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# Prepregnancy handling of antineoplastic drugs and risk of miscarriage in female nurses

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ABSTRACT

*Purpose:* To examine the association betweenantineoplastic drug (AD) handling and risk of miscarriage.
*Methods:* Nurses' Health Study-3 participants self-reported AD administration and engineering controls (ECs) and personal protective equipment (PPE) use at baseline. We estimated the hazard ratio (HR) of miscarriage in relation to baseline AD handling using multivariable Cox proportional regression.
*Results:* Overall, 2440 nurses reported 3327 pregnancies, with 550 (17%) ended in miscarriages. Twelve percent of nurses self-reported currently handling AD and 28% previously handling AD. Compared with nurses who never handled AD, nurses who handled AD at baseline had an adjusted HR of miscarriage of 1.26 (95% confidence interval [CI], 0.97–1.64). This association was stronger after 12-weeks gestation (HR=2.39 [95% CI, 1.13–5.07]). Nurses who did not always use gloves had HR of 1.51 (95% CI, 0.91–2.51) compared with 1.19 (95% CI, 0.89–1.60) for those always using gloves; nurses who did not always use gowns had HR of 1.32 (95% CI, 0.95–1.83) compared with 1.19 (95% CI, 0.81–1.75) for nurses always using gowns.
*Conclusions:* We observed a suggestive association between AD handling and miscarriage, particularly among nurses who did not consistently use PPE and EC with stronger associations for second trimester losses.



## Introduction

There are more than 4.4 million registered nurses, licensed practical/vocational nurses (LPN/LVN), and nursing students in the United States [1]. More than 85% are female, and approximately 85% of the nurses aged younger than 30 years work in hospitals [2]. Nurses are exposed to occupational hazards, including anesthetic gases, antiviral drugs, disinfectants, ionizing radiation, and antineoplastic drugs (ADs) [3]. Despite current safety guidelines, ADs are still commonly detected in the workplace (e.g., surface wipes and air sampling) and in biological fluids of workers handling ADs [4–6].

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Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

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Pregnancy loss is the most common adverse pregnancy outcome [7]. Overall, 30%–40% of all conceptions result in miscarriage, often before the pregnancy is clinically recognized, and 10%–15% of clinically recognized pregnancies end before 20 weeks' gestation [7]. Although chromosomal abnormalities explain approximately 50% of miscarriages, the remaining 50% are likely related to environmental factors and may be preventable [8].

The National Toxicology Program (NTP) recently conducted a systematic review of occupational exposure to ADs and reproductive outcomes and concluded there is moderate evidence that occupational AD exposure is associated with increased risk of miscarriage, particularly among nursing and pharmacy personnel [4]. NTP identified 16 studies reporting miscarriages in exposed women or in female partners of men occupationally exposed to ADs. However, only 2 of the 16 studies were based in the United States, and none involved a prospective cohort study. In addition, only four of these studies examined exposures occurring after the year 2000; earlier studies may not reflect current health care occupational exposures or safety training and practices. Furthermore, few studies evaluated the use of exposure controls, such as engineering controls (ECs) and personal protective equipment (PPE).

The objective of this study was to further examine the association between handling of ADs by female nurses and use of exposure controls with risks of miscarriage in a large, prospective cohort of female nurses using contemporary data. We hypothesized that occupational exposure to ADs would be associated with higher risk of miscarriage, and risk would be reduced if exposure controls were used while handling ADs.

## Methods

### *Study population*

The Nurses' Health Study 3 is an ongoing, internet-based prospective cohort of nurses in the United States and Canada, which started enrolling in 2010 [9]. Female nurses (registered nurses, LPN/LVN, and nursing students) born on January 1, 1965, or later were eligible to enroll. Questionnaires were sent every 6 months to participants to update their information on lifestyle and medical characteristics. In each update questionnaire, participants were asked about their pregnancy and pregnancy intention status. Nurses who were pregnant or trying to get pregnant at any of these questionnaires were invited to answer additional questions about their pregnancies between gestational weeks 20 and 25 and approximately 8 weeks after the estimated due date. Because not all eligible nurses agree to answer the mid-pregnancy and postpregnancy questionnaires, all participants were also asked to update their information on all pregnancies taking place after baseline—including outcome, duration, and diagnosis of major complications for each pregnancy—in a Supplementary Reproductive Questionnaire (SRQ) introduced in 2017 and repeated every 30 months thereafter. As of November 1, 2018, a total of 16,543 participants had answered the SRQ, of whom 15,573 were premenopausal female nurses. Among these, we identified 2544 nurses who (1) were working as a nurse and provided information on AD exposure at baseline, (2) were not pregnant at baseline, and (3) after baseline, had a pregnancy with a reported outcome (in the SRQ, mid-pregnancy, and/or post-pregnancy questionnaires). Participants could contribute more than one pregnancy to the analysis; however, we censored pregnancy outcomes occurring after the first analyzed miscarriage in the primary analysis (to avoid reverse causation that could result from behavioral change after an adverse outcome [10]). This left 3327 pregnancies from 2440 nurses (Supplemental Fig. 1). The Institutional Review Boards of the Brigham and Women's Hospital (Boston, MA) and the National Institute for Occupational Safety and Health (Cincinnati, OH) approved the study. Completion of the web-based questionnaires was considered implied informed consent.

### *AD assessment*

Nurses provided information about occupational exposures, including ADs, on the baseline questionnaire. Nurses were asked, "Have you ever handled antineoplastic agents to patients? (Other terms used for antineoplastic agents include chemotherapeutic drugs, cytotoxic drugs and anticancer drugs)?" Participants answering yes were asked how long during their career they had been handling ADs and how much total time over an average week in the past month was spent handling ADs. In 2012, we added additional questions on the physical forms of AD (liquid, pills, or both) handling to the baseline questionnaire (i.e., not all participants were asked this question and referred hereafter as "not reported"). Nurses who reported handling ADs in the past month were asked how often they used ECs (designated room or area, drug delivery system with luer-lock style fittings, absorbent pads, and needleless systems) and PPE (chemotherapy or latex gloves, water-resistant gown or outer garment with closed front and tight cuffs, and eye protection [safety glasses, goggles, and face shield]).

### *Outcome assessment*

Nurses were asked in the SRQ to report the outcome of their pregnancies and the gestational age when each pregnancy ended. Pregnancy outcomes included livebirth (singletons or multiple), miscarriage (fetal death <20 gestational weeks), stillbirth (fetal death ≥20 gestational weeks), induced abortion, or tubal (ectopic) pregnancy. We evaluated the risk of miscarriage but could not evaluate the risk of stillbirths because of the small numbers of events (550 miscarriages vs. 11 stillbirths). Gestational age was the underlying time variable. Gestational age at pregnancy end was self-reported in categories (<8, 8–11, 12–19, 20–27, 28–31, 32–36, 37–39, 40–42, and ≥43 gestational weeks).

### *Covariate assessment*

We collected information on potential confounders from the baseline questionnaire. We considered age, body mass index (BMI) based on self-reported weight and height, smoking, race/ethnicity, marital status, and other occupational exposures (number of hours worked per week; frequency of lifting or moving a heavy load at work; shift work; and occupational exposure at baseline to ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized antiviral drugs). We did not adjust for nulligravidity to avoid overadjustment if ongoing occupational characteristics were related to the inability to get pregnant [11,12].

### *Statistical analysis*

We classified nurses into three categories of AD handling: never, before baseline only, and at baseline. We also collapsed the "never" and "prior to baseline only" into "not at baseline" for comparison with "at baseline." We tested for differences in demographic, lifestyle, and reproductive characteristics across categories of AD handling using $\chi^2$ tests (or Fisher's exact test where appropriate) for categorical variables and Kruskal–Wallis tests for continuous variables. We further classified nurses who reported handling ADs at baseline according to physical form (pills, infusion [with or without pills], or not reported). To examine the impact of individual

exposure controls, we compared results between nurses who always used the exposure control versus nurses who never or sometimes used it by including interaction terms in our multivariable models (exposure control*AD handling) and reported *P* for multiplicative interaction.

We estimated the hazard ratio (HR) and 95% confidence intervals (95% CIs) of miscarriage in relation to AD handling using Cox proportional hazard regression models modified for discrete-time data. We used robust sandwich variance estimates to account for the within-woman correlation between pregnancies. We conducted unadjusted, age-adjusted, and multivariable-adjusted analyses. Final models were adjusted for a priori selected demographic variables, including age, BMI, and smoking status. We repeated the analysis with further adjustment for race/ethnicity, work hours per week, frequency of lifting or moving a heavy load at work, shift work, marital status, and occupational exposures at baseline (ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs). In addition, we estimated HR of early (<12 gestational weeks) and late miscarriage (12 to <20 gestational weeks).

We conducted several sensitivity analyses, including restricting the data to the closest pregnancy after baseline exposure assessment (i.e., one pregnancy per nurse) and restricting to planned pregnancies only. To assess the robustness of the results to modeling assumptions, we also conducted all analyses using log-binomial regression using generalized estimating equations with an exchangeable working correlation structure to account for the within-nurse correlation between pregnancies. We estimated the relative risk of miscarriage from the log-binomial models (instead of HR) in relation to AD handling. We also repeated the HR analysis after excluding ectopic pregnancies and induced abortions, which might have ended in miscarriage if they had lasted longer. We conducted all analyses using SAS 9.4 (SAS Institute, Inc., Cary, NC) and considered a significance level of $P < .05$.

## Results

A total of 2440 nurses reported 3327 pregnancies within a median of 3 years after baseline (range: 1–8 years); 87% of the pregnancies were planned. Among nurses included in the analysis, 67% had one pregnancy, 29% had two pregnancies, and 4% had three or four pregnancies. Of those 2440 nurses, 40% reported ever handling AD (28% only before baseline and 12% at baseline). Of the

**Table 1**
Age-standardized* baseline demographic and occupational characteristics of nurses ($n = 2440$) by categories of antineoplastic drug handling

| Age-standardized* baseline demographic and occupational characteristics | Never ($n = 1476$) | Yes, only prior to baseline ($n = 680$) | Yes, at baseline ($n = 284$) |
|---|---|---|---|
| Age, y | 29.6 (4.4) | 30.4 (4.1) | 29.0 (3.9) |
| BMI, kg/m$^2$ | 25.0 (5.4) | 25.0 (5.3) | 25.5 (5.8) |
| Race, % | | | |
| White | 94.1 | 95.4 | 94.5 |
| Black | 2.2 | 1.4 | 2.8 |
| Asian | 2.7 | 2.6 | 3.1 |
| American Indian | 0.7 | 1.2 | 1.4 |
| Hawaiian | 0.2 | 0.2 | 0.3 |
| Hispanic ethnicity | 3.2 | 2.9 | 5.0 |
| Smoking status, % | | | |
| Never smoker | 79.6 | 80.3 | 77.5 |
| Former smoker | 4.6 | 3.0 | 3.7 |
| Current smoker | 15.9 | 16.8 | 18.4 |
| Married, % | 64.3 | 62.6 | 57.7 |
| Nulligravidity, % | 55.1 | 57.2 | 61.7 |
| Nulliparity, % | 64.7 | 68.6 | 73.9 |
| Highest nursing degree, % | | | |
| Doctoral degree | 1.6 | 1.0 | 0.3 |
| Master's degree | 23.4 | 20.4 | 14.9 |
| RN or Bachelor's degree | 71.5 | 77.3 | 82.2 |
| LPN/LVN | 2.1 | 0.4 | 2.3 |
| Associate's degree | 0.8 | 0.8 | 0 |
| Nursing student | 0.7 | 0.1 | 0.2 |
| Typical work schedule, % | | | |
| Days only | 55.6 | 53.7 | 42.9 |
| Evenings only | 5.0 | 4.2 | 8.5 |
| Nights only | 17.3 | 16.7 | 22.0 |
| Rotating with nights | 17.0 | 21.0 | 23.3 |
| Rotating no nights | 5.0 | 4.4 | 3.3 |
| Hours/week of nursing work, % | | | |
| 1–20 h/wk | 10.7 | 7.0 | 0.9 |
| 21–40 h/wk | 68.7 | 69.5 | 76.3 |
| >40 h/wk | 20.6 | 23.5 | 22.8 |
| Frequency of occupational moving or lifting heavy loads, % | | | |
| None | 34.0 | 29.4 | 13.2 |
| 1–5 times per day | 40.6 | 40.0 | 43.6 |
| 6–15 times per day | 20.7 | 24.6 | 34.8 |
| >15 times per day | 4.6 | 6.0 | 8.4 |
| Occupational co-exposures, % | | | |
| High-level disinfectants | 13.9 | 16.8 | 25.5 |
| Ionizing radiation | 2.3 | 4.1 | 4.4 |
| Aerosolized drugs | 0.8 | 0.9 | 1.5 |
| Anesthetic gases | 11.2 | 7.4 | 5.4 |

Values are means (SD) or percentages and are standardized to the age distribution of the study population.
Values for age are not age adjusted.
High-level disinfectants included glutaraldehyde, orthophthalaldehyde, peracetic acid, and hydrogen peroxide.
N = number of nurses; RN = registered nurse.
* Values for age are not age-adjusted.

3327 pregnancies, 550 (17%) ended in miscarriage, 11 in stillbirth, 67 in induced abortion, 38 in ectopic pregnancies, and 2661 in livebirth. At enrollment, the mean age was 29.7 years (SD = 4.3 years), and the mean BMI was 25.0 (SD = 5.47) kg/m$^2$. Nurses who handled ADs at baseline were less likely to have advanced nursing degrees, more frequently lifted heavy objects at work, more likely to work nonday shifts, had more high-level disinfectant exposure, and were less likely to be married or to have ever been pregnant at baseline compared with those who never handled ADs (Table 1). Among nurses who handled ADs at baseline, 77% reported that they always used gloves and 44% always used gowns when handling ADs (Table 2). Among those who always used gowns, 94% always used gloves as well.

In the multivariable analysis, compared with nurses who reported never handling AD, nurses handling AD only before baseline had an HR of miscarriage of 1.08 (95% CI, 0.89–1.31) and nurses handling AD at baseline had an HR of miscarriage of 1.26 (95% CI, 0.97–1.64), after adjusting for age, BMI, and smoking (Table 3). The patterns were similar after further adjustment for race/ethnicity, work hours per week, frequency of lifting or moving a heavy load at work, marital status, shift work, and occupational exposures at baseline (ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs; Table 3). The association between AD handling and miscarriage appeared to be stronger for losses after gestation week 12 than for earlier losses (Table 4).

We observed consistent patterns of higher risk of miscarriage associated with AD handling among nurses who did not consistently use exposure controls relative to nurses who did (Fig. 1 and Table 5). Among those who handled AD at baseline, compared with nurses who reported never handling AD, the HR was highest among nurses who did not always use a drug delivery system with luer-lock style fittings (HR, 1.73; 95% CI, 1.13–2.65) compared with an HR of 1.10 (95% CI: 0.81–1.51) for nurses who reported always using luer-lock style fittings (Fig. 1). Similarly, nurses who did not always use gloves had a higher HR for miscarriage (1.51 [95% CI, 0.91–2.51]) than those who always used gloves (1.19 [95% CI, 0.89–1.60]). Also, nurses who did not always use needleless systems had HR 1.65 (95% CI: 1.02–2.67) compared with 1.16 (95% CI, 0.86–1.56) for nurses who always used needleless systems.

We also observed similar patterns in sensitivity analyses after restricting the data to the closest pregnancy after baseline exposure assessment and to the planned pregnancies only (Table 4, Supplemental Tables 1 and 2). HRs were also similar after excluding ectopic pregnancies and induced abortions. When we conducted the analyses using log-binomial regression, relative risks were similar to HRs.

## Discussion

This is the first prospective study of prepregnancy handling of ADs with miscarriage in a contemporary cohort of female nurses in the United States and Canada and the first to examine the impact of exposure controls on these relationships. We observed a higher risk of miscarriage among nurses who handled ADs at baseline compared with those who never handled ADs, especially for second trimester losses, and among nurses who reported inconsistent use of ECs or PPE.

Previous studies of occupational exposure to ADs suggested associations with adverse reproductive outcomes, including miscarriage, fetal loss, congenital malformations, and lower mean birth weight [13]. Many ADs are teratogenic and cytotoxic. Some ADs work via cytotoxicity to rapidly proliferating cancer cells; they may affect the rapidly developing fetus similarly [14]. The developing fetus is particularly sensitive to chemical toxicity because of the incomplete development of systems for biotransformation and elimination [15].

Our results are consistent with the recent systematic review by the NTP [4]. After reviewing 16 studies, NTP concluded that there was moderate evidence that occupational exposure to ADs is associated with increased risk of miscarriage, particularly among nurses and pharmacy personnel [4]. All 16 epidemiological studies reviewed used retrospective exposure characterization including case–control studies [16–19], retrospective cohort studies [3,20–22], and cross-sectional studies [23–30]. In addition, studies assessed exposure data in participants as early as 1970, with only four of the studies reporting data collected after 2000; the most recent data were from 2011 to 2013 [25]. Furthermore, only two studies were conducted in the United States, including our previous study in a different nursing cohort, where we observed higher odds of miscarriage in nurses exposed ≥1 h/d to ADs (OR, 1.94; 95% CI, 1.32–2.86) [3]. Similarly in the United States, a cross-sectional study of nurses and pharmacy personnel reported higher odds of miscarriage (OR, 1.5; 95% CI, 1.2–1.8) among those who either prepared or handled ADs during pregnancy and/or handled the excreta of patients who were taking ADs than unexposed participants [27].

**Table 2**
Prevalence of exposure control use among nurses who handled ADs at baseline ($n$ = 284) who reported being pregnant after baseline ($n$ = 385 pregnancies)

| Use of exposure controls during antineoplastic drug handling at baseline | Number of nurses ($n$ = 284) | Number of pregnancies, ($n$ = 385) | Percentage of nurses |
|---|---|---|---|
| Designated room or area | | | |
| Always used | 126 | 169 | 44 |
| Never or sometimes used | 158 | 216 | 56 |
| Drug delivery system with luer-lock style fittings | | | |
| Always used | 209 | 286 | 74 |
| Never or sometimes used | 75 | 99 | 26 |
| Plastic-backed absorbent pad | | | |
| Always used | 61 | 81 | 21 |
| Never or sometimes used | 223 | 304 | 79 |
| Needleless system | | | |
| Always used | 223 | 304 | 79 |
| Never or sometimes used | 61 | 81 | 21 |
| Latex or chemotherapy gloves | | | |
| Always used | 220 | 302 | 77 |
| Never or sometimes used | 64 | 83 | 23 |
| Water-resistant gown or outer garment | | | |
| Always used | 126 | 169 | 44 |
| Never or sometimes used | 158 | 216 | 56 |
| Eye protection (safety glasses, goggles, face shield) | | | |
| Always used | 52 | 68 | 18 |
| Never or sometimes used | 232 | 317 | 82 |

**Table 3**
HR of miscarriage associated with antineoplastic drug handling among 2440 female nurses who reported being pregnant after baseline (3327 pregnancies)

| Handling of antineoplastic drug* | Miscarriages/total pregnancies | Unadjusted HR (95% CI) | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI)† | Multivariable-adjusted HR (95% CI)‡ |
|---|---|---|---|---|---|
| Ever handled AD | | | | | |
| Never handled AD | 313/2012 | Ref | Ref | Ref | Ref |
| Yes, prior to baseline | 165/930 | 1.15 (0.94, 1.39) | 1.08 (0.89, 1.31) | 1.08 (0.89, 1.31) | 1.06 (0.87,1.29) |
| Yes, at baseline | 72/385 | 1.22 (0.94, 1.58) | 1.27 (0.98, 1.66) | 1.26 (0.97, 1.64) | 1.23 (0.94, 1.61) |
| Baseline handled AD | | | | | |
| Not at baseline (never or prior) | 478/2942 | Ref | Ref | Ref | Ref |
| Yes, at baseline | 72/385 | 1.17 (0.91, 1.50) | 1.24 (0.96, 1.60) | 1.23 (0.95, 1.59) | 1.20 (0.93, 1.56) |
| Physical form of AD at baseline | | | | | |
| Never handled AD | 313/2012 | Ref | Ref | Ref | Ref |
| Pills only | 25/128 | 1.25 (0.82, 1.92) | 1.20 (0.79, 1.84) | 1.18 (0.77, 1.81) | 1.17 (0.76, 1.80) |
| Infusion (infusion only + both pills and infusion) | 19/88 | 1.46 (0.90, 2.39) | 1.15 (0.71, 1.86) | 1.11 (0.69, 1.81) | 1.12 (0.68, 1.82) |
| Not reported§ | 193/1099 | 1.14 (0.94, 1.36) | 1.12 (0.93, 1.35) | 1.13 (0.94, 1.35) | 1.10 (0.91, 1.32) |

Ref = reference.
* Antineoplastic drug handling was assessed at baseline only (at enrollment).
† Adjusted for age, BMI, and smoking status (the main model).
‡ Further adjustment for race/ethnicity, work hours per week, frequency of lifting or moving a heavy load at work, marital status, shift work, and occupational exposures at baseline (ionizing radiation, high-level disinfectants, anesthetic gases, and aerosolized drugs).
§ Not reported because questions introduced later in the study.

Our data showed that although the excess risk of miscarriage persisted when nurses reported always using EC or PPE, the risk was even higher among the nurses who reported not always using these exposure controls. This demonstrates the importance of systematic application of the hierarchy of controls, including ECs, administrative controls (e.g., training and education), work practice controls (e.g., ensuring adequate supplies of safety equipment), and PPE [31]. Although the highest HRs were associated with a lack of consistent use of luer-lock style fittings or needleless systems, these responses were not applicable for all the nurses in our analysis (e.g., those who only handled intact pills), and we did not collect data on the physical form of the drug for all participants. Luer-lock or similar fittings and needleless systems are commonly used in contemporary oncology settings, although it is possible they were not always used during the earlier period of our data collection. However, it is possible that the elevated HRs indicate that these nurses worked in facilities that lacked management commitment to health and safety or had higher AD contamination. Prior research has shown that the type of facility, frequent training and familiarity with safe handling guidelines, and perceived management commitment to safety were the strongest predictors of EC and PPE use among health care workers handling ADs [32–34]. Furthermore, PPE and EC use were the strongest predictors of not being exposed to ADs via skin contact, leaks, or spills [32–34].

Our study had limitations. We assessed AD handling at baseline only, and the nurses' pregnancy outcomes occurred up to 8 years later. Nurses could have changed their AD handling or exposure control use when handling ADs. This would have led to exposure misclassification when we considered baseline exposure as a proxy for preconception or early pregnancy exposure. However, the patterns were similar when we restricted the data to the pregnancy closest to exposure assessment and to the planned pregnancies only. If AD handling practices changed over time, we would have expected results to be weaker with longer time between baseline and pregnancy. Moreover, if nurses altered AD handling practices when they were pregnant or planning a pregnancy, we would have expected to find weaker associations among planned pregnancies versus all pregnancies. Neither scenario was consistent with our data. In addition, we previously reported that nurses are unlikely to change their glove and gown use because of a pregnancy attempt or pregnancy [35]. Although we did not have the statistical power to analyze data on the physical forms of AD handled, it is possible nurses handling intact pills only were less likely to have worn gloves or gowns. Also, we found that the association of AD handling with miscarriage was stronger for losses after 12 weeks gestation than for earlier losses. Although this difference could point to a biological mechanism, for example, toward this exposure being more relevant to euploid losses, which tend to happen later in gestation than aneuploid losses, this estimate is based on a small number of

**Table 4**
Adjusted HR† of early and late miscarriage associated with antineoplastic drug handling among female nurses who reported being pregnant after baseline

| | Early miscarriage | | Late miscarriage | |
|---|---|---|---|---|
| Handling of antineoplastic drug‡ | 503 Early miscarriage <12 gestational weeks | 3327 Pregnancies from 2440 nurses | 47 Late miscarriage 12 to <20 gestational weeks | 2736 Pregnancies from 2055 nurses |
| Handling of antineoplastic drug | Early miscarriage/total pregnancies | Multivariable-adjusted HR (95% CI)* | Late miscarriage/total pregnancies | Multivariable-adjusted HR (95% CI)* |
| Ever handled AD | | | | |
| Never handled | 290/2012 | Ref | 23/1659 | Ref |
| Yes, prior to baseline | 151/930 | 1.07 (0.87, 1.31) | 14/763 | 1.23 (0.63, 2.41) |
| Yes, at baseline | 62/385 | 1.17 (0.88, 1.55) | 10/314 | 2.39 (1.13, 5.07)* |
| Baseline handled AD | | | | |
| Not at baseline (never or prior) | 441/2942 | Ref | 37/2422 | Ref |
| Yes, at baseline | 62/385 | 1.14 (0.87, 1.51) | 10/314 | 2.22 (1.10, 4.49)* |

Ref = reference.
* Denotes statistically significant.
† Adjusted for age, BMI, and smoking status.
‡ Antineoplastic drug handling was assessed at baseline only (at enrollment).

exposed cases ($n = 10$) and should be interpreted cautiously. Finally, because this is an observational study, we cannot exclude the possibility of residual confounding particularly because of other physical hazards and hazardous chemicals and male factor exposures.

Our study also had several strengths. First, this is the first study that prospectively examined the association between AD handling and miscarriage in a large prospective cohort. Second, examining the use of exposure controls allowed us to address the most clinically relevant and practical question: whether their use reduces the risk of miscarriage associated with AD handling. This is the first study that examined not only glove use but also several other exposure controls, including multiple ECs and other PPE. Finally, this study assessed AD handling and use of exposure controls in a contemporary cohort, better representing current exposure scenarios, availability of exposure controls, training, and hazard awareness.

In conclusion, we observed a suggestive positive association between occupational handling of ADs and higher risk of miscarriage, particularly among nurses who did not consistently use PPE and EC. These associations appeared to be more evident among second trimester losses. Considering the continued reports of widespread AD contamination in health care facilities (measured in surface wipes, air samples, and biological fluids of workers handling ADs) [4–6] and prior studies reporting lack of adherence to safe handling guidelines [32–36]. we reiterate the importance of minimizing exposures through training in safe handling procedures for hazardous drugs and use of recommended exposure controls. Our findings can be used to raise awareness among nurses and employers regarding AD hazards, safe handling guidelines, and systematic implementation of the hierarchy of controls to mitigate workplace hazards.

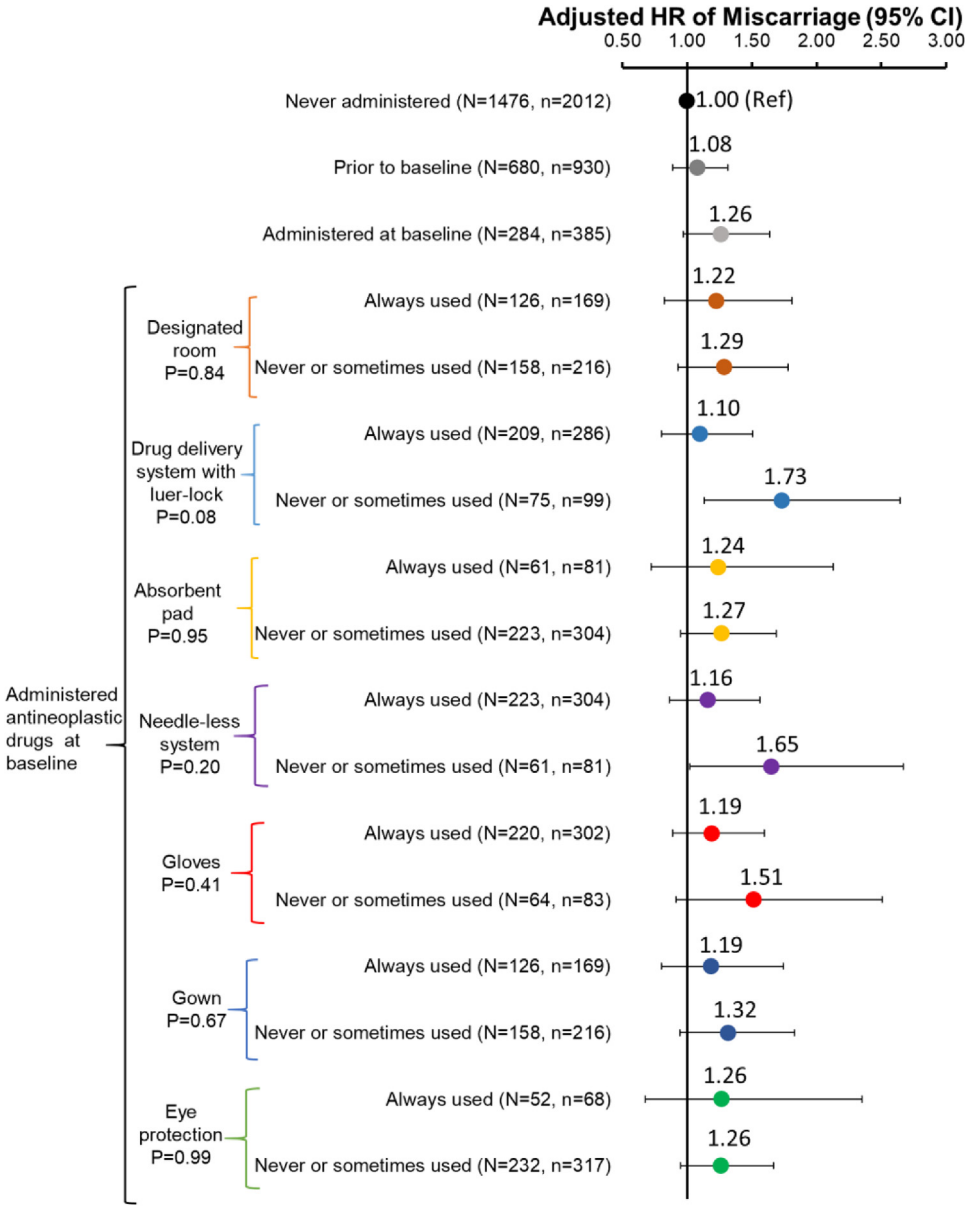


**Fig. 1.** Adjusted hazard ratio of miscarriage associated with each type of exposure control used during the handling of antineoplastic drugs among 2440 female nurses who reported being pregnant after baseline (3327 pregnancies). [1]Adjusted for age, BMI, and smoking status. Ref, reference; N, number of nurses; n, number of pregnancies. *P* values shown are for interaction.

**Table 5**
Adjusted* HR of miscarriage associated with each type of exposure controls used during the handling of ADs at baseline among female nurses who reported being pregnant after baseline

| Antineoplastic drug handling | 2440 Nurses who reported being pregnant after baseline (3327 pregnancies) | | | 2440 Nurses including only the closest pregnancy to baseline (2440 pregnancies) | | | 2092 Nurses who reported being pregnant after baseline only including planned pregnancies (2910 pregnancies) | | |
|---|---|---|---|---|---|---|---|---|---|
| | (*N*, *n*) | HR (95% CI) | *P* interaction | (*N*, *n*) | HR (95% CI) | *P* interaction | *N*, *n* | HR (95% CI) | *P* interaction |
| Never handled | (*N* = 1476, *n* = 2012) | Ref | — | (*N* = 1476, *n* = 1476) | Ref | | *N* = 1248, *n* = 1739 | Ref | — |
| Prior to baseline | (*N* = 680, *n* = 930) | 1.08 (0.89, 1.31) | — | (*N* = 680, *n* = 680) | 1.11 (0.90, 1.37) | | *N* = 598, *n* = 831 | 1.07 (0.87, 1.32) | — |
| Use of exposure controls during antineoplastic drug handling at baseline | (*N* = 284, *n* = 385) | — | — | (*N* = 284, *n* = 284) | — | | *N* = 246, *n* = 340 | — | — |
| Designated room or area | | | | | | | | | |
| Always used | (*N* = 126, *n* = 169) | 1.22 (0.83, 1.81) | .84 | (*N* = 126, *n* = 126) | 1.19 (0.78, 1.83) | .57 | *N* = 108, *n* = 149 | 1.21 (0.80, 1.84) | .70 |
| Never or sometimes used | (*N* = 158, *n* = 216) | 1.29 (0.93, 1.78) | | (*N* = 158, *n* = 158) | 1.02 (0.68, 1.52) | | *N* = 138, *n* = 191 | 1.34 (0.96, 1.88) | |
| Drug delivery system with luer-lock style fittings | | | | | | | | | |
| Always used | (*N* = 209, *n* = 286) | 1.10 (0.81, 1.51) | .08 | (*N* = 209, *n* = 209) | 0.93 (0.64, 1.35) | .08 | *N* = 181, *n* = 256 | 1.14 (0.82, 1.58) | .12 |
| Never or sometimes used | (*N* = 75, *n* = 99) | 1.73 (1.13, 2.65) | | (*N* = 75, *n* = 75) | 1.55 (0.96, 2.50) | | *N* = 65, *n* = 84 | 1.73 (1.10, 2.71) | |
| Plastic-backed absorbent pad | | | | | | | | | |
| Always used | (*N* = 61, *n* = 81) | 1.24 (0.72,2.13) | .95 | (*N* = 61, *n* = 61) | 1.08 (0.58, 1.99) | .95 | *N* = 54, *n* = 74 | 1.29 (0.74, 2.25) | .99 |
| Never or sometimes used | (*N* = 223, *n* = 304) | 1.27 (0.95, 1.69) | | (*N* = 223, *n* = 223) | 1.10 (0.78, 1.54) | | *N* = 192, *n* = 266 | 1.28 (0.95, 1.74) | |
| Needleless system | | | | | | | | | |
| Always used | (*N* = 223, *n* = 304) | 1.16 (0.86, 1.56) | .20 | | 1.00 (0.70, 1.42) | .25 | *N* = 192, *n* = 270 | 1.14 (0.83, 1.56) | .07 |
| Never or sometimes used | (*N* = 61, *n* = 81) | 1.65 (1.03, 2.67) | | (*N* = 61, *n* = 61) | 1.45 (0.84, 2.51) | | *N* = 54, *n* = 70 | 1.90 (1.17, 3.09) | |
| Latex or chemotherapy gloves | | | | | | | | | |
| Always used | (*N* = 220, *n* = 302) | 1.19 (0.89, 1.60) | .41 | (*N* = 220, *n* = 220) | 1.04 (0.73, 1.47) | .50 | *N* = 191, *n* = 267 | 1.19 (0.88, 1.62) | .28 |
| Never or sometimes used | (*N* = 64, *n* = 83) | 1.51 (0.91, 2.51) | | (*N* = 64, *n* = 64) | 1.29 (0.73, 2.28) | | *N* = 55, *n* = 73 | 1.65 (0.97, 2.80) | |
| Water-resistant gown or outer garment | | | | | | | | | |
| Always used | (*N* = 126, *n* = 169) | 1.19 (0.81, 1.75) | .67 | (*N* = 126, *n* = 126) | 0.92 (0.57, 1.48) | .32 | *N* = 111, *n* = 151 | 1.22 (0.82, 1.81) | .70 |
| Never or sometimes used | (*N* = 158, *n* = 216) | 1.32 (0.95, 1.83) | | (*N* = 158, *n* = 158) | 1.23 (0.85, 1.79) | | *N* = 135, *n* = 189 | 1.34 (0.95, 1.90) | |
| Eye protection (safety glasses, goggles, face shield) | | | | | | | | | |
| Always used | (*N* = 52, *n* = 68) | 1.26 (0.68, 2.35) | .99 | (*N* = 52, *n* = 52) | 1.09 (0.56, 2.14) | .99 | *N* = 43, *n* = 58 | 1.20 (0.61, 2.34) | .81 |
| Never or sometimes used | (*N* = 232, *n* = 317) | 1.26 (0.95, 1.67) | | (*N* = 232, *n* = 232) | 1.09 (0.78, 1.52) | | *N* = 203, *n* = 282 | 1.30 (0.97, 1.75) | |

N = number of nurses; n = number of pregnancies; Ref = reference.
* Adjusted for age, BMI, and smoking status.

## CRediT authorship contribution statement

**Feiby L. Nassan:** Formal analysis, Writing - original draft, Writing - review & editing. **Jorge E. Chavarro:** Writing - original draft, Writing - review & editing, Investigation, Methodology. **Candice Y. Johnson:** Methodology, Writing - original draft, Writing - review & editing. **James M. Boiano:** Writing - original draft, Writing - review & editing. **Carissa M. Rocheleau:** Writing - original draft, Writing - review & editing. **Janet W. Rich-Edwards:** Writing - original draft, Writing - review & editing. **Christina C. Lawson:** Writing - original draft, Writing - review & editing.

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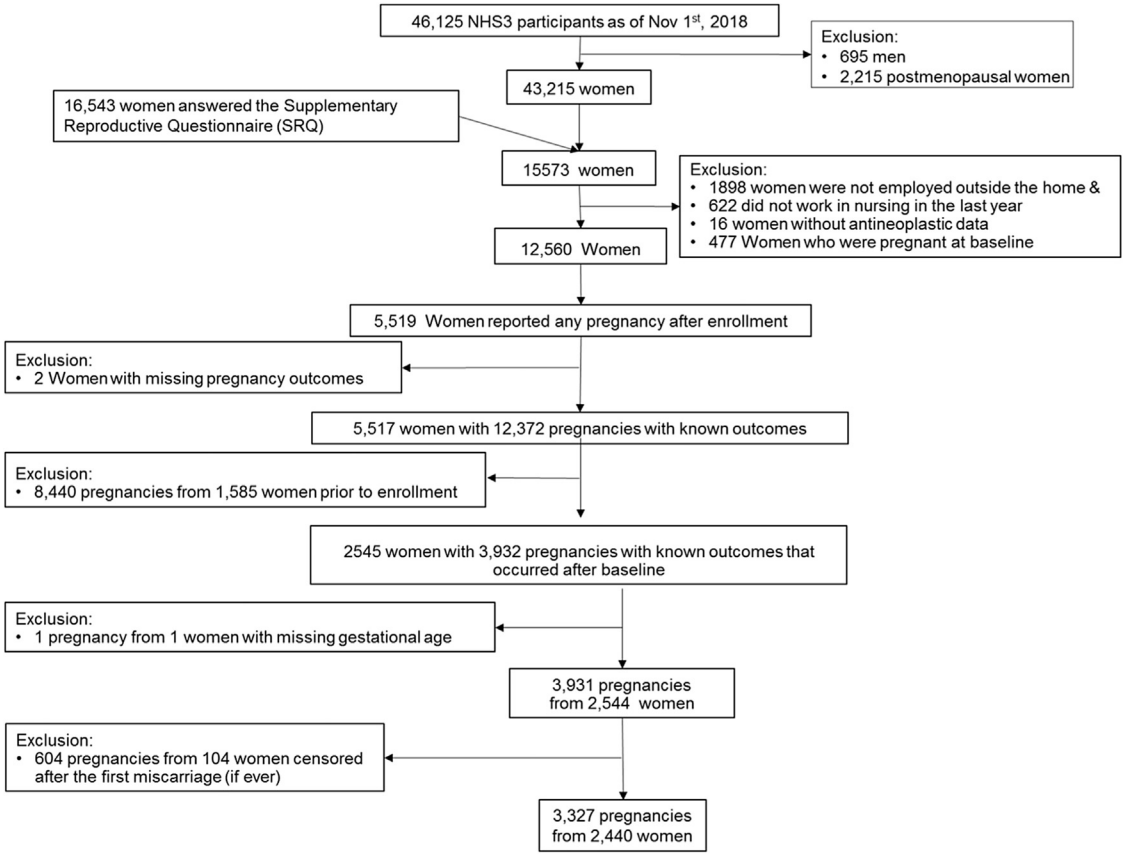
## Appendix




**Supplemental Figure 1.** Flowchart for the final sample size.

**Supplemental Table 1**
HR of miscarriage associated with antineoplastic drug handling among 2440 female nurses who reported being pregnant after baseline including their closest reported pregnancy (2440 pregnancies)

| Handling of antineoplastic drug | Miscarriages/total pregnancies | Unadjusted HR (95% CI) | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI)* |
|---|---|---|---|---|
| Ever handled AD† | | | | |
| Never handled AD | 193/1476 | Ref | Ref | Ref |
| Yes, prior to baseline | 105/680 | 1.19 (0.96, 1.47) | 1.11 (0.90, 1.38) | 1.11 (0.90, 1.37) |
| Yes, at baseline | 44/284 | 1.05 (0.77, 1.42) | 1.11 (0.81, 1.50) | 1.09 (0.80, 1.48) |
| Baseline handled AD | | | | |
| Not at baseline (never or prior) | 298/2156 | Ref | Ref | Ref |
| Yes, at baseline | 44/284 | 0.99 (0.74, 1.33) | 1.07 (0.79, 1.44) | 1.06 (0.78, 1.42) |
| Physical form of AD at baseline | | | | |
| Never handled AD | 193/1476 | Ref | Ref | Ref |
| Pills only | 21/112 | 1.13 (0.73, 1.76) | 1.09 (0.70, 1.70) | 1.07 (0.69, 1.67) |
| Infusion (infusion only + both pills and infusion) | 16/81 | 1.36 (0.83, 2.21) | 1.06 (0.65, 1.74) | 1.04 (0.64, 1.71) |
| Not reported‡ | 112/771 | 1.13 (0.92, 1.38) | 1.12 (0.91, 1.38) | 1.12 (0.91, 1.37) |

Ref = reference.
* Adjusted for age, BMI, and smoking status.
† Antineoplastic drug handling was assessed at baseline only (at enrollment).
‡ Not reported because questions introduced later in the study.

**Supplemental Table 2**
HR of miscarriage associated with antineoplastic drug handling among 2092 female nurses who reported being pregnant after baseline including only their planned pregnancies (2910 pregnancies)

| Handling of antineoplastic drug | Miscarriages/total pregnancies | Unadjusted HR (95% CI) | Age-adjusted HR (95% CI) | Multivariable-adjusted HR (95% CI)* |
|---|---|---|---|---|
| Ever handled AD† | | | | |
| Never handled AD | 275/1739 | Ref | Ref | Ref |
| Yes, prior to baseline | 149/831 | 1.15 (0.94, 1.41) | 1.07 (0.87, 1.32) | 1.07 (0.87, 1.32) |
| Yes, at baseline | 66/340 | 1.26 (0.96, 1.65) | 1.30 (0.99, 1.71) | 1.29 (0.98, 1.69) |
| Baseline handled AD | | | | |
| Not at baseline (never or prior) | 424/2570 | Ref | Ref | Ref |
| Yes, at baseline | 66/340 | 1.20 (0.92, 1.56) | 1.27 (0.98, 1.66) | 1.26 (0.96, 1.64) |

Ref = reference.
* Adjusted for age, BMI, and smoking status.
† Antineoplastic drug handling was assessed at baseline only (at enrollment).