$) or failed to provide information on occupational exposure to ADs ($n = 4$), leaving 2649 nurses eligible for analysis.

2.2 | Exposure assessment

The baseline questionnaire collects information about selected occupational exposures including ADs, ionizing radiation, aerosolized drugs, high-level disinfectants, and anesthetic gases as well as work schedule, and heavy lifting. All eligible nurses were first asked "have you ever administered antineoplastic agents to patients? (Other terms used for antineoplastic agents include chemotherapeutic drugs, cytotoxic drugs, and anticancer drugs.)?" Participants who indicate having administered ADs are then asked how long during their career they had been administering ADs (<6 months, ≥6 and <12 months, 1-5 years, 6-10 years, 11-20 years, or >20 years), and how much total time was spent handling ADs over an average week in the past month (1, 2-3, 4-5, 6-10, or >10 times/wk). Additional questions on AD administration were added to the baseline questionnaire in 2012 (and were thus not asked of all participants), which included if the administration was via infusion, pills, or both; and if the pills were usually crushed. Nurses reporting administering ADs in the past month were also asked to report how often they used engineering controls and personal protective equipment (PPE), collectively referred to as exposure controls (ECs) in this paper. Engineering controls included: use of a designated room or area, drug delivery system with Luer-lock (or other similar types) fittings, absorbent pads, and needleless systems. PPE included chemotherapy or latex gloves, water-resistant gowns or outer garments with a closed front and tight cuffs, and eye protection (safety glasses, goggles, face shield). Response categories for EC use were "always", "sometimes", and "never". We combined "sometimes" and "never" responses due to low frequency. To assess effect modification by EC use, we further cross-classified nurses currently administering ADs according to "never or sometimes use" and "always use" for EC. We also further subcategorized the "always use" according to the type of ECs individually that were always used and the physical form of the ADs.

2.3 | Outcome assessment

Nurses were asked if they were currently pregnant or actively trying to become pregnant in each follow-up questionnaire. Those who reported actively trying to get pregnant were asked to report the

current duration of their ongoing pregnancy attempt. Specifically, they were asked: "For how many months have you been actively trying to get pregnant?" Response categories included: 1 month or lesser, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months, 1 to 2 years, and 3 years or longer. We used a respondent's first report of an ongoing pregnancy attempt after the baseline questionnaire as the outcome. As such, the majority of current durations were reported on questionnaire 2 (51%) followed by questionnaires 3 (16%), 4 (13%), 5 (11%), and 6 (9%). Self-report of the duration of pregnancy attempt is considered a valid methodology for the assessment of fecundity among pregnancy planners.[10,11]

2.4 | Covariate assessment

We obtained information on potential confounding variables from the baseline questionnaire. We considered age, body mass index (BMI) based on self-reported weight and height, race/ethnicity, highest nursing degree, pregnancy history, smoking, marital status, and other occupational exposures including frequency of nursing work, frequency of lifting or moving a heavy load, and current exposure at baseline to ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs.

2.5 | Statistical analysis

Nurses were classified into three categories of AD administration: "never", "administration prior to baseline", and "current administration at baseline". We tested for any differences in demographic, lifestyle, and reproductive characteristics across categories of AD administration using χ^2 tests (or the Fisher exact test where appropriate) for categorical variables and Kruskal-Wallis tests for continuous variables. Nurses reporting current administration of ADs were further classified according to physical form (pills, liquid [with or without pill], or not reported) of ADs administered, duration (<1, 1-5, or ≥6 years), and frequency (once/wk or ≥2 times/wk), and cross-classified according to use of EC.

We used the current duration approach in which information on the current duration of the ongoing pregnancy attempt collected cross-sectionally is used to make inferences about the actually realized waiting times to pregnancy (TTP).[12] This approach has been used before to assess fecundity.[13,14] We used accelerated failure time models with log-normal distribution to estimate time ratios (TR) and 95% confidence intervals (95% CI) as a measure of relative fecundity.[14] TRs can be interpreted as the ratio of the median duration of pregnancy attempts between the compared groups, a TR greater than one indicates a longer time to pregnancy and lower fecundity.

Models were adjusted for a priori selected demographic and occupational variables including age, race, BMI, smoking status, marital status, work hours per week, frequency of lifting or moving a heavy load, and current exposure at baseline to ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs. We did not include the pregnancy history in the main analysis to avoid over-adjustment if ongoing work characteristics are related to the inability to get pregnant, which could manifest as nulligravidity[15,16] but we included it in a sensitivity analysis. To assess the robustness of the results to the modeling assumptions, we conducted additional sensitivity analyses which included using a generalized gamma distribution for the outcome, restricting the analysis to nurses with current durations of pregnancy attempt reported within 2 years of the baseline exposure assessment, truncating the durations of pregnancy attempt at 12 months, and fitting models without adjusting for the other occupational exposures and further adjusting for the typical work schedule. We also conducted a sensitivity analysis using finer categories for the frequency of ADs administration. We explored effect modification by age (<37 or >37 years), BMI (<25 or >25 kg/m^2), smoking status (never vs ever smokers), and gravidity (nulligravid vs gravid) by adding cross-product interaction terms in the final multivariable model. Data were analyzed using SAS 9.4 (SAS Institute, Inc, Cary, NC) and a significance level of $P < .05$.

3 | RESULTS

The estimated proportions of women not pregnant after 12 and 24 months were 13% and 4%, respectively. Forty-one percent ($n = 1077$) of nurses reported ever administering ADs in their careers with 30% ($n = 786$) only in the past and 11% ($n = 291$) currently at baseline. The mean (standard deviation) age and BMI at baseline were 30.7 years (4.7) and 26.0 kg/m^2 (6.4), respectively. On average, nurses who administered ADs before baseline were slightly older, had lower BMI, worked more hours, lifted heavy objects more frequently, and were slightly less likely to be nulligravid than nurses who never administered ADs (Table 1). Nurses who administered ADs currently at baseline worked more hours, lifted heavy objects more frequently, and were more likely to be married and nulligravid than nurses who never administered ADs (Table 1). 20.4% of the nurses who administered ADs currently at baseline were working in night shifts only.

Of the nurses who had ever administered ADs ($n = 1077$), 507 (47%) had done so for 1 to 5 years. Among nurses for whom we had information about the physical form of the ADs administered ($n = 302$), 52% handled only pills and 48% handled liquids with or without pills. The overall prevalence of the consistent use of each individual exposure control ranged from 17% for eye protection to 83% for gloves (Table S1). Most (93%) nurses consistently used some type of EC (Table S2) and most often, this EC was gloves. Use of ECs was high regardless of the frequency of AD administration. Among women who used just one EC, 79% used gloves only and among women using two or more EC, 91% used gloves (Table S2).

Current, past, or ever administration of ADs was not associated with the ongoing duration of pregnancy attempt in unadjusted or adjusted analyses (Table 2). When the duration of AD administration was examined, nurses who currently administered ADs and had been doing so for 6 years and over had a 27% (95% CI: 6%-53%) longer duration of pregnancy attempt than nurses who never handled ADs.

TABLE 1 Age-standardized[a] baseline demographic and occupational characteristics of nurses attempting pregnancy according to antineoplastic drug administration ($n = 2649$)

	Never ($n = 1572$)	Yes, before baseline ($n = 786$)	Yes, at baseline ($n = 291$)
Age, y[a]	30.4 (4.7)	31.2 (4.6)	30.5 (4.8)
BMI, kg/m^2	26.1 (6.7)	25.6 (6.1)	26.2 (6.1)
Hispanic ethnicity, %	4.7	3.2	3.9
Race, %			
White	91.9	92.2	89.4
Black	1.4	2.5	2.5
Asian	2.2	2.6	3.4
Smoking status, %			
Never smoker	79.2	78.3	77.8
Former smoker	4.5	3.1	4.7
Current smoker	16.3	18.4	17.5
Married, %	65.0	64.7	68.8
Nulligravidity, %	61.1	59.6	62.2
Highest nursing degree, %			
PhD	1.5	0.9	1.6
MS	23.1	22.1	13.1
RN or BSN	69.9	74.8	82.9
LPN/LVN	2.6	0.4	1.7
Associate's degree	1.0	1.3	0.7
Nursing student	1.9	0.4	0
History of thyroid disease	1.1	0.8	0
History of diabetes	1.0	1.0	1.0
Typical work schedule, %			
Days only	57.1	57.8	46.8
Evenings only	5.0	5.9	5.0
Nights only	17.4	16.4	20.4
Rotating, with nights	16.0	15.9	24.5
Rotating, no nights	4.4	4.1	3.2
H/wk of nursing work, %			
1-20	9.5	6.2	1.9
21-40	65.6	68.0	66.1
>40	25.0	25.8	32.0
Frequency of occupational moving or lifting heavy loads, %			
None	34.6	28.0	13.6
1-5 times/d	39.3	41.1	47.7
6-15 times/d	20.6	24.2	30.5
>15 times/d	5.5	6.7	8.1
Current coexposures, %			
High-level disinfectants	17.5	20.1	27.2
Ionizing radiation	5.3	6.9	9.5
Aerosolized drugs	0.9	0.8	3.2
Anesthetic gases	11.5	7.9	5.3
Menstrual cycle length, %			
≤25 d	12.3	11.7	8.0
26-39 d	86.6	88.2	91.6
≥40 d	1.1	0.2	0.4
Regular menstrual cycles, %	82.1	78.7	80.3

Notes: Values are means (SD) or percentages and are standardized to the age distribution of the study population.
High-level disinfectants included glutaraldehyde, orthophthalaldehyde, peracetic acid, and hydrogen peroxide.
There were statistically significant differences between categories.
Abbreviations: BMI, body mass index; BSN, Bachelor of Science in Nursing; LPN, Licensed Practical Nurse; LVN, Licensed Vocational Nurse; MS, Masters of Science; n, number of nurses; PhD, Doctorate of Philosophy; RN, Registered Nurse.
[a]Values for age are not age-adjusted.

However, this difference disappeared after adjusting for age (TR = 1.01, 95% CI: 0.85-1.21); multivariable-adjusted analyses showed no association either (Table 2). Among nurses currently administering ADs, frequency of administering ADs over the past month and the physical form of AD administration were unrelated to the current duration of pregnancy attempt in all analyses (Table 2).

We then considered whether the use of EC modified the association of AD administration with fecundity (Table 3). In these analyses, nurses who currently administered ADs but did not always use EC ($n = 21$) had a longer median current duration of pregnancy attempt than nurses who had never handled ADs in the unadjusted and adjusted analyses, but none of the estimates were statistically significant (Table 3). When we considered the type of EC individually used when administering ADs, no clear association patterns emerged (Figure 1).

The results were consistent in the sensitivity analyses without coadjustment for other occupational exposures, with further adjustment for gravidity, the typical work schedule, restricting the follow-up period to 2 years after baseline, truncating time to pregnancy attempt to 1 year or specifying a generalized γ outcome distribution for the current duration of pregnancy attempt (Table S3) or using finer categories of the exposure frequency (Table S4).

4 | DISCUSSION

We prospectively evaluated the association between administration of antineoplastic drugs (AD), use of EC, and fecundity in a contemporary cohort of nurses in the United States and Canada. In contrast to our hypothesis, we found no association between AD administration and fecundity in this cohort. Given the high frequency of EC use in this population, these results cannot rule out the possibility that ADs have adverse effects on fecundity in the absence of consistent EC use, or among nurses who did not plan their pregnancies.

Two previous studies have evaluated the association of AD administration with fecundity with only one study using the time to pregnancy approach.[8] In a case-control study of nurses and pharmacists in the United States (405 cases and 1215 controls), Valanis et al.[17] reported that occupational handling of chemotherapeutic drugs before the onset of infertility was associated with

TABLE 2 Association of occupational administration of ADs with fecundity among women attempting pregnancy ($n = 2649$)

	n (%)	Median pregnancy attempt, mo (IQR)	Unadjusted TR	(95% CI)	Adjusted TR[a]	(95% CI)
Ever administered AD						
Never administered	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
Yes	1077 (40.7)	3 (1, 9)	1.06	0.97-1.16	1.01	0.93-1.09
Ever administered AD						
Never administered	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
Yes, before baseline	786 (29.7)	3 (1, 9)	1.08	0.98-1.18	1.02	0.93-1.12
Yes, at baseline	291 (11.0)	3 (1, 8)	1.02	0.89-1.17	0.98	0.85-1.12
Baseline administered AD						
Not at baseline (Never or prior)	2358 (89.0)	3 (1, 8)	1 (REF)	–	1 (REF)	–
Yes, at baseline	291 (11.0)	3 (1, 8)	1.00	0.87-1.14	0.97	0.85-1.10
Duration of AD administration						
Never administered	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
<1 y	415 (15.7)	3 (1, 10)	1.10	0.98-1.24	1.08	0.96-1.21
1-5 y	507 (19.1)	3 (1, 8)	0.97	0.87-1.09	0.95	0.85-1.06
6+ y	155 (5.9)	4 (1, 12)	1.27	1.06-1.53	1.01	0.85-1.21
Frequency of AD administration in past month						
Never administered	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
Yes, before baseline	786 (29.7)	3 (1, 9)	1.08	0.98-1.18	1.02	0.93-1.12
1 time/wk at baseline	135 (5.1)	3 (1, 11)	1.16	0.96-1.41	1.14	0.95-1.37
≥2 times/wk at baseline	156 (5.9)	2.5 (1, 7)	0.91	0.76-1.10	0.86	0.72-1.02
Physical form of AD at baseline						
Never administered	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
Pills only	156 (5.9)	3 (1, 8)	1.05	0.87-1.26	1.05	0.88-1.26
Typical pills only	121 (4.6)	3 (1, 8)	1.07	0.87-1.31	1.08	0.88-1.31
Crushed pills only	35 (1.3)	3 (1, 7)	0.98	0.68-1.42	0.97	0.68-1.39
Liquids only	37 (1.4)	4 (1, 10)	1.21	0.84-1.74	1.05	0.74-1.48
Both pills and liquids	109 (4.1)	3 (1, 9)	1.15	0.93-1.43	1.11	0.90-1.38
Not reported	775 (29.3)	3 (1, 10)	1.04	0.95-1.15	0.98	0.90-1.08

Abbreviations: AD, antineoplastic drugs; CI, confidence interval; IQR, interquartile range; *n*, number of nurses; REF, reference; TR, time ratio.
[a]Adjusted for age, race, BMI, smoking status, marital status, hours worked per week, frequency of occupational moving or lifting a heavy load, and current exposure to ionizing radiation, high-level disinfectants, anesthetic gas, and aerosol drugs.

TABLE 3 Association between exposure control used during the administration of antineoplastic drugs and fecundity among women attempting pregnancy (n = 2649)

	n (%)	Median pregnancy attempt, mo (IQR)	Unadjusted TR	(95% CI)	Adjusted TR[a]	(95% CI)
Antineoplastic drug administration						
Never	1572 (59.3)	3 (1, 7)	1 (REF)	–	1 (REF)	–
Yes, before baseline	786 (29.7)	3 (1, 9)	1.08	0.98-1.18	1.02	0.93-1.12
Yes, at baseline						
Exposure controls not always used	21 (0.79)	4 (2, 11)	1.33	0.83-2.15	1.25	0.79-1.96
Exposure controls always used	270 (10.2)	3 (1, 8)	1.00	0.87-1.15	0.96	0.83-1.10

Abbreviations: CI, confidence interval; IQR, interquartile range; n, number of nurses; REF, reference; TR, time ratio.
[a]Adjusted for age, race, BMI, smoking status, marital status, hours worked per week, frequency of occupational moving or lifting a heavy load, and current exposure to ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs.

self-reported infertility (defined as having tried to have a child for at least 2 years without success). However, this study[17] in addition to relying on a retrospective report of exposure and outcome did not consider EC use in their analysis. In a retrospective, pregnancy-based cohort of Dutch nurses, Fransman et al.[8] assessed whether AD exposure was associated with the duration of pregnancy attempt before the nurses' most recent pregnancy. AD exposure was estimated based on the measurement of dermal exposure to cyclophosphamide (glove pairs and handwashing samples) coupled with the self-reported frequency of tasks routinely performed by Dutch oncology nurses (preparation, administration, handling patient urine, washing a patient, removing bed sheets, and cleaning toilets). The 177 Dutch nurses who were in the highest tertile of antineoplastic drug exposure took a longer time to conceive (median of 3 months) compared to nurses with no exposure to ADs (n = 663) (median of 2 months) (adjusted hazard ratio = 0.8; 95% CI = 0.6-0.9). This study, however, could not exclude the possibility of differential recall and measurement error of time to pregnancy because the data on TTP were collected retrospectively up to 7 years in the past. This study also included only gravid women, which could cause bias if exposure to ADs is associated with sterility. In addition, Fransman et al.[8] did not thoroughly investigate the use of ECs, other than gloves, which could have modified this association. Most important, in this study, the dermal exposure assessment was done after the outcome and therefore the temporality of exposure assessment in relation to outcome assessment is problematic for causal inference.

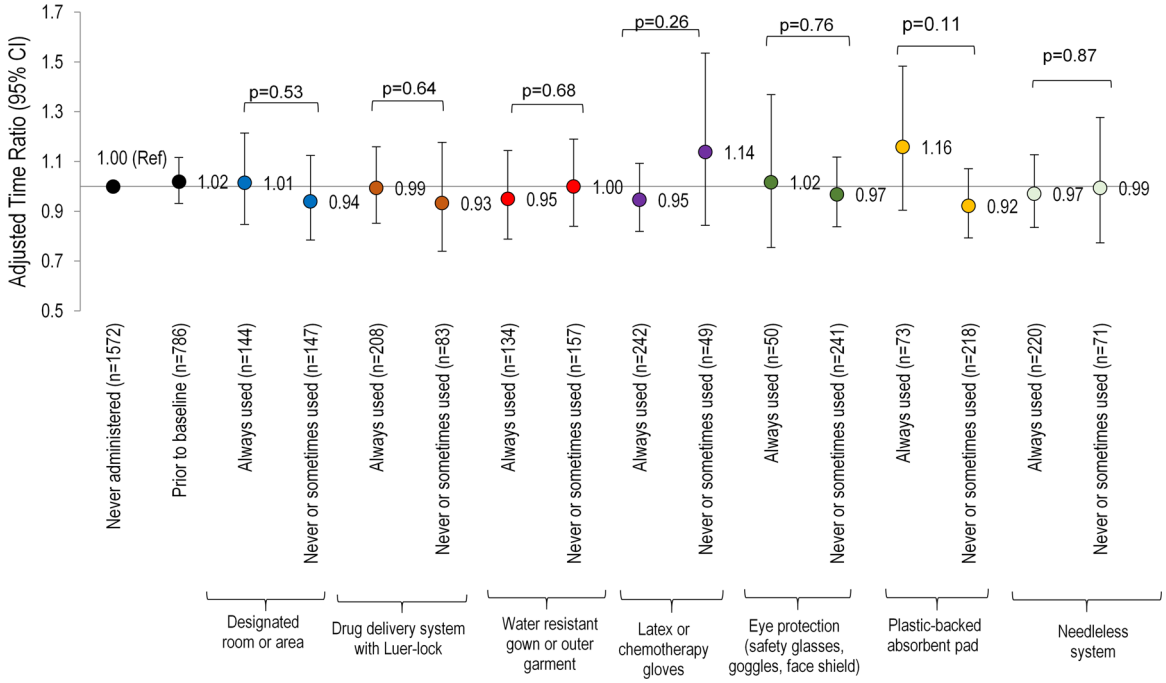

FIGURE 1 Association between each type of exposure control used during the administration of antineoplastic drugs (ADs) and fecundity among women attempting pregnancy (N = 2649). Accelerated failure time models with log-normal distribution (adjusted for age, race, body mass index, smoking status, marital status, hours worked per week, frequency of occupational lifting/moving a heavy load, and current exposure to radiation, disinfectants, anesthesia gas, and aerosol drugs) were used to estimate the time ratios (TR) and 95% confidence interval. EC, exposure control; N, number of nurses; Ref, reference [Color figure can be viewed at wileyonlinelibrary.com]

Previous studies on occupational exposure to ADs have suggested associations with fetal loss, spontaneous abortion, malformations in offspring, and lower mean birth weight of offspring.[6] The most consistent association with the reproductive outcomes was a small incremental risk for spontaneous abortions in female staff working with cytotoxic agents, according to a systematic review and meta-analysis.[18] However, most of these studies occurred in earlier time periods when fewer ECs were available to protect the nurses from exposures to ADs.[6] It is possible that the reproductive toxicity of ADs was dramatically decreased by consistent use of ECs. This hypothesis is in agreement with our findings and with results from previous studies. For example, Skov et al.[5] did not observe increased adverse reproductive outcomes including miscarriages, malformations, low birth weight, and preterm birth in occupationally exposed pregnant nurses to ADs in a retrospective cohort. Similar to our study, Skov et al.[5] attributed the null results to the lower exposure compared to the other studies due to the safety measures implemented in the oncology departments in Denmark in the 1980s, which protected healthcare personnel from adverse reproductive outcomes of ADs.

While true lack of association given the highly prevalent use of EC in this population is a plausible explanation for the results, alternate explanations must be considered. First, selection bias may arise if AD administration is associated with pregnancy planning and if unplanned pregnancies had longer or shorter waiting times to pregnancy. However, the current waiting time to pregnancy is, by definition, undefined among nonplanners making this assumption untestable. Furthermore, baseline prevalence of AD administration was comparable among women in this cohort who eventually became pregnant and who planned (41%) or did not plan (36%) their pregnancy, making this bias less likely. Second, it is important to consider the "infertile worker effect",[19] whereby women who do not get pregnant are more likely to remain in the workforce and may be more exposed to occupational factors than women who become pregnant and may subsequently leave the workforce. However, the distribution of current duration of pregnancy attempt did not differ between women who were working in nursing (median [IQR] TTP = 3 [1-8] months) and women who were not employed outside home at baseline (median TTP = 3 [1-10] months), making this explanation unlikely.

Our study had limitations. First, we assessed AD administration only at baseline and the nurses' pregnancy attempts occurred up to 3 years after the baseline questionnaire. In that time, nurses could have changed jobs or their use of AD or ECs when administering chemotherapy, leading to misclassification of exposure. However, other data from our cohort suggests that nurses are unlikely to change their occupational exposures because of a pregnancy or pregnancy attempt.[20] Second, we did not have detailed information about use of EC such as double vs single gloves, training on safe handling, engineering controls, barriers for not using EC, such as availability of EC, and whether the nurses might have been exposed to ADs in any nontraditional work settings for example, caring for someone at home. We do not know the nurses' specialties, although we expect that they worked in a variety of settings as ADs are used in many departments besides just the oncology floors. However, it is possible that nurses working in oncology departments might be more likely to consistently use ECs assuming they received better safety training on hazardous drugs. We also lacked information about the facility type or size, which could also affect the safety training for AD administration. Third, although we adjusted for various confounders, the possibility of unmeasured or residual confounding cannot be completely ruled out, particularly due to other hazardous chemicals and physical hazards, frequency of sexual intercourse, and male factor fertility. We tried to minimize the possibility of bias that may arise from the very long duration of pregnancy attempts that might be due to over-representation of infertile women by conducting a sensitivity analysis in which we changed this cutoff to 1 year, which was consistent with the primary analysis. Another limitation is that we did not have information on what physical form of AD all nurses administered (pills, liquids, or both), which may have influenced what type of EC was used, because this question was added in 2012. Finally, although we had a large sample size overall, in the analyses involving specific ECs, we had small sample sizes in some groups which decreased the statistical power for detecting a significant association. We conducted a post hoc power analysis. The study had 80% power to detect at least 12% change in the time ratio of the median time to pregnancy in the never vs ever analysis and 19% in the current vs noncurrent analysis. The detectable effect size was larger for the other subanalysis (Table S5) but was large enough to detect associations of similar magnitude to those previously reported in the literature.[8]

Our study had several strengths. This is the first study in the United States to assess the association between AD administration in nurses and fecundity. Second, because administration of ADs in healthcare is not uncommon and nurses' exposure to ADs is unlikely to be completely eliminated, collecting information on the use of ECs allowed us to address the more clinically relevant question of whether the association between administration of ADs and fecundity was modified by the use of ECs. Third, since our cohort was restricted to nurses with many socioeconomic factors that might be confounders were accounted for by design. Fourth, we were able to include both highly fertile women (who are excluded from many prospective cohorts) and involuntarily infertile women (who are excluded from retrospective pregnancy cohorts) by using the current duration approach, as compared to the more traditional time to pregnancy approaches. Finally, assessment of the administration of the ADs by the nurses preceded the ascertainment of the ongoing duration of pregnancy minimizing the possibility of differential misclassification of the outcome.

In sum, the administration of ADs did not appear to have an impact on fecundity in a cohort of nurses planning for pregnancy with a high prevalence of consistent ECs. Our results may not be generalizable to women who are less compliant with PPE use or with less availability to ECs. Therefore, it is possible that we did not observe an association between occupational exposure to AD and reduced fecundity because of lower exposure due to the more prevalent use of effective ECs. Nevertheless, it is reassuring that ECs designed to reduce occupational exposure during the administration of ADs may be effective in minimizing the adverse health effects of these drugs.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

AUTHOR CONTRIBUTIONS

FLN performed the statistical analysis and wrote the manuscript; CCL technically reviewed the analysis, CCL, AJG, CYJ, JMB, JWR-E, and JEC reviewed and edited the manuscript; JEC and CCL designed the research study; FLN and JEC had the primary responsibility for the final content. All authors read and approved the final manuscript.

ETHICS APPROVAL AND INFORMED CONSENT

The Institutional Review Boards of the Brigham and Women's Hospital (Boston, Massachusetts) and the National Institute for Occupational Safety and Health (Cincinnati, Ohio) approved the study. Completion of the web-based questionnaires was considered as implied informed consent.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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