Nurses With Dermal Exposure to Antineoplastic Drugs

Reproductive Outcomes

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Background: Nurses and other hospital workers are exposed to antineoplastic drugs during daily activities. Previous studies suggest that antineoplastic drugs at occupational exposure levels may be toxic to reproduction, but these studies are not consistent or conclusive.

Methods: Self-administered questionnaires were completed by 4393 exposed and nonexposed nurses employed between 1990 and 1997 (79% response). Questions were asked about pregnancy outcome, work-related exposures, and lifestyle. Exposure to antineoplastic drugs was estimated using task-based dermal exposure measurements and self-reported task frequencies. Time to pregnancy was modeled using survival analysis, and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for other reproductive outcomes using multiple logistic regression analysis. Associations were further explored by nonparametric regression modeling.

Results: Nurses highly exposed to antineoplastic drugs took longer to conceive than referent nurses (adjusted hazard ratio = 0.8; CI = 0.6–0.9). Exposure to antineoplastic drugs was associated with premature delivery (OR per unit increase in ln[exposure] = 1.08; CI = 1.00–1.17) and low birth weight (OR per unit increase in ln [exposure] = 1.11; 1.01–1.21). Penalized smoothed spline plots corroborated these log-linear relations. Spontaneous abortion, stillbirth, congenital anomalies, and sex of offspring appeared not to be related to exposure to antineoplastic drugs.

Conclusion: Antineoplastic drugs may reduce fertility and increase poor neonatal outcomes among occupationally exposed oncology nurses.

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Nurses and other hospital workers are exposed to antineoplastic drugs during daily activities. For example, low levels of antineoplastic drugs have been found in oncology nurses' urine.[1–3] Some studies have evaluated exposure by inhalation,[4,5] but most evidence indicates that dermal exposure is the major route of exposure.[2,5,6] Few studies have addressed possible adverse health effects of this occupational exposure. Antineoplastic drugs, when administered to patients at therapeutic doses, are known to cause congenital malformations and fetal death.[7–9] Some studies have suggested that antineoplastic drugs at occupational exposure levels may be toxic to reproduction, but these studies are not consistent or conclusive.[10–15]

The present study focuses on toxic effects on reproduction among nurses working with patients treated with antineoplastic drugs. Previous analyses from this questionnaire study, reported in Dutch,[16] indicated an elevated risk of toxic effects on reproduction among oncology nurses. Additional information on exposure to antineoplastic drugs based on quantitative dermal exposure measurements enabled us to study dose–response relations between reproduction and exposure to antineoplastic drugs.

METHODS

Study Participants

All 121 hospitals in The Netherlands were asked to identify female nurses between 22 and 37 years of age (ie, reproductive age) from their personnel files. These nurses must have been employed for at least 2 months between 1990 and 1997 as an oncology nurse or as a nurse in orthopedics, obstetrics/gynecology, or surgery. Oncology nurses were selected because of their risk for exposure to antineoplastic drugs. Nurses from the other departments were selected as a reference group lacking exposure to antineoplastic drugs but with similar levels of education, socioeconomic status, and occupational conditions.

Questionnaire

Questionnaires focused only on the most recent pregnancy while working in a hospital and consisted of questions on pregnancies, lifestyle factors, and work conditions and characteristics. Occupational questions included specific questions on the frequency of tasks involving antineoplastic drugs (preparation, administering, handling patient urine,

washing patients, removing bed sheets, and cleaning activities) as well as the use of protective equipment.

Adverse reproductive effects were prolonged time to pregnancy, spontaneous abortion (miscarriage before the 20th week of a confirmed pregnancy), stillbirth (miscarriage in or after the 20th week of a confirmed pregnancy), premature delivery (live birth before the 37th week of pregnancy), low birth weight (≤2500 g), sex of offspring (percentage boys), and congenital malformations (according to the European Surveillance of Congenital Anomalies [EUROCAT] definitions and International Classification of Diseases, 10th Revision coding). We excluded malformations due to monogenetic causes (β-thalassemia, Williams-Beuren syndrome) and minor congenital malformations.

Exposure Assessment and Assignment

Exposure levels were retrospectively assigned to each nurse based on reported weekly task frequencies during the first month of pregnancy (or the period that nurses tried to get pregnant). Exposure were based on 5 tasks routinely performed by Dutch oncology nurses (preparation, administration, handling patient urine, washing a patient, removing bed sheets, cleaning toilets) and on the reported use of gloves during these tasks. Each task was assigned an exposure level estimated by collecting glove pairs used by nurses during the preparation of antineoplastic drugs (N = 8), administration of the drugs (N = 29), or handling patient urine (N = 11) (Table 1). Cyclophosphamide (a frequently used antineoplastic drug) was used as a marker for exposure to antineoplastic drugs. Glove pairs were collected in a subset of 6 hospitals in 1996 and 1997, extracted, and analyzed for cyclophosphamide using a previously described gas chromatography–tandem mass spectrometry method.[31] To complement these task exposures, dermal exposure measurements (glove pairs and handwashing samples) from a recently published study[6] (samples collected between 2001 and 2003 in 4 hospitals) were used to retrospectively estimate dermal exposure levels to the hands during washing a patient, removing bed sheets, and cleaning a patient's toilet (Table 1). In The Netherlands, these tasks are routinely performed by oncology nurses and have been found to cause dermal exposure to cyclophosphamide.[6] Glove protection factors for each task were obtained from the same study and were used to assess actual exposure levels defined as exposure to skin of the hands (underneath gloves).

Multiplication of these task-based dermal exposure levels by reported task frequencies (taking into account the reported use of gloves) produced for each nurse in the cohort a total estimated of dermal exposure per week during the first month of pregnancy (or the period during which the nurse tried to get pregnant). To allow categorical analyses, exposed nurses were divided into tertiles of the exposure distribution. Nurses who did not perform any of the tasks with antineoplastic drugs, but who worked at a department where antineoplastic drugs were frequently handled, were assigned a background exposure estimate of 0.5 times the lowest value of the exposure distribution. The nonexposed reference group consisted of nurses who did not work with patients treated with antineoplastic drugs or at a department where these drugs were frequently used.

Statistical Analysis

Data were analyzed using SAS statistical software (version 9.1; SAS Institute, Cary, NC). To allow categorical analyses, nurses were divided into a nonexposed group, a background exposed group, and 3 exposure categories based on the tertiles (0.20 μg/week and 0.74 μg/week) of the exposure distribution. Crude and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated by means of logistic regression analysis (PROC LOGISTIC) using the nonexposed nurses as the reference group. For time to pregnancy, we computed crude and adjusted hazard ratios (fecundability ratios) and 95% CIs using a discrete logistic model to handle ties in PROC PHREG. Nurses who tried to get pregnant but never succeeded were included as censored values. To investigate the possibility for medical intervention bias, time-to-pregnancy data were censored at 1 year or at the time the couple first sought medical help.[17] The log-linear

TABLE 1. Measurements (Gloves and Hand Wash Samples) of Cyclophosphamide (CP) Collected in the Present Study (1996–1997) and in a Study by Fransman et al[6] (2001–2003) and the Exposure Estimates Assigned to Each Task in the Exposure Assessment

	1996–1997 (this study)			2001–2003[6]						Actual Dermal Exposure Levels Assigned to Each Task (μg/task)	
	CP on Gloves (μg/task)			CP on Gloves (μg/task)			CP on Hands (μg/task)				
Task	No.*	Geometric Mean	(Range)	No.*	Geometric Mean	(Range)	No.*	Geometric Mean	(Range)	No Gloves Used	Gloves Used
Preparing	8	27.0	(1.79–207.4)	26	0.07	(0.01–5.42)	26	0.01	(0.01–0.04)	31.9	4.87
Administering	29	0.04	(0.01–26.3)	0			0			0.05	0.01
Handling urine	11	0.09	(0.01–8.45)	26	0.02	(0.01–0.13)	26	0.02	(0.01–0.14)	0.19	0.10
Washing patient	0			10	0.19	(0.04–0.75)	10	0.03	(0.01–0.10)	0.21	0.03
Removing bed sheets	0			8	0.02	(0.01–0.05)	8	0.02	(0.01–0.17)	0.05	0.02
Cleaning toilet	0			19	0.06	(0.01–0.80)	19	0.01		0.07	0.01

*No. of measurements.

association between time to pregnancy and exposure to antineoplastic drugs was evaluated using a discrete logistic hazard model (PROC PHREG) using natural log-transformed exposure data.

To describe associations between specific dichotomized reproductive outcomes and natural log-transformed exposure to antineoplastic drugs, odd ratios were computed per one-unit increase in natural log-transformed exposure using logistic regression analysis (PROC LOGISTIC). These associations were further explored by nonparametric regression modeling (smoothing) using generalized additive models (PROC GAM).[18] Generalized crossvalidation was used to select the smoothing parameter degrees of freedom.[18] If the relation was not biologically plausible, it was limited to 3 degrees of freedom.

All statistical models were adjusted for potential confounders selected a priori (ie, age at conception; parity; smoking, alcohol consumption, and coffee consumption dur-

TABLE 2. Outcome of Last Pregnancy While Working in a Hospital and Personal, Lifestyle, and Work-Related Characteristics of the Study Population During the First Month of Pregnancy (or the Period During Which They Tried to Get Pregnant) by Exposure Category

			Antineoplastic Drug Exposure (μg/wk)		
	Nonexposed (n = 663)	Background-Exposed (n = 324)	Low (≤0.20) (n = 178)	Medium (0.21–0.74) (n = 177)	High (>0.74) (n = 177)
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Pregnancy 1990–1997					
One or more deliveries between 1990 and 1997	555 (84)	279 (86)	146 (82)	145 (82)	134 (76)
Pregnant during questionnaire survey	66 (10)	24 (7)	12 (7)	15 (9)	17 (10)
Tried without success to get pregnant between 1990 and 1997	42 (6)	21 (7)	20 (11)	17 (10)	26 (15)
Personal					
Age at conception* (yr)					
≤25	19 (3)	4 (1)	8 (5)	13 (8)	3 (2)
26–30	333 (54)	175 (58)	81 (53)	90 (58)	82 (54)
31–35	252 (41)	120 (40)	64 (42)	51 (33)	65 (43)
>35	9 (2)	4 (1)	0 (0.0)	1 (1)	1 (1)
Parity (>1 child)	306 (46)	156 (48)	71 (40)	77 (44)	66 (37)
Lifestyle					
Smoking†	152 (23)	65 (20)	40 (23)	44 (25)	45 (26)
Alcohol†	381 (58)	191 (59)	103 (58)	107 (61)	118 (67)
Coffee†	514 (78)	249 (77)	141 (79)	139 (79)	138 (78)
Multivitamin‡	74 (11)	45 (14)	28 (16)	22 (12)	14 (8)
Folic acid‡	223 (34)	116 (36)	61 (34)	53 (30)	63 (36)
Work-related					
Lifting >10 kg§	579 (88)	278 (86)	169 (95)	164 (93)	169 (96)
Carrying >10 kg§	304 (47)	136 (42)	74 (42)	66 (38)	67 (38)
Standing >2 h§	484 (73)	246 (76)	133 (75)	137 (78)	116 (66)
High work pressure¶	573 (87)	282 (87)	162 (91)	163 (93)	167 (94)
Occupational contact with:					
Alcohol	579 (88)	291 (90)	161 (90)	161 (92)	164 (93)
Disinfecting/sterilizing agents	401 (61)	208 (64)	124 (70)	128 (73)	121 (68)
Disinfecting cleaning agents	434 (66)	251 (78)	135 (76)	138 (78)	143 (81)
Solvents	64 (10)	36 (11)	27 (15)	18 (10)	41 (23)
Ionizing radiation	228 (35)	94 (29)	96 (54)	88 (50)	95 (54)
Nonionizing radiation	173 (26)	91 (28)	48 (27)	54 (31)	45 (25)
Antibiotics	611 (93)	314 (97)	169 (95)	175 (99)	170 (96)
Bone cement	26 (4)	13 (4)	5 (3)	5 (3)	2 (1)

*For nurses who only tried to get pregnant but never succeeded, the age at the moment they start trying to get pregnant was used.
†Percentage who reported having smoked/consumed alcohol/consumed coffee during the first month of pregnancy (or the period that they tried to get pregnant).
‡Percentage who reported to having taken multivitamins/folic acid before or during pregnancy (or the period that they tried to get pregnant).
§Percentage who reported to having ever lifted >10 kg/carried >10 kg/stood >2 h during the first month of pregnancy (or the period that they tried to get pregnant).
¶Percentage who regularly worked under time pressure during the first month of pregnancy (or the period that they tried to get pregnant).

ing the first month of pregnancy; and intake of multivitamins and/or folic acid during pregnancy). Other work-related factors were also considered as potential confounders: ever lifting or carrying more than 10 kg or standing more than 2 hours during the first month of pregnancy; regular high-pressure work during pregnancy; and work-related contact with alcohol, disinfecting agents, solvents, radiation, antibiotics, or bone cement during the first month of pregnancy. Adjustments for potential confounders did not alter the results.

RESULTS

Characteristics of Study Participants

Of the 121 hospitals approached, 83 (69%) agreed to participate in the study. In total, 5546 female nurses of reproductive age were identified who worked at least 2 months in a hospital between 1990 and 1997 as an oncology nurse or at one of the preselected reference departments. Of these, 4393 completed and returned the questionnaire (response rate = 79%). Of these nurses, 2426 had been pregnant at least once between 1990 and 1997 or were pregnant at the time of completing the questionnaire or tried to get pregnant between 1990 and 1997. A large proportion (N = 739) of referent nurses were excluded because they reported exposure to anesthetic gases (another known toxic compound to reproduction). There was no apparent anesthetic gas exposure among oncology nurses and therefore this exposure could not be adjusted for. There were 1519 nurses who met the requirements for one of the exposure categories (working with antineoplastic drugs, the background exposure group, or the nonexposed reference group) either during pregnancy or during the period they were trying to get pregnant.

The outcome of the most recent pregnancy and characteristics of study participants during the first month of this pregnancy are shown in Table 2. Nurses in all exposure groups had a similar age at conception, and nurses were similar in lifestyle factors and levels of physical and chemical factors at work (other than antineoplastic drugs). Nurses in the highest exposure category differed somewhat from referent nurses in a few work-related factors (lifting more than 10 kg, standing more than 2 hours, high work pressure, and work-related exposure to solvents) (Table 2).

Reproductive Outcomes

There were 177 nurses in the highest tertile of antineoplastic drug exposure (>0.74 μg/week), 177 nurses with medium exposure (between 0.20 and 0.74 μg/week), 178 nurses with low exposure (≤0.20 μg/week), 324 nurses with background exposure (0.002 μg/week), and 663 nonexposed referent nurses. The survival analyses (Table 3) suggest a prolonged time to pregnancy for highly exposed nurses compared with the reference group. The "hazard" of getting pregnant was lower with an adjusted hazard ratio of 0.8 (95% CI = 0.6–0.9). This corresponds to an increase of 1 month in time to pregnancy (median time to pregnancy was 2 months for nonexposed nurses and 3 months for highly exposed nurses). Censoring time to pregnancy at 1 year or at the time the couple first sought medical help did not alter the hazard ratio (for both censoring scenarios, the adjusted hazard ratio was 0.8, CI = 0.6–1.0).

The proportions of reproductive disorders and adjusted odds ratios for the exposure categories suggest an increased risk for delivering a child with low birth weight among highly exposed nurses (adjusted OR = 2.1; CI = 0.9–4.7) (Table 3).

TABLE 3. Associations of Antineoplastic Drug Exposure With Reproductive Outcomes

	Antineoplastic Drug Exposure (μg/wk)							
	Nonexposed* (n = 663)		Background Exposure (n = 324)			Low (≤0.20) (n = 178)		
	Mean or Percent†	Effect Measure‡	Mean or Percent†	Effect Measure‡ Crude (95% CI)	Adjusted§ (95% CI)	Mean or Percent†	Effect Measure‡ Crude (95%CI)	Adjusted§ (95% CI)
Time to pregnancy (months)‖	5.5	1.0	6.5	0.9 (0.8–1.1)	0.9 (0.8–1.1)	6.6	0.9 (0.7–1.0)	0.9 (0.7–1.0)
Spontaneous abortion¶	5.5	1.0	6.5	1.2 (0.7–2.2)	1.0 (0.6–2.0)	6.8	1.3 (0.6–2.7)	1.2 (0.6–2.7)
Stillbirth¶	0.4	1.0	0.4	1.0 (0.1–11.1)	0.9 (0.1–10.0)	1.4	3.8 (0.5–27.5)	3.3 (0.5–24.5)
Premature delivery (<37 wk)#	6.3	1.0	3.6	0.6 (0.3–1.2)	0.6 (0.3–1.2)	6.8	1.1 (0.5–2.3)	1.1 (0.5–2.4)
Low birth weight (≤2500 g)#	4.0	1.0	3.3	0.8 (0.4–1.9)	0.9 (0.4–2.0)	7.0	1.8 (0.8–4.1)	2.0 (0.9–4.5)
Sex of offspring (% boys)#	50.6	1.0	53.1	1.1 (0.8–1.5)	1.1 (0.8–1.4)	55.1	1.2 (0.8–1.8)	1.2 (0.8–1.7)
Congenital malformations#**	3.0	1.0	5.4	1.9 (0.9–4.0)	1.9 (0.9–4.2)	3.9	1.3 (0.5–3.8)	1.5 (0.5–4.3)

(*Continued*)

*Reference category.

†Mean for time to pregnancy; percent for all other outcomes.

‡Hazard ratio for time to pregnancy; odds ratio for all other outcomes.

§Adjusted for age at conception (or age at start of trying to get pregnant), parity, smoking status, alcohol consumption, coffee consumption, multivitamin intake, and folic acid intake.

‖For all (ended or ongoing) pregnancies and nurses trying to get pregnant; n = 1,519.

¶Nurses who tried to get pregnant or were pregnant during the survey were excluded; n = 1,259.

#Only for pregnancies ended in a live birth; n = 1,147.

**Congenital malformations were included according to EUROCAT definitions and International Classification of Diseases, 10th Revision coding. Malformations due to monogenetic causes (β-thalassemia, Williams-Beuren syndrome) and minor congenital malformations were excluded.

This corresponds to a 45 g lower birth weight compared with nonexposed nurses. Low-exposed nurses also appeared to have an increased risk for delivering a child with low birth weight. No obviously increased risks were detected among exposed nurses compared with referent nurses for spontaneous abortion, stillbirth, premature delivery, or congenital malformations. The sex ratio at birth was unaffected. Background-exposed nurses had similar or lower proportions of adverse reproduction outcomes as nonexposed nurses, except for congenital malformations (Table 3).

Table 4 shows positive log-linear relations between (natural log-transformed) exposure to antineoplastic drugs and the risk of premature delivery (OR per unit increase in ln[exposure] = 1.08; CI = 1.00–1.17) and low birth weight (OR per unit increase in ln[exposure] = 1.11; CI = 1.01–1.21). These increases were not apparent in the categorical analyses. There was also a log-linear relation with prolonged time to pregnancy (hazard ratio per unit increase in ln[exposure] = 0.98; CI = 0.96–1.00). The penalized smoothed spline plots corroborate these log-linear relations and suggest an increasing risk of premature delivery (Fig. 1) and low birth weight (Fig. 2) at the higher end of the exposure distribution (dermal exposure greater than 3 μg/week).

Results of the regression analyses were not influenced by potential confounding factors as indicated by the marginal differences between crude odds ratios and odds ratios adjusted for age at conception, parity, and lifestyle factors during pregnancy (smoking status, alcohol consumption, coffee consumption, multivitamin intake, and folic acid intake) (Table 2).

TABLE 4. Log-Linear Association of Antineoplastic Drug Exposure With Reproductive Outcomes

	Effect Measure* per 1-Unit Increase in ln (exposure)	(95% CI)
Time to pregnancy†	0.98	(0.96–1.00)
Spontaneous abortion‡	1.01	(0.93–1.10)
Stillbirth‡	1.20	(0.98–1.47)
Premature delivery§	1.08	(1.00–1.17)
Low birth weight§	1.11	(1.01–1.21)
Sex of offspring§	1.00	(0.96–1.05)
Congenital malformations§‖	0.97	(0.86–1.09)

*Unadjusted discrete hazard ratio for time to pregnancy; unadjusted odds ratio for all other outcomes.

†For all (ended or ongoing) pregnancies and nurses trying to get pregnant; n = 1,519.

‡Nurses who tried to get pregnant or were pregnant during the survey were excluded; n = 1,259.

§Only for pregnancies ended in a live birth; n = 1,147.

‖Congenital malformations were included according to EUROCAT definitions and International Classification of Diseases, 10th Revision coding. Malformations due to monogenetic causes (β-thalassemia, Williams-Beuren syndrome) and minor congenital malformations were excluded.

DISCUSSION

Results of this study provide some evidence of a prolonged time to pregnancy among nurses with highest exposure to antineoplastic drugs (>0.74 μg/week) compared with referent nurses with no exposure to antineoplastic drugs. Positive log-linear relations were also found between dermal exposure to antineoplastic drugs and the risk of premature delivery and low birth weight. Analyses with smoothed spline

TABLE 3. (*Continued*)

Antineoplastic Drug Exposure (μg/wk)					
Medium (0.21–0.74) (n = 177)			High (>0.74) (n = 177)		
Mean or Percent†	Effect Measure‡ Crude (95%CI)	Adjusted§ (95% CI)	Mean or Percent†	Effect Measure‡ Crude (95%CI)	Adjusted§ (95% CI)
5.5	1.0 (0.8–1.2)	1.0 (0.8–1.2)	7.2	0.7 (0.6–0.9)	0.8 (0.6–0.9)
5.6	1.0 (0.5–2.3)	0.8 (0.3–2.0)	6.9	1.3 (0.6–2.8)	1.2 (0.6–2.7)
1.4	3.9 (0.5–27.7)	4.3 (0.6–32.1)	0.7	2.1 (0.2–23.1)	1.8 (0.2–21.0)
6.9	1.1 (0.5–2.4)	0.9 (0.4–2.1)	8.8	1.4 (0.7–3.0)	1.4 (0.7–2.9)
4.0	1.0 (0.4–2.7)	1.1 (0.4–2.9)	8.1	2.1 (0.9–4.7)	2.1 (0.9–4.7)
48.4	0.9 (0.6–1.4)	0.9 (0.6–1.3)	53.6	1.1 (0.7–1.7)	1.1 (0.7–1.7)
3.1	1.1 (0.3–3.2)	1.2 (0.4–3.6)	2.7	0.9 (0.3–3.1)	0.9 (0.3–3.3)

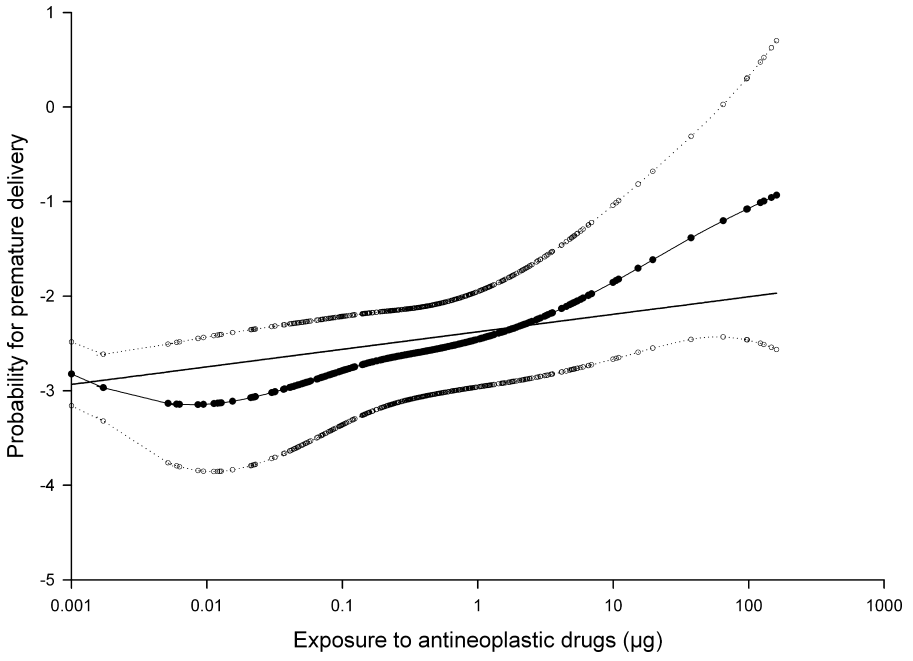

FIGURE 1. Exposure to antineoplastic drugs and premature delivery. Penalized smoothed spline plot (filled black circles) with smoothed 95% CI (open black circles) and linear regression line (black line). Smoothed spline: degrees of freedom = 3.0; linear function: OR per one-unit increase in ln(exposure) = 1.08 (95% CI = 1.00–1.17).

plots corroborate these relations and confirmed that log-linear models describe the relation in a satisfactory way. Spontaneous abortion, stillbirth, congenital malformations, and sex of offspring appeared not to be related to exposure to antineoplastic drugs in any of the analyses.

Retrospective studies are susceptible to bias. A response rate of 79% is acceptable and reduces the potential for selection bias. The fact that the study was introduced as a study on reproductive outcomes among nurses (not specifically focused on exposure to antineoplastic drugs) probably reduced the potential for selection and information bias with regard to that specific exposure. Because the present study investigated reproductive outcome retrospectively up to 7 years previously, there is a potential for differences in accuracy by length of recall. However, pregnancy outcomes are usually recalled accurately by the mother because of the personal impact (spontaneous abortion or stillbirth) or because the information is explicitly documented at birth (pregnancy duration, birth weight, sex, congenital malformations). Women are able to recall time to pregnancy many years later

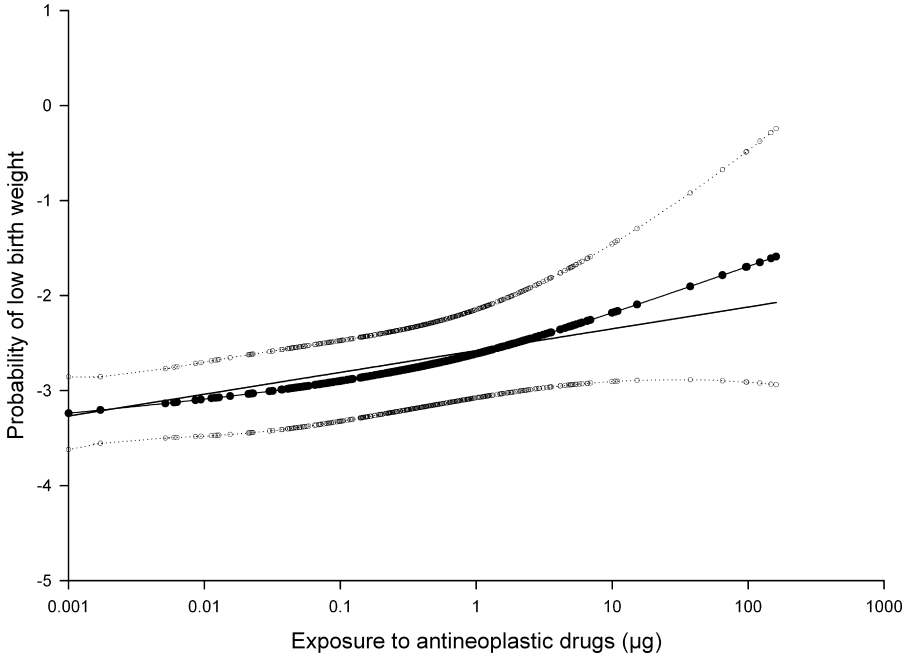

FIGURE 2. Exposure to antineoplastic drugs and low birth weight. Penalized smoothed spline plot (filled black circles) with smoothed 95% CI (open black circles) and linear regression line (black line). Smoothed spline: degrees of freedom = 1.53; linear function: OR per one-unit increase in ln(exposure) = 1.11 (95% CI = 1.01–1.21).

with surprising accuracy.[19–22] Confounding bias is not likely to have occurred. Only minor differences were observed between crude and adjusted parameter estimates and odds ratios. Covariables included in the models showed associations in the expected directions, which supports their validity.

Women who receive chemotherapy during pregnancy (with doses 3 million times higher than observed in this study) have been shown to be at high risk of spontaneous abortion, fetal death, and malformations.[7,23] Previous studies on occupational exposure to antineoplastic drugs have suggested associations with fetal loss, malformations, and spontaneous abortion,[10,11,14,24] but no quantitative exposure assessment was performed in any of these studies. Because these took place in earlier time periods when nurses were less protected from exposures to antineoplastic drugs, it is plausible that exposure levels were higher than in the present study. Thus, the available evidence suggests increased risks of spontaneous abortion and fetal death at higher exposure levels than those estimated in the present study.

Dermal exposure assessment to antineoplastic drugs was based on the measurement of dermal exposure to cyclophosphamide. Although patterns of exposure to antineoplastic drugs other than cyclophosphamide are not well studied, we made the assumption that the pattern of dermal exposure to other antineoplastic drugs would be similar to dermal exposure to cyclophosphamide. Task-based dermal exposure levels were measured in 1996–1997 and 2001–2003, whereas information on pregnancy outcomes was retrospectively collected for the period between 1990 and 1997. To the degree that exposure has declined over time, the measured exposure levels may underestimate exposure of nurses during the earlier years of our study.

Exposure assessment was based on measured task-based dermal exposure multiplied by individual task frequencies as reported on questionnaires. Variability in task frequencies was small (median frequencies for all tasks were one or 2 times per week; range, 0–100 times) compared with variability in estimated exposure intensity (range, 0.002–31.9 μg/week). This means that misclassification is most likely found in the estimated dermal exposure levels. The large variability in exposure to antineoplastic drugs was due to differences between workers (associated with differences in technology, work practice, and so on) and day-to-day variability in exposure (eg, due to splashes on the hands). Additional knowledge of determinants of exposure for each of the tasks would improve the exposure estimates and would better account for the variability between workers in exposure intensity within each task. Nevertheless, the (geometric) mean value for each task was considered to be a representative estimate of dermal exposure for each nurse while performing a specific task with antineoplastic drugs.

The current median dermal exposure level to antineoplastic drugs for the entire Dutch population of oncology nurses has been estimated to be 0.65 μg/week (10th percentile = 0.12 μg/week; 90th percentile = 3.2 μg/week),[25] which is close to the cut point for high exposure in our study. This implies that a large proportion of nurses may be at risk for a prolonged time to pregnancy, premature delivery, and delivering a child with low birth weight. As awareness among nurses working with these hazardous drugs increases, exposure during pregnancy may be avoided.

Our data suggest quantitative relations between dermal exposure to antineoplastic drugs among nurses and reproductive health effects. Such exposure should be regarded as a potential occupational risk for women who are pregnant or attempting pregnancy. Recent regulations to reduce contamination levels and protect hospital workers from occupational exposure to antineoplastic drugs[26–30] may be especially important for women of reproductive age.

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REFERENCES

1. Sessink PJM, Boer KA, Scheefhals APH, et al. Occupational exposure to antineoplastic agents at several departments in a hospital. Environmental contamination and excretion of cyclophosphamide and ifosfamide in urine of exposed workers. *Int Arch Occup Environ Health*. 1992;64:105–112.
2. Sessink PJ, van de Kerkhof MC, Anzion RB, et al. Environmental contamination and assessment of exposure to antineoplastic agents by determination of cyclophosphamide in urine of exposed pharmacy technicians: is skin absorption an important exposure route? *Arch Environ Health*. 1994;49:165–169.
3. Ensslin AS, Stoll Y, Pethran A, et al. Biological monitoring of cyclophosphamide and ifosfamide in urine of hospital personnel occupationally exposed to cytostatic drugs. *Occup Environ Med*. 1994;51:229–233.
4. Kiffmeyer TK, Kube C, Opiolka S, et al. Vapour pressures, evaporation behaviour and airborne concentrations of hazardous drugs: implications for occupational safety. *Pharm J*. 2002;268:331–337.
5. Kromhout H, Hoek F, Uitterhoeve R, et al. Postulating a dermal pathway for exposure to anti-neoplastic drugs among hospital workers. Applying a conceptual model to the results of three workplace surveys. *Ann Occup Hyg*. 2000;44:551–560.
6. Fransman W, Vermeulen R, Kromhout H. Dermal exposure to cyclophosphamide in hospitals during preparation, nursing and cleaning activities. *Int Arch Occup Environ Health*. 2005;78:403–412.
7. Cardonick E, Iacobucci A. Use of chemotherapy during human pregnancy. *Lancet Oncol*. 2004;5:283–291.
8. Ebert U, Loffler H, Kirch W. Cytotoxic therapy and pregnancy. *Pharmacol Ther*. 1997;74:207–220.
9. Zemlickis D, Lishner M, Degendorfer P, et al. Fetal outcome after in utero exposure to cancer chemotherapy. *Arch Intern Med*. 1992;152:573–576.
10. Selevan SG, Lindbohm ML, Hornung RW, et al. A study of occupational exposure to antineoplastic drugs and fetal loss in nurses. *N Engl J Med*. 1985;313:1173–1178.
11. Stücker I, Caillard JF, Collin R, et al. Risk of spontaneous abortion among nurses handling antineoplastic drugs. *Scand J Work Environ Health*. 1990;16:102–107.
12. Stücker I, Mandereau L, Hémon D. Relationship between birthweight and occupational exposure to cytostatic drugs during or before pregnancy. *Scand J Work Environ Health*. 1993;19:148–153.
13. Valanis BG, Vollmer WM, Steele P. Occupational exposure to antineoplastic agents: self-reported miscarriages and stillbirths among nurses and pharmacists. *J Occup Environ Med*. 1999;41:632–638.
14. Hemminki K, Kyyronen P, Lindbohm ML. Spontaneous abortions and malformations in the offspring of nurses exposed to anaesthetic gases, cytostatic drugs, and other potential hazards in hospitals, based on registered information of outcome. *J Epidemiol Community Health*. 1985;39:141–147.
15. Skov T, Maarup B, Olsen JH, et al. Leukaemia and reproductive outcome among nurses handling antineoplastic drugs. *Br J Ind Med*. 1992;49:855–861.

16. Peelen S, Roeleveld N, Heederik D, et al. *Reproductie-toxische effecten bij ziekenhuispersoneel.* Den Haag, The Netherlands: Elsevier bedrijfsinformatie BV; 1999.
17. Weinberg CR, Baird DD, Wilcox AJ. Sources of bias in studies of time to pregnancy. *Stat Med*. 1994;13:671–681.
18. Hastie T, Tibshirani RJ. *Generalized Additive Models*, 1st ed. New York: Chapman & Hall; 1990.
19. Rothman K, Greenland S. *Modern Epidemiology*, 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 1998.
20. Joffe M, Villard L, Li Z, et al. Long-term recall of time-to-pregnancy. *Fertil Steril*. 1993;60:99–104.
21. Baird DD, Weinberg CR, Rowland AS. Reporting errors in time-to-pregnancy data collected with a short questionnaire. Impact on power and estimation of fecundability ratios. *Am J Epidemiol*. 1991;133:1282–1290.
22. Joffe M, Villard L, Li Z, et al. A time to pregnancy questionnaire designed for long term recall: validity in Oxford, England. *J Epidemiol Community Health*. 1995;49:314–319.
23. Williams SF, Schilsky RL. Antineoplastic drugs administered during pregnancy. *Semin Oncol*. 2000;27:618–622.
24. Valanis BG, Vollmer WM, Labuhn KT, et al. Occupational exposure to antineoplastic agents and self-reported infertility among nurses and pharmacists. *J Occup Environ Med*. 1997;39:574–580.
25. Meijster T, Fransman W, van Hemmen JJ, et al. A probabilistic assessment of the impact of interventions on the exposure to antineoplastic agents of oncology nurses. *Occup Environ Med*. 2006;63:530–537.
26. NIOSH-Alert. Preventing occupational exposures to antineoplastic and other hazardous drugs in health care settings. Cincinatti. Available at: www.cdc.gov/niosh/docs/2004&cjs0025;165/pdfs/2004&cjs0025;165. pdf. 2004.
27. Hilhorst SKM, Miedema EP, Tijssen SCHA, et al. *Blootstelling aan cytostatica in ziekenhuizen: Stand der techniek op het gebied van beheersmaatregelen.* Den Haag, The Netherlands: Ministry of Social Affairs and Employment; 2001.
28. Ministry of Social Affairs and Employment. Arboconvenant academische ziekenhuizen. Den Haag, The Netherlands. Available at: www.arboconvenantacademischeziekenhuizen.nl/. 2004.
29. Health & Safety Executive. Safe handling of cytotoxic drugs. HSE Information Sheet MISC615. United Kingdom. Available at: www.hse.gov.uk/. 2003.
30. WorkSafe Victoria. Handling cytotoxic drugs in the workplace. Victoria, Australia. Available at: www.workcover.vic.gov.au/. 2003.
31. Sessink PJM, Scholtes MM, Anzion RBM, et al. Determination of cyclofosfamide in urine by gas chromatography–mass spectrometry. *J Chromatogr B Biomed Appl*. 1993;616:333–337.

