

## OBSTETRICS

# Occupational exposures among nurses and risk of spontaneous abortion

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**OBJECTIVE:** We investigated self-reported occupational exposure to antineoplastic drugs, anesthetic gases, antiviral drugs, sterilizing agents (disinfectants), and X-rays and the risk of spontaneous abortion in US nurses.

**STUDY DESIGN:** Pregnancy outcome and occupational exposures were collected retrospectively from 8461 participants of the Nurses' Health Study II. Of these, 7482 were eligible for analysis using logistic regression.

**RESULTS:** Participants reported 6707 live births, and 775 (10%) spontaneous abortions (<20 weeks). After adjusting for age, parity, shift

work, and hours worked, antineoplastic drug exposure was associated with a 2-fold increased risk of spontaneous abortion, particularly with early spontaneous abortion before the 12th week, and 3.5-fold increased risk among nulliparous women. Exposure to sterilizing agents was associated with a 2-fold increased risk of late spontaneous abortion (12-20 weeks), but not with early spontaneous abortion.

**CONCLUSION:** This study suggests that certain occupational exposures common to nurses are related to risks of spontaneous abortion.

**Key words:** antineoplastic agents, health personnel, occupational exposure, pregnancy

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Over 3 million women are employed as nurses,<sup>1</sup> representing 4% of all employed women in the US.<sup>2</sup> Nurses are potentially exposed to several suspected reproductive hazards, including anesthetic gases, antineoplastic (chemotherapy) drugs, antiviral drugs, sterilizing agents (disinfectants), and X-rays (ionizing radiation).<sup>3-9</sup> Though the nursing profession is a critical component of the health care system, the effect of commonly encountered occupational expo-

sure on reproductive health remains unclear within this predominantly female occupation.

Many previous studies of nursing exposures and spontaneous abortion lack adequate numbers of exposed cases to allow adjustment for confounders. Even though awareness of hazardous drug exposure has increased, protocols to reduce exposure of health care personnel to these chemicals have been insufficient to eliminate the exposure.<sup>10,11</sup> To clarify

previous study results, we investigated the association between reported occupational exposures and risk of spontaneous abortion among participants of the Nurses' Health Study II.

## MATERIALS AND METHODS

The Nurses' Health Study II was established in 1989 as a prospective cohort study of 116,430 U.S. nurses, aged 25 to 42, in 14 states. Participants completed mailed questionnaires regarding their medical and reproductive history at baseline and were sent follow-up questionnaires every 2 years. In the 2001 questionnaire, participants were asked if they had experienced at least 1 pregnancy since 1993 and had worked as a nurse during the most recent of those pregnancies. If so, participants were asked whether they would be willing to complete a mailed supplemental questionnaire regarding occupational activities during their most recent pregnancy.

Among the 101,681 respondents to the 2001 biennial questionnaire, 11,177 (11%) had a pregnancy since 1993 during which they worked as a nurse. Willingness to complete the supplemental survey was indicated by 9547 (85%) participants; 8461 (89%) of these women completed and re-

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turned the supplemental survey they were mailed, resulting in an overall participation rate of 76% for the supplement. Because multiple pregnancies per woman are not independent events, we asked only about the most recent pregnancy.

Pregnancies ending in an induced abortion ( $n = 147$ ), ectopic pregnancy ( $n = 57$ ), molar pregnancy ( $n = 13$ ), or multiple pregnancy ( $n = 235$ ), as well as 7 pregnancies with a missing pregnancy outcome, were excluded. Stillbirths, defined as a pregnancy loss after 20 weeks' gestation, were also excluded ( $n = 42$ ). Pregnancies were excluded if the participant reported that the pregnancy was not confirmed by a clinical or over-the-counter pregnancy test ( $n = 130$ ), as well as pregnancies without data on the year the pregnancy ended ( $n = 31$ ) or the length of the pregnancy ( $n = 22$ ). Women who reported working less than 1 hour per week as a nurse during the first trimester of pregnancy ( $n = 65$ ), or who did not provide information on shift work ( $n = 24$ ), anesthetic gases ( $n = 19$ ), sterilizing agents ( $n = 91$ ), antineoplastic drugs ( $n = 14$ ), antiviral drugs ( $n = 33$ ), or X-rays ( $n = 49$ ) were also excluded. In total, 979 (11.6%) women were excluded, leaving data on 7482 women in the analysis.

For each trimester of pregnancy, the following questions were asked: "On average how many hours per day did you work with the following agents?" and the following categories, with examples, were given "a. Anesthetic gases (eg, nitrous oxide, halothane, enflurane, isoflurane)," "b. Anticancer drugs (eg, Cytosan, Fluroplex, Adrucil, Etoposide, 5-FU)," "c. Antiviral drugs (eg, gancyclovir or the interferons)," "d. Sterilizing agents (eg, ethylene oxide, formaldehyde, glutaraldehyde)," and "e. X-ray radiation." Data on work schedule, night work, average hours worked per week, frequency of lifting 25 pounds or more at work, hours per day of standing or walking at work, smoking, alcohol consumption, and caffeine consumption were also collected for each trimester of pregnancy. From the main biennial questionnaires, data were also available on age, race/ethnicity, body mass index (BMI), medication use, parity, and prior spontaneous abortion.

Participants reported the outcome of the index pregnancy as a single live birth, stillbirth, twins, triplets+, induced abortion, tubal/ectopic pregnancy, miscarriage, or molar pregnancy. Categorical information on pregnancy duration was reported on the supplemental survey as weeks since last menstrual period ( $<8$ , 8-11, 12-19, 20-23, 24-27, 28-31, 32-36, 37-41 [full-term], and  $\geq 42$  weeks). Pregnancies ending involuntarily before 20 weeks' gestation were classified as spontaneous abortions.

Completion of the self-administered questionnaire was considered implied informed consent. The study and informed consent procedure were approved by the institutional review board of the Brigham and Women's Hospital.

Descriptive statistics (frequency, range, and age-adjusted means) were calculated for selected maternal characteristics. The relationship between spontaneous abortion and first-trimester exposure to anesthetic gases, antineoplastic agents, sterilizing agents, antiviral drugs, and X-rays was examined in univariable and multivariable analyses. We modeled age as a continuous variable. Because the risk of spontaneous abortion rose exponentially with age, we also included a quadratic age term (age-squared) in the models. Exposure categories were dichotomized as 1+ hour per day vs  $<1$  hour per day for all reported exposures.

For univariable and multivariable analyses, we used logistic regression to compute the odds ratio (OR) using SAS software (SAS Institute, Cary, NC). Covariates that changed the estimate by 10% or more were retained in the final multivariable model.

We first considered the associations of these individual exposures with risk of spontaneous abortion, adjusted for age. Our full multivariable model included all 5 work exposures of interest, age, parity, and work schedule. The addition of lifestyle and other factors, such as cigarette smoking, caffeine consumption, alcohol consumption, BMI, race/ethnicity, lifting at work, and standing at work did not change the estimated effects by more than 10%. Because previous occurrence of spontaneous abortion could have been due to the same environmen-

tal or occupational exposures studied in the index spontaneous abortion, and to avoid possible bias, we did not adjust for previous spontaneous abortion in these analyses.<sup>12</sup> Our primary analysis looked at all spontaneous abortions as the outcome. In our secondary analysis, we stratified by the timing of the spontaneous abortion, because early and late spontaneous abortion may be controlled by different mechanisms, and the percentage of spontaneous abortions caused by chromosomal abnormalities decreases as gestational age increases.<sup>13</sup> For this analysis, early spontaneous abortion is modeled as  $<12$  weeks' gestation, and late spontaneous abortion as 12-20 weeks. For the analysis of late spontaneous abortions, early spontaneous abortions were excluded ( $n = 575$ ). To assess statistically significant differences between early and late models, we calculated  $P$  values for common effects with a  $\chi^2$  test statistic using the maximum likelihood estimates from the logistic regression. We also assessed interactions between parity and each exposure by modeling a cross-product interaction term in a model containing the main effects of parity and the exposure, as well as other covariates.

## RESULTS

Among 7482 eligible participants, the pregnancies of 775 (10%) ended in spontaneous abortion. Seventy-four percent of those ended before the 12th week of pregnancy ( $n = 575$ ). The year of the pregnancies ranged from 1993-2002 (the mean year was 1996), with 82% occurring between 1993 and 1998. The spontaneous abortion rate varied by specialty area; the lowest rates were for medical/surgical and critical care (8.4% and 8.8%, respectively), and the highest rates for home health/community and oncology (13.1% for each). However, 32% of nurses specified "other" as their specialty area (11.0% spontaneous abortion rate).

Table 1 shows age-adjusted prevalence of selected characteristics of eligible participants by pregnancy outcome. Women whose pregnancies ended in spontaneous abortion were older and less likely to be parous than those with live births. Prior

TABLE 1

Demographic and lifestyle factors<sup>a</sup> by pregnancy outcome

Study subject characteristics	Spontaneous abortion <20 weeks' gestation n = 775 (10.4%)		Live birth n = 6707 (89.6%)	
Maternal prepregnancy BMI <sup>b</sup> Mean, range, (SD)	25.3, 16.1–50.0 (5.7)		24.3, 15.0–50.0 (4.9)	
Maternal age (y) Mean, range, (SD)	39.5, 30–51 (3.8)		36.4, 29–50 (3.4)	
Maternal age category	n	%	n	%
≤30	6	0.8	175	2.6
31–35	112	14.5	2609	38.9
36–40 (referent)	344	44.4	3113	46.4
41+	313	40.4	810	12.1
Race				
African American <sup>c</sup>	5	0.4	42	0.7
Asian	12	1.1	119	1.9
White	719	92.5	6229	92.8
Hispanic	11	1.3	101	1.5
Other	15	2.2	100	1.5
Missing	13	2.5	116	1.7
Parous	535	68.2	5698	84.6
Previous spontaneous abortion	394	44.9	2296	34.9
First-trimester lifestyle factors				
Caffeinated coffee servings <sup>d</sup>				
None (reference)	412	55.1	4151	61.6
≤1 cup per day	232	28.8	1874	28.1
≥2 cups per day	130	15.8	676	10.2
Missing	1	0.4	6	0.1
Caffeinated soda/tea servings <sup>d</sup>				
None (reference)	379	45.7	3191	47.9
≤1 serving per day	284	38.4	2781	41.2
≥2 servings per day	112	15.9	720	10.7
Missing	0	0.0	15	0.2
Alcoholic beverage servings <sup>d</sup>				
None (reference)	584	76.8	5459	81.2
<1 drink per week	120	14.8	926	13.9
≥1 drink per week	70	8.3	315	4.8
Missing	1	0.1	7	0.1
Smoked cigarettes per day				
None (reference)	710	92.2	6316	94.2
≥1 cigarette per day	65	7.6	389	5.8
Missing	0	0.0	2	0.0

BMI, body mass index.

<sup>a</sup> Percentages for all variables except maternal age are directly standardized by year of age at current pregnancy; <sup>b</sup> BMI (kg/m<sup>2</sup>) recorded on the most recent questionnaire before the current pregnancy;<sup>c</sup> 101 participants were missing data on race; <sup>d</sup> Servings of caffeinated/alcoholic beverages = 8 oz coffee, 12 oz soda, 8 oz hot tea, 16 oz iced tea, 12 oz beer, 6 oz wine, 1 oz liquor.Lawson. Spontaneous abortion risk in nurses. *Am J Obstet Gynecol* 2012.

TABLE 2

Occupational factors<sup>a</sup> by pregnancy outcome

Variable	Spontaneous abortion <20 weeks' gestation n = 775 (10.4%)		Live birth n = 6707 (89.6%)	
Self-reported occupational exposures <sup>b</sup>				
“On average, how many hours per day did you work with the following agents:”				
“Anesthetic gases (eg, nitrous oxide, halothane, enflurane, isoflurane)?”				
<1 (reference)	706	90.6	6133	91.5
1-4	30	3.9	234	3.5
4-8	29	4.3	274	4.1
9+	10	1.2	66	1.0
“Anticancer drugs (eg, Cytosan, Fluroplex, Adrucil, etoposide, 5-FU)?”				
<1 (reference)	727	92.8	6453	96.2
1-4	39	5.8	202	3.0
4-8	8	1.3	45	0.7
9+	1	0.1	7	0.1
“Antiviral drugs (eg, gancyclovir) or the interferons?”				
<1 (reference)	724	93.1	6333	94.5
1-4	45	6.2	354	5.2
4-8	6	0.8	16	0.2
9+	0	0.0	4	0.1
“Sterilizing agents (eg, ethylene oxide, formaldehyde, glutaraldehyde)?”				
<1 (reference)	699	90.7	6210	92.7
1-4	68	8.5	435	6.4
4-8	8	0.7	51	0.7
9+	0	0.0	11	0.2
“X-ray radiation?”				
<1 (reference)	650	81.5	5781	86.3
1-4	116	17.1	852	12.6
4-8	8	1.2	61	0.9
9+	1	0.2	13	0.2
Work schedule <sup>b</sup>				
“What schedule did you usually work? If most of work hours are between 8 AM-4 PM, then it is day”; if 4 PM-midnight, then it is “evening”; if midnight-8 AM, then it is “night.”				
Shift				
Days only (reference)	536	66.7	4573	68.6
Nights only	89	12.7	575	8.5
Rotating shifts including nights	54	7.4	433	6.4
Day/evening rotating; no nights	96	13.2	1126	16.5
Hours worked, h/wk				
1-20	158	24.7	1707	25.2
21-40	397	49.0	3846	57.4
41+	220	26.2	1154	17.4

Cytosan; Baxter Healthcare Corporation, Deerfield, IL. Fluroplex; manufactured for Allergan, Inc., Irvine, CA, by Contract Pharmaceuticals Limited, Mississauga, Ontario, Canada. Adrucil; Teva Parenteral Medicines, Inc., Irvine, CA. 5-FU and etoposide are generic.

<sup>a</sup> Percentages for all variables except maternal age are directly standardized by year of age at current pregnancy; <sup>b</sup> Trimester-specific occupational exposures and work schedule were collected by questionnaire.

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spontaneous abortion, higher consumption of caffeinated beverages and alcohol, and cigarette smoking were also more common among pregnancies ending in spontaneous abortion. Occupational exposures were reported more often in spontaneously aborted pregnancies, particularly exposure to antineoplastic drugs, which was reported nearly twice as often compared with live births (Table 2). As previously reported,<sup>14</sup> women whose pregnancies failed were more likely to have worked the night shift and to have worked long hours during the first trimester than women with live births.

Table 3 provides estimated odds ratios and 95% confidence intervals (CIs) for the associations between occupational exposures and spontaneous abortion in 3 models. First, we evaluated the associations between each individual exposure and spontaneous abortion (adjusted for age), showing increased risks for spontaneous abortion with reported exposure to antineoplastic drugs, sterilizing agents, and X-rays. When simultaneously adjusting for age and all 5 work exposures, these 3 exposures were still associated with spontaneous abortion, though X-ray exposure was of borderline statistical significance. Further adjustment for parity, shift work, and hours worked per week had modest impact, and showed that nurses reporting occupational exposure to antineoplastic drugs had a 94% increased risk of spontaneous abortion, whereas exposure to sterilizing agents had a 39% increased risk. To evaluate if exclusion of pregnancies not confirmed by a pregnancy test resulted in any bias, we analyzed the final model without this exclusion, and the results were nearly identical.

Because nulliparous women might have underlying subfertility that may make them more susceptible to effects of reproductive hazards, we conducted a secondary analysis by parity. We evaluated the multiplicative interaction between each exposure and parity (yes/no), adjusted for age, shift work, hours worked, and each of the occupational exposures. There were 240 (19.2%) spontaneous abortions among the 1249 nulliparous women and 535 spontaneous abortions among the 6233 parous women (8.9%). Only antineoplastic drugs appeared to interact with

TABLE 3

### Association between occupational exposures during the first trimester and spontaneous abortion

Occupational exposures	Odds ratio (95% confidence interval)		
	Age-adjusted models <sup>a</sup>	Combined exposures <sup>b</sup>	Full model <sup>c</sup>
<b>Anesthetic gases</b>			
<1 h per day (reference)	1.0	1.0	1.0
1+ h per day	1.07 (0.81–1.40)	0.85 (0.63–1.17)	0.88 (0.65–1.21)
<b>Antineoplastic agents</b>			
<1 h per day (reference)	1.0	1.0	1.0
1+ h per day	1.97 (1.41–2.76)	2.03 (1.39–2.97)	1.94 (1.32–2.86)
<b>Antiviral agents</b>			
<1 h per day (reference)	1.0	1.0	1.0
1+ h per day	1.28 (0.93–1.76)	0.93 (0.65–1.34)	0.92 (0.64–1.32)
<b>Sterilizing agents</b>			
<1 h per day (reference)	1.0	1.0	1.0
1+ h per day	1.46 (1.12–1.91)	1.46 (1.09–1.95)	1.39 (1.03–1.87)
<b>X-ray radiation</b>			
<1 h per day (reference)	1.0	1.0	1.0
1+ h per day	1.31 (1.05–1.62)	1.27 (1.01–1.60)	1.22 (0.97–1.55)

<sup>a</sup> The age-adjusted model evaluated each exposure independently, adjusting for age; <sup>b</sup> The combined exposures model tested each work exposure with all work exposures, adjusting for age; <sup>c</sup> The full model includes all work exposures, adjusting for age, parity, shift work, and hours worked.

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parity (interaction  $P = .04$ ), with stronger associations among nulliparous women (3.50; 95% CI, 1.79–6.87) than among parous women (1.44; 95% CI, 0.88–2.36).

Because early spontaneous abortions may have different causes than later pregnancy loss,<sup>13</sup> we conducted a subanalysis stratified by gestational age of the pregnancy for early loss (<12 weeks' gestation,  $n = 575$ ) vs late loss (12–20 weeks' gestation,  $n = 200$ ). The results—adjusted for all work exposures, age, parity, shift work, and hours worked per week—are shown in Table 4. The stratified analysis shows that reported exposures to antineoplastic drugs (OR, 2.13; 95% CI, 1.39–3.27) and, to a lesser extent, X-rays (OR, 1.31; 95% CI, 1.01–1.71) were associated with an increased risk for early pregnancy loss. Reported exposure to sterilizing agents was associated with later pregnancy loss (OR, 2.10; 95% CI, 1.29–3.41) but not with early spontaneous abortion; the difference between the 2 models was statistically significant ( $P$  value = .04).

### COMMENT

We found that exposure to some of the agents commonly used by health care workers, including antineoplastic drugs, sterilizing agents, and X-rays, were associated with an increased risk of spontaneous abortion. Antineoplastic drugs are handled by nurses, pharmacists, physicians, operating room personnel, workers in veterinary practices, and manufacturers; exposures can occur during manufacture, preparation, administration, and contact with patient waste products.<sup>15</sup> Recognized as teratogenic and mutagenic, antineoplastic agents act on rapidly proliferating cells and are therefore of particular concern for a developing fetus.<sup>16–18</sup> Previous studies have had mixed results, and many suffer from limited sample sizes. The 3 largest studies<sup>19–21</sup> showed increased risks for spontaneous abortion with self-reported first-trimester exposure through handling or mixing, mostly among oncology nurses or pharmacists (ORs ranging from 1.5–2.3)



TABLE 4

## Association between occupational exposures during the first trimester and early vs late spontaneous abortion

Occupational exposures	Odds ratio (95% confidence interval)		
	Early spontaneous abortion (<12 wk) <sup>a</sup> n = 575	Late spontaneous abortion (12-20 wk) <sup>a,b</sup> n = 200	Difference of effect estimates between early and late <sup>c</sup> <i>P</i> value
Anesthetic gases			
<1 h per day (reference)	1.0	1.0	
1+ h per day	0.94 (0.66–1.33)	0.79 (0.44–1.42)	.6
Antineoplastic agents			
<1 h per day (reference)	1.0	1.0	
1+ h per day	2.13 (1.39–3.27)	1.39 (0.68–2.84)	.3
Antiviral agents			
<1 h per day (reference)	1.0	1.0	
1+ h per day	0.76 (0.50–1.18)	1.35 (0.75–2.44)	.1
Sterilizing agents			
<1 h per day (reference)	1.0	1.0	
1+ h per day	1.13 (0.80–1.60)	2.10 (1.29–3.41)	.04
X-ray radiation			
<1 h per day (reference)	1.0	1.0	
1+ h per day	1.31 (1.01–1.71)	0.98 (0.63–1.53)	.3

<sup>a</sup> Adjusted for all work exposures, age, parity, shift work categories, and hours worked per week; <sup>b</sup> Excludes the 575 pregnancies ending in early spontaneous abortion; <sup>c</sup> To assess statistically significant differences between early and late spontaneous abortion models, we calculated *P* values for common effects with a  $\chi^2$  test statistic using the maximum likelihood estimates from the logistic regressions.

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in samples that included from 18 to 223 exposed cases. Other studies did not find statistically significant associations<sup>22–27</sup> with ORs ranging from 0.7–2.8, and limited sample sizes (3 to 34 exposed cases). A metaanalysis pooled the results of 5 studies<sup>19–21,24,25</sup> and found an overall adjusted increased risk of 46% (95% CI, 11–92%).<sup>28</sup> Only 1 of these studies<sup>25</sup> occurred after safe handling measures were first recommended in 1985.<sup>29,30</sup> However, since 1985, several exposure studies still report drug contamination on work surfaces in pharmacies and patient rooms.<sup>31</sup> The National Institute for Occupational Safety and Health recently updated the recommendations for safe handling of antineoplastic drugs.<sup>32</sup>

Our findings regarding exposure to sterilizing agents is consistent with our previously reported association of sterilizing agents with risk of preterm birth (relative risk, 1.9; 95% CI, 1.1–3.4).<sup>33</sup> Glutaraldehyde, formaldehyde, ethylene oxide, orthophthalaldehyde, peracetic acid, and hydrogen peroxide are used to

disinfect medical equipment and surgical instruments. Ethylene oxide and formaldehyde are recognized as carcinogenic and mutagenic, but there have been few studies in humans to evaluate their reproductive toxicity,<sup>3,23,34,35</sup> and most had limited sample sizes. Information regarding safe exposure levels for pregnant women is lacking. Future studies should build on these findings to clarify which specific sterilizing agents may pose risks to pregnant nurses, the specific context in which they are being used, and the efficacy of safe handling practices.

Though it is well-known that an acute dose of ionizing radiation is a reproductive hazard, the reproductive risks associated with occupational exposure to X-rays during pregnancy are not well defined.<sup>36</sup> The current occupational exposure limit for ionizing radiation to the fetus of a pregnant worker is 5 mSv (0.5 rem) cumulative during the course of the pregnancy, with a monthly equivalent dose limit of 0.5 mSv.<sup>37</sup> Factors associated with the level of radiation include

the source, distance from the source, use of a shielded control booth or leaded apron, and gestational age at the time of exposure. Health care workers, dental assistants, and veterinarians can be exposed via X-rays, CT scans, fluoroscopies, radioactive isotopes, and radioactive implants; these are listed in order of increasing relative biologic effectiveness. A recent study found a 3-fold higher spontaneous abortion rate among women occupationally exposed to radioisotopes compared to X-rays,<sup>38</sup> suggesting a dose-response relationship. In addition, staff who use mobile X-ray machines may find it difficult to follow guidelines to reduce exposure.<sup>7</sup> A radiation safety officer can advise workers on atypical or nonstandard procedures where radiation exposure is unavoidable.

Anesthetic gases have long been of concern to nurses, dental workers, and veterinarians, though our study did not show an association with spontaneous abortion.<sup>6,39</sup> A metaanalysis of studies that were conducted in the absence of

scavenging systems reported increased risks for spontaneous abortion.<sup>40</sup> Studies of dental and veterinary offices have found increased risks of spontaneous abortion in practices where anesthetic gases were not scavenged.<sup>41,42</sup> More recent studies show inconsistent results, possibly because of sample size limitations<sup>42-44</sup> or because of the heterogeneity of exposure. Although appropriate engineering controls are commonplace in many hospital operating rooms, smaller medical facilities (such as dental, veterinary, or pediatric offices) may be less vigilant in controlling exposures. In addition, reduced ability of pediatric patients and veterinary animals to voluntarily cooperate during gas administration procedures could hamper the effectiveness of scavenging. Therefore, though our study supports the idea that the use of engineering controls has reduced the risk of spontaneous abortion, it does not rule out possible effects on pregnancy in smaller facilities.

We could find no previous studies of occupational exposure to antivirals and spontaneous abortion. Because certain antivirals are considered to be teratogenic to animals, and are contraindicated during pregnancy according to the FDA, pregnant health care workers should be advised of potential risks when administering aerosolized antivirals.<sup>45</sup>

Though recall error is a potential limitation of our study, we attempted to minimize it by keeping the recall period relatively short ( $\leq 8$  years, mean of 5 years).<sup>46</sup> In addition, Nurses' Health Study participants have been shown to self-report health data accurately for several medical conditions.<sup>47-49</sup> Moreover, self-report of the duration of drug handling by pharmacists has been shown to be valid.<sup>50</sup>

However, there is still potential for recall bias, because the pregnancy outcomes were reported on the same instrument that collected occupational exposures. Though we cannot directly measure recall bias, we do not believe it is likely to explain our findings. First, we observed substantially different odds ratios for early vs late spontaneous abortions for antineoplastic agents and sterilizing agents. This observation is consistent with biologic mechanisms, and it is not

expected that recall bias would be differential based on whether the spontaneous abortion was early or late. In addition, we would expect recall bias to be highest for agents with the most awareness of potential hazard,<sup>51</sup> such as X-rays<sup>52</sup>; however, we noted only a small excess risk associated with exposure to X-rays.

An important limitation of our study is that we were not able to collect information on measures to control exposures, such as use of gloves, respirators, lead aprons, ventilation, or scavenging systems, nor did we collect information on types of agents being used, forms of administration, or sources of radiation. Future studies could improve on the current study with a more detailed exposure assessment instrument; such data are currently being collected in the Nurses' Health Study III.

The large sample size, narrow recall period, and ability to control for multiple exposures are improvements over previous studies. Though the homogeneity of the nurses in our study with respect to socioeconomic status and education may decrease generalizability, it also likely reduced confounding. Unlike previous studies, we were also able to distinguish between early and late spontaneous abortions, which likely follow different mechanisms and causes, with early spontaneous abortions having a higher likelihood of being caused by chromosomal abnormalities.<sup>13</sup> Therefore, it is possible that earlier spontaneous abortions could be due to exposures that are mutagenic, whereas later spontaneous abortion may be the result of teratogenic exposures or exposures that affect the mother's ability to carry the infant to term. Further research is indicated to explore the differences we see in our data.

In conclusion, we found increased risks for spontaneous abortion with reported exposures to antineoplastic drugs, sterilizing agents, and X-rays. Although antineoplastic drugs and X-rays are known reproductive hazards, US nurses are still reporting exposures to these during pregnancy. We encourage nurses who are pregnant, or who wish to become pregnant, to work with their employers and their health care providers to

reduce exposures during pregnancy and lactation. ■

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