

# Leukaemia and reproductive outcome among nurses handling antineoplastic drugs

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## Abstract

During the past decades conclusive evidence has accumulated that alkylating antineoplastic drugs (ADs) can cause cancer, most notably acute non-lymphocytic leukaemia, and that most ADs are reprotoxic. Studies on health workers handling ADs have shown significantly increased risks for miscarriages (two studies) and malformations (two studies). The present study monitored the risk for cancer and adverse reproductive outcome among Danish nurses handling ADs. No increased risks were found for miscarriages, malformations, low birth weight, or preterm birth among the offspring of nurses handling ADs during pregnancy. The sex ratio was normal. The relative risk (RR) for leukaemia was significantly increased (10.65) but based on only two cases, one of acute myeloblastic and one of chronic myeloid leukaemia. From the available exposure data occupational exposures to ADs were apparently higher in the studies that have reported increased risks for miscarriages and malformations than in the present one. Regarding reproductive outcome the study gives some confidence that the safety measures which were implemented in the oncology departments around 1980 can protect the health personnel against adverse effects of ADs

on reproduction. As the study is as yet the only negative one in a well protected setting, it should be followed up by other studies of well protected health personnel handling ADs. The findings concerning the leukaemia risk, although based on small numbers, encourage larger studies.

Antineoplastic drugs (ADs) constitute a heterogeneous group of chemicals that share the ability to inhibit tumour cell growth while exerting tolerable toxicity on normal body cells. They have been used in the treatment of malignant diseases for more than 40 years, and the number of cancers eligible for medical treatment has been steadily expanding.

During the past decade conclusive evidence has accumulated that treatment of malignant as well as non-malignant diseases with alkylating ADs carries a substantial risk of second malignancies, most notably acute non-lymphocytic leukaemia.<sup>1</sup> Bladder cancer caused by the alkylating agent cyclophosphamide was first shown among patients treated with immunosuppressive drugs for non-malignant diseases.<sup>2-4</sup> In animal studies, all tested ADs have shown teratogenicity or embryotoxicity.<sup>1,5,6</sup>

Two studies of nurses occupationally exposed to ADs showed relative risks (RRs) for miscarriages of 2.30 (95% confidence interval (95% CI) 1.20-4.39) and 1.70 (95% CI 1.0-2.8) respectively.<sup>7,8</sup> No safety measures were taken during drug preparation in these study groups. Two other studies have shown increased risks for congenital malformations among health personnel handling ADs; a Finnish study found an odds ratio (OR) of 4.7 ( $p = 0.02$ ) for malformations in the offspring of nurses handling ADs,<sup>9</sup> and a Canadian study found eight malformations compared to 4.05 expected ( $p = 0.05$ ) in offspring of nurses and doctors who had administered ADs early in pregnancy.<sup>10</sup> No information on safety measures was given in these studies. There were no clusters of specific malformations.

We have carried out a study of leukaemia and non-Hodgkin's lymphoma among physicians who have worked with ADs.<sup>11</sup> The RR for leukaemia was 2.85 (95% CI 0.51-16.02). No other studies of cancer risk related to occupational exposure to ADs exist.

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The exposure of health personnel to ADs has been assessed in several studies including air pollution measurements and measurements of biological effects such as urine mutagenicity or cytogenetic effects in lymphocytes. Falck *et al* found significantly higher mutagenicity in urine from oncology nurses than from controls when no safety measures were taken.<sup>12</sup> After implementation of such measures mutagenicity decreased.<sup>13</sup> Subsequently, several groups have studied urinary mutagenicity in nurses and pharmacists handling ADs. Positive results have been found,<sup>14-18</sup> but the use of laminar air flow hoods and other safety precautions have been associated with negative findings.<sup>14-16, 18</sup> except in one study.<sup>19</sup> Four studies of oncology nurses have found increased sister chromatid exchange and chromosomal aberrations in lymphocytes from exposed nurses compared with those from control groups,<sup>19-22</sup> but negative studies have also appeared.<sup>23, 24</sup>

Awareness regarding safe handling of ADs surfaced around 1980. Subsequently, guidelines for health workers handling these drugs were issued by authorities in several countries including Denmark, but great concern exists about the possible adverse health effects of occupational exposure. The purpose of this study was to monitor the risk for cancer and adverse reproductive outcomes among health workers handling ADs in Denmark.

### Material and methods

The study group included female nurses who potentially had been exposed to ADs through their work in one of the five 'old' oncology departments in Denmark. Four of these have operated throughout the whole period in which nurses have taken part in the preparation or administration of ADs—that is, since the early 1970s. The last one started in 1976. An internal control group of about double the number of potentially exposed nurses was established by identifying nurses employed in the same period in other departments in the same hospitals, assumed to be comparable with the oncology departments with regard to lifting, shiftwork, and general work strain.

All nurses were identified by means of records kept by the administration at the hospitals. The identity was verified in the central population register. Thirty seven persons could not be identified and were excluded from the study. Included in the cohort thereafter were 1282 nurses from oncology departments and 2572 from control departments. The criterion of exposure was preparation or administration of ADs. The head nurses of the oncology departments provided data about preparation and administration of the drugs for individual cohort members. In two of the departments old lists existed of the weekly number and type of treatments given in the departments. Since all day-shift nurses had

participated equally in this work the individual exposure could be quantified as number of treatments prepared, or administered, or both a week. In two other departments, the head nurses (assisted by senior staff members) indicated the exposure semiquantitatively as high, medium, low, and no exposure. In the last (and smallest) of the oncology departments exposure could only be given as yes or no.

For the analyses, the quantitative assessments were aggregated with the semiquantitative by grouping four or more treatments a week as high exposure, two to three treatments a week as medium, one treatment a week as low, and none as no exposure. Observations with yes or no information only were not included in the semiquantitative analyses. Information about safety measures was collected by interview with head nurses and senior staff members.

### IDENTIFICATION OF OUTCOME

The outcomes of interest (miscarriages, congenital malformations, birth weight, gestational age and prematurity, and cancer) were identified through record linkages by means of the unique 10 digit identification number possessed by all Danes. All children born by the study nurses during 1973-88 were identified in the Danish birth register, which has been computerised since 1973. Multiple births were excluded. Remaining were 286 children born to mothers employed in oncology departments during pregnancy and 770 children born to mothers employed in reference departments during pregnancy (table 1). With only five stillbirths in the two groups together, this outcome was not analysed.

Data about miscarriages came mainly from the hospital discharge register, which has operated since 1977. Induced abortions were added from the register of induced abortions, and a few miscarriages were added from the register of congenital malformations, which has operated since 1983. Eighteen abortions were identified among nurses employed in oncology departments during pregnancy and 65 abortions among nurses employed in control departments during pregnancy in the period 1977-88 (table 1).

Malformations were identified by linkage with the hospital discharge register, the Danish birth register, and the register of congenital malformations. Sixteen children with malformations were identified among the offspring of nurses employed in oncology departments during pregnancy and 43 among the offspring of nurses employed in control departments during pregnancy in the period 1973-88.

Incident cancers in the group of oncology nurses were identified in the Danish cancer registry until 31 December 1987. The Danish cancer registry has operated since 1943. ORs of miscarriages were computed as the compared groups of miscarriages

Table 1 Reproductive outcomes in 275 nurses working in oncology departments and 765 nurses working in reference departments during pregnancy

	Mother employed in oncology department during pregnancy	Mother employed in reference department during pregnancy
Miscarriages (1977-88):		
All pregnancies	18	65
First pregnancies only	12	44
Malformations (1973-88):		
All pregnancies	16	43
First pregnancies only	10	35
Induced abortions (1977-88):		
All pregnancies	45	126
First pregnancies only	32	91
Ectopic pregnancies (1977-88):		
All pregnancies	5	14
First pregnancies only	5	12
Births (1977-88):		
All pregnancies	213	604
First pregnancies only	161	461
Births (1973-88):		
All pregnancies	286	770
First pregnancies only	226	618

divided by all other pregnancies (births, stillbirths, induced abortions, and ectopic pregnancies). Odds ratios of malformations were computed as the compared groups of malformations divided by all other births. Age standardised point estimates and 95% confidence intervals (95% CIs) were computed with the EGRET software package, as were the logistic regression analyses. Birth weight was analysed with multiple linear regression modelling using the SAS software package.

The outcome of two pregnancies in the same woman may not be independent and it is usually considered correct to include only one pregnancy per woman in any given analysis. Therefore, the analyses of miscarriages and malformations were done both on material restricted to the first employed pregnancy of any study nurse and on material including all employed pregnancies of the study nurses. Because the point estimates differed little, in some instances only the unrestricted results are presented to preserve power. The material available for analysis of birthweight, gestational age, and sex ratio was larger, and for these outcomes the restricted analyses are presented.

Standardised incidence ratios (SIRs) were calculated with PYRS software for cancer in the group of nurses who had worked in oncology departments and had handled ADs, with Danish national rates as the standard. The internal reference group was not used for comparison in the analysis of cancer because much precision would have been lost. To ensure comparability with the standard rates a person in the study group could be included with more than one cancer case, provided they were at different sites. A person was considered exposed from first date of exposure until death, emigration, or end of follow up on 31 December 1987, whichever came first. In all the

analyses observations with missing values for one or more of the relevant variables were excluded.

The study was approved by the Danish Data Protection Agency and the ethical committees. The oncology nurses were informed through their journal.

## Results

### MISCARRIAGES

The crude OR for miscarriages among those handling ADs during pregnancy compared with the control group employed in other departments was 0.76 (95% CI 0.38-1.43). Inclusion of all nurses employed in oncology departments, whether exposed or not, changed the OR to 0.78 (95% CI 0.43-1.37). Standardisation according to the age of the mother changed the risk estimate from 0.76 to 0.74 only (table 2).

The analysis by exposure level showed a significantly increased risk among those in the low exposure category, and, if anything, an inverse dose-response relation (table 3). The ORs for the periods before and after implementation of safety measures (before 1980 *v* 1980 or later) differed little (table 2), but the precision of the point estimates was low, especially for the period before 1980.

### MALFORMATIONS

The crude OR for malformations among those handling ADs during pregnancy compared with the control group employed in other departments was 1.02 (95% CI 0.47-2.06). Inclusion of all nurses employed in oncology departments, whether exposed or not, changed the OR to 1.00 (95% CI 0.52-1.85). Standardisation according to the age of the mother changed the risk estimate from 1.02 to

Table 2 Odds ratios for miscarriages, malformations, and low birth weight among nurses handling ADs during pregnancy compared with nurses working in reference departments during pregnancy

	1973/7-88		1973/7-9		1980-8	
	OR	(95% CI)	OR	(95% CI)	OR	(95% CI)
Miscarriages (1977-88):						
All pregnancies	0.74	(0.40-1.38)	1.10	(0.19-4.56)	0.70	(0.31-1.44)
First pregnancies only	0.80	(0.38-1.69)	—	—	—	—
Malformations (1973-88):						
All pregnancies	0.99	(0.50-1.96)	0.20	(0.00-1.32)	1.57	(0.64-3.58)
First pregnancies only	0.70	(0.29-1.70)				
Low birth weight ( $\leq 2500$ g) (1973-88):						
First children only	1.06	(0.42-2.67)	0.94	(0.20-4.45)	1.13	(0.36-3.54)

ORs adjusted for age.

0.99 only (table 2). There were no clusters of specific malformations.

The risk estimate for the high exposure category was highest (OR 1.36), followed by the category of pregnancies in which the nurse had been employed in an oncology department but had not handled ADs (table 4). The number of miscarriages in each exposure category was small. The OR for the periods before the implementation of safety measures was lower than after, but again the precision of the risk estimate was low (table 2).

#### BIRTH WEIGHT AND GESTATIONAL AGE

The mean birth weight among children liveborn to mothers handling ADs during pregnancy was 3397 g compared with 3455 g in the control group.

An exposure may affect the birth weight by shortening the duration of gestation or by decreasing the intrauterine growth rate. In the present material, the mean gestational age for liveborn children of mothers in the exposed group was 39.64 weeks compared with 39.69 weeks in the control group. Thus the duration of gestation was practically identical between the groups.

To adjust for possible confounding, the growth rate was analysed in a multiple linear regression model that, as well as the exposure, included the available data on known risk factors—namely, gestational age, pregnancy order, and the sex of the child. These three factors showed the expected associations. Handling ADs during pregnancy was

associated with a 56 g lowering of the birth weight, but the association was not significant at the 5% level (table 5).

In an alternative analysis of birth weight, low birth weight was defined as 2500 g or less and normal birth weight as more than 2500 g. The OR for low birth weight according to this definition among those exposed to ADs was 1.06 (95% CI 0.42-2.67) (table 2). The risk estimates for the periods before and after implementation of safety measures (earlier than 1980 *v* 1980 or later) differed little.

#### SEX RATIO

A small preponderance of boys was found in the exposed group with an OR for being a boy of 1.12 (95% CI 0.79-1.61). No trend was seen with increasing exposure (data not shown).

#### CANCER

A total of 794 nurses handling ADs contributed 5636 person-years at risk. The number of observed cancer cases (14) was close to the expected (11.69) corresponding to an RR of 1.20 (table 6). The only significantly increased site was lymphatic and haematopoietic tissue where the increased risk was due to two cases of leukaemia, giving an RR for leukaemia of 10.65 (95% CI 1.29-38.5).

One of the patients with leukaemia had prepared five treatments of ADs a week during the period 1974-7. In 1977 she developed Hodgkin's disease (stage 2b) and had radiation therapy exclusively. A

Table 3 Miscarriages among nurses employed in oncology departments during pregnancy compared with nurses working in reference departments during pregnancy 1977-88

Exposure group	No of miscarriages	No of other pregnancies	OR*	(95% CI)
Reference group	65	744	1.00	reference
Not handling ADs in oncology department	3	49	0.67	(0.20-2.26)
Low exposure group	4	12	3.74	(1.17-12.0)
Intermediate exposure group	3	49	0.71	(0.22-2.36)
High exposure group	5	110	0.49	(0.19-1.26)

\*Estimated by unconditional logistic regression model including age.

Table 4 Congenital malformations in the offspring of nurses employed in oncology departments compared with nurses working in reference departments during pregnancy 1973–88

Exposure group	No of malformations	No of births	OR*	(95% CI)
Reference group	43	770	1.00	reference
Not handling ADs in oncology department	4	60	1.21	(0.42–3.49)
Low exposure group	0	28	—	—
Intermediate exposure group	2	52	0.66	(0.15–2.81)
High exposure group	7	91	1.36	(0.59–3.14)

\*Estimated by unconditional logistic regression model including age.

few months later she developed acute myeloblastic leukaemia. The other case of leukaemia (chronic myeloid) was diagnosed in 1987 in a nurse who had prepared five treatments a week for four months in 1982.

### Discussion

The overall risk estimates were not increased for miscarriages, malformations, low birth weight, or preterm birth among the offspring of nurses handling ADs during pregnancy. The sex ratio was normal. The RR for leukaemia was significantly increased, but this was based on only two cases, one of acute myeloblastic and one of chronic myeloid leukaemia.

No information was available about possible confounding factors such as tobacco smoking and alcohol consumption for adverse reproductive outcome. Instead of collecting this information, we chose to identify a control group as similar to the study group as possible except for the exposure to ADs. One advantage of this method is that it is likely to avoid confounding, not only from known risk factors but also from any unknown risk factors. The control group of nurses employed in the same hospitals is identical to the study group with regard to social group and employment, and is probably comparable for work load and smoking and drinking habits. The

lack of any age confounding indicates that a certain degree of homogeneity between the groups was actually achieved. By identifying outcomes and exposures through registers and hospital departments respectively, we avoided a possible recall bias, which could be a serious problem in a study in which the study subjects are conscious of the possible association between the exposure and the outcome. By identifying the control group among nurses working in the same hospitals at the same time as the oncology nurses, we aimed to avoid a selection bias that might result from different hospital admission rates between the two groups. The abortion rate in the control group was 65 of 809 (8.0%); (table 1), which compares well with the rate of 8.47% for the Danish population found by Modvig.<sup>25</sup>

The study included the time before as well as after the implementation of safety measures in the Danish oncology departments. Miscarriages could be followed up, however, from 1977 only, when the hospital discharge register started, and although in principle the registration of malformations goes back until 1973 with the medical birth register, many malformations are only identified in the hospital discharge register (which has operated since 1977 only), and the registration of malformations in the period 1973–6 is therefore less complete than afterwards. Finally, fewer nurses took part in the preparation and administration of ADs in the 1970s. For these reasons, the number of miscarriages and malformations available for analysis before 1980 was limited, and the lack of consistent differences between the risk estimates for miscarriages and malformations before and after 1980 should not lead to the conclusion that no increased risks existed in the unprotected setting before 1980.

The overall risk estimates for miscarriages and malformations, which are then mainly estimating the risk in the well protected setting after 1980, had acceptable precision, and some confidence in the lack of excess risks for adverse reproductive outcome in this period can also be gained from the consistency between the findings for all outcomes, and from the lack of dose-response relations.

Two studies have found increased risks for miscarriages among nurses handling ADs. A French

Table 5 Gestational age and birth weight in the offspring of nurses handling ADs in oncology departments compared with reference departments during pregnancy 1973–88\*

	Employed in reference department	Handling ADs in oncology department
Mean birth weight (g)	3455	3397
Mean gestational age (weeks)	39.69	39.64
<i>Regression analysis of birthweight</i>		
Gestational age in weeks (g per week)	191	p < 10 <sup>-4</sup>
Male sex	122 g	p < 10 <sup>-4</sup>
Pregnancy order > 1	151 g	p < 10 <sup>-4</sup>
Handling ADs	-56 g	p = 0.11

\*One pregnancy per woman.

Table 6 Incidence of cancer among nurses handling antineoplastic drugs in oncology departments

Site	Obs	Exp	RR	(95% CI)
All malignant neoplasms (ICD-7 140-205)	14	11.69	1.20	(0.65-2.01)
Lymphatic and haematopoietic tissues (ICD-7 200-205)*	3	0.56	5.37	(1.11-15.7)
NHL (ICD-7 200, 202)	0	0.20	—	—
Hodgkin's disease (ICD-7 201)*	1	0.12	8.35	(0.21-46.5)
Multiple myeloma (ICD-7 203)	0	0.05	—	—
Leukemia (ICD-7 204)*	2	0.19	10.65	(1.29-38.5)
Mycosis fungoides (ICD-7 205)	0	0.01	—	—

\*One person was counted as two cancer cases, (Hodgkin's disease and acute myeloblastic leukaemia). The diagnosis of Hodgkin's disease was made a few months before the onset of leukaemia, and was treated with radiation only. This person (diagnosed 1978) had prepared around five treatments a week during 1974-7. The other person with leukaemia (chronic myeloid, diagnosed 1987) had prepared around five treatments a week for four months in 1982.

ICD-7 = International Classification of Diseases, 7th revision.

study included nurses who on average had prepared 18.3 perfusions per week without safety measures.<sup>8</sup> Thus the exposure was substantially higher than in the present study. In a Finnish study, only a few treatments a week had been prepared. This is more like the Danish situation, but no safety measures were taken.<sup>7</sup> In the studies that have reported increased risks for malformations<sup>9,10</sup> the exposure data are not sufficiently detailed to allow a comparison with the present study. Thus from the available exposure data there would not seem to be any inconsistency between the findings in these studies and the present one.

The precision of the risk estimate for leukaemia was low, although formally the risk was significantly increased. The two leukaemia cases both have some special traits, but when we compute the expected number of cases in the study group, this figure also includes the special cases such as secondary leukaemia after treatment. Finally, it should be taken into consideration that an increased RR for leukaemia was indicated, although also based on small numbers, in our study of physicians handling ADs.<sup>11</sup>

Studies of patients treated with ADs have left no doubt that ADs may cause cancer and animal studies have consistently shown an adverse reproductive outcome. The exposure to ADs has been assessed in many studies, and although it has been shown that the exposure of the health personnel is smaller than the doses received by patients treated with ADs,<sup>15,18,20</sup> the study of the risk of cancer and adverse reproductive outcome among the health personnel is important for two reasons. Firstly, from the worker's protection point of view it is important to monitor the possible risk. Secondly, assessment of the effects in humans of low dose exposures to agents known to be genotoxic at high doses is important.

Regarding reproductive outcome the present study gives some confidence that the safety measures implemented in the Danish oncology departments around 1980 can protect health personnel against

adverse effects of ADs on reproduction. As the study is as yet the only negative one in a well protected setting, it should be followed up by other studies of well protected health personnel handling ADs. The findings concerning the risk of leukaemia, although based on small numbers, encourage larger studies.

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