## Miller, Diane M. (CDC/NIOSH/EID)

**From:** Karius, Diana [KARIUSD@ccf.org]
**Sent:** Monday, October 12, 2009 10:28 AM
**To:** NIOSH Docket Office (CDC)
**Subject:** Chemotherapy exposure
**Attachments:** CaseStudySurfaceContaminationOfCyclophosphamide.Acampora.05.pdf; Cardonick_Elyce1 use of chemo_nurses.pdf

Regarding NIOSH docket number 150. I have issues with the NIOSH and ONS recommendations for workers. Many articles state that nurses should be given a choice of alternative work while 1) attempting to conceive 2) pregnant 3) breast feeding. This puts the employer at great hardship. The fact that pregnancy falls under the disabilities act may mean that the employer would need to hold a position open for 2 years or more. Most nurses currently working are of child bearing age. We have had up to 5 nurses in one area trying to conceive or are pregnant. Considering that all recommendations are based on old exposure data from the 80's and 90's this is not very responsible. Some studies are from Europe but have not yet been reproduced for validity. I have reviewed the ONS references the 2007 Frandsen study quotes old data compared to an updated version of wearing gloves. The abstract they have also cited which seems to have found significant impact on fetal outcomes has never become a published article that we can locate to analyze. It seems that there is a continuous regurgitation of what everyone says without any new significant facts. We know what happens if you don't wear PPE. We don't know what happens if you do follow all the recommendations. Most new data cite an overwhelming increase in **environmental** exposure. So does this mean that pregnant workers cannot even be in the area? What about males? Men can father a child at any age so does this mean that a man should never be administering chemotherapy? The long range impact on recommendations should be thought through more carefully. We have no exposure data utilizing current PPE and closed administration systems for nurses administering. Most data comes from the pharmacy tech prospective. If we are to be following evidence based practice then that is what we need to make any real determinations. My colleague and I have just submitted a study proposal to ONS to do just that. The fact that at times we need to treat pregnant women with chemotherapy is intriguing. It seems that actual damage or fetal loss if associated more with some specific agents, but not all agents have proven to be harmful.
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# A Case Study: Surface Contamination of Cyclophosphamide due to Working Practices and Cleaning Procedures in Two Italian Hospitals

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**The efficacy of preventive and organisational measures implemented in Italy to prevent the contamination of cytotoxic drug preparation rooms has been investigated, and oncologic wards of two Italian hospitals were examined. The sampling strategy was based not only on potential sources of contamination but also on responses to detailed questionnaires on workplace practices and work organisation. Wipe samples were taken from different surfaces of preparation rooms, before and after the work shift, over a span of a month. Cyclophosphamide was taken as the marker drug that reflects exposure to cytotoxic drugs, being measurable by GC/MS. In one of the two hospitals (Hospital A), a large amount of cyclophosphamide was found, both before and after shift, on the workbench (median value, 2.55 μg $dm^{-2}$, before shift), on the floor between the operator working position and the waste bin (>10 μg $dm^{-2}$, after shift), as also on door handles and storage shelves. No quantifiable levels of cytotoxic drug were detected in the second hospital investigated (Hospital B). These results could be attributed to the efficacy of cleaning procedures and working practices. In fact, both hospitals were provided with vertical-laminar airflow hoods and the (male) nurses had attended special training courses; but in Hospital A, cleaning procedures were carried out without substances used specifically for the cleaning of surfaces contaminated by cytotoxic drugs such as sodium hypochlorite. Working practices did not include Luer Lock devices. Cyclophosphamide concentrations found in both hospitals, compared with the quantities of drug handled, gave evidence of the importance of the correct handling of cytotoxic agents as a major tool in reducing contamination levels. The results reveal the insufficiency of the risk management measures which do not take into account working practices that are prevailing, and stress the necessity for periodic environmental monitoring, indispensable for evolving effective procedures to prevent antineoplastic drug exposure.**

*Keywords:* cyclophosphamide; environmental monitoring; wipe test; working conditions

## INTRODUCTION

Despite their therapeutic effect, many of the antineoplastic drugs have mutagenic, teratogenic, or carcinogenic properties (Black and Livingston, 1990a,b; Otto and Rubben, 2004), where a no-effect threshold dose cannot be identified (Stahlmann *et al.*, 1985; Rogers, 1987; Baxter, 1991). As a consequence, there has been concern over potential exposure to and its after effects on healthcare workers who handle cytotoxic or antineoplastic drugs; and in the past 10 years numerous guidelines have been issued for the management of antineoplastic drugs (Canadian Society of Hospital Pharmacists, 1984; American Society of Hospital Pharmacists, 1990; Allwood *et al.*

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1997; Goodman, 1998). There is a large number of published studies that have been carried out both in Europe and in the USA, examining exposure of hospital staff to cytotoxic drug. These studies include measurements of environmental and surface contamination and the amount of drugs detectable in the urine of staff involved both in the preparation of cytotoxic drugs and in their administration to patients (Hirst *et al.*, 1984; Sessink *et al.*, 1992, 1995, 1997; Ziegler *et al.*, 2002).

In Italy, labour legislation relating to the healthcare of workers exposed to chemical agents includes both Legislative Decrees and Guidelines issued by National Agencies for workers protection (I.S.P.E.S.L., Istituto Superiore per la Prevenzione e la Sicurezza sul Lavoro, Institute for Labour Safety and Prevention). Legislative Decrees, such as 626/1994, 66/2000 and 25/2002 (D. Lgs. 626/1994; D.Lgs 66/2000; D.Lgs. 25/2002), incorporating European Directives (89/391/CE, 89/654/CE, 89/655/CE, 89/656/CE, 90/269/CE, 90/270/CE, 90/394/CE, 90/679/CE, 93/88/CE, 95/63/CE, 97/42/CE, 98/24/CE, 99/38/CE); and, in the particular case of antineoplastic agents, specific Guidelines have been issued in 1999 and 2000 (G.U. 236/1999; I.S.P.E.S.L., 1999). Nevertheless, only a few studies (Minoia *et al.*, 1999a,b; Perico *et al.*, 2003) are reported in the literature on the monitoring of Italian hospitals; and although strict health and safety rules have been established and implemented, the potential health hazard for persons handling these drugs is still a matter of concern for hospital staff members.

The aim of the present study was to verify if, and how, Italian Guidelines were actually implemented, i.e. if they were efficacious in lowering contamination levels, and if the exposure risk on wards where antineoplastic drugs were handled was appropriately controlled. To achieve this, the hospitals for study had to be chosen randomly, suitable questionnaires framed and responses obtained, and contamination levels measured. In particular, two Italian hospitals were examined by analysing data obtained from detailed questionnaires about preventive measures, working practices and cleaning procedures; and an environmental monitoring of surfaces of drug preparation rooms that was carried out. Since cyclophosphamide has been identified to be the most suitable of indicators of potential exposure to antineoplastic drugs mixtures (G.U. 236/1999, Italy), the environmental monitoring was carried out by measuring cyclophosphamide levels in wipe samples.

## MATERIALS AND METHODS

### *Study design*

Sampling procedures were instituted in two Italian hospitals, referred to as Hospitals A and B. The two

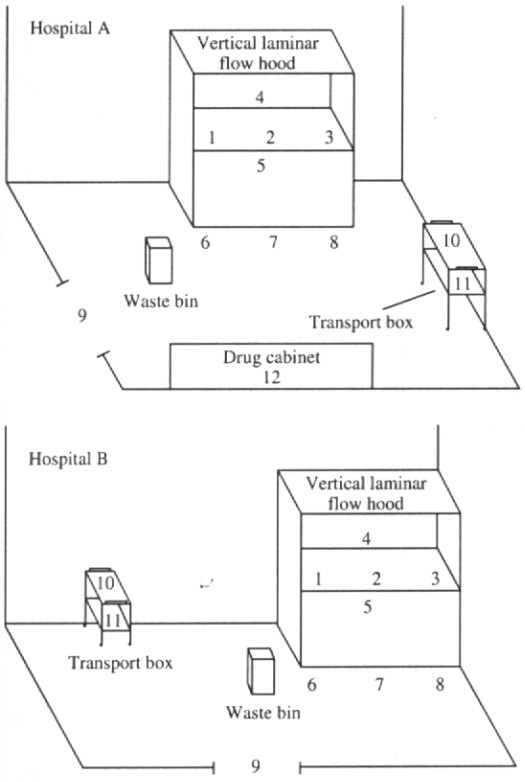


**Fig. 1.** Antineoplastic drug preparation rooms. Sampling spots location. 1–3, workbench; 4, external vertical plane of the hood; 5, internal vertical plane of the hood; 6–8, floor; 9, door handle; 10 and 11, upper and lower planes of transport boxes; 12, drug storage cabinet handle.

hospitals were asked to provide detailed plans of the arrangement of rooms and from which twelve sampling surfaces were selected, based on potential sources of contamination. Figure 1 shows a schematic representation of drug preparation rooms. Sampling spots from 1 to 8 were intended to investigate contamination arising from possible spillage of cyclophosphamide during vial handling: sampling spots 1–5 were located on the workbench and on the internal and external fore planes of the laminar flow hood used during the drug preparations; sampling spots 6–8 were on the floor near the operator work location. The contamination of objects such as door handles, transport box surfaces and drug-safety cabinets (sampling spots 9–12) would indicate that either the gloves, used as a protective measure, are not immediately removed after drug preparation, or that the outer surfaces of vials are contaminated, as recently reported in literature (Mason *et al.*, 2003).

Environmental monitoring was carried out by collecting wipe samples over the span of a month, at three different times: before and after work shifts on the same day in positions of close proximity, and 15 times after one single drug preparation that included cyclophosphamide, without cleaning the workbench. Samples collected before a shift were intended to verify the efficacy of cleaning procedures

followed by the hospital cleaning staff. Since the tasks of (male) nurses included both drug preparation and cleaning of workbenches after each single preparation, the working method as a whole was investigated by collecting after-work samples, although the samples collected after one single preparation (without workbench cleaning) are related exclusively to the drug handling procedure.

The working organisation was investigated using a questionnaire on the following aspects: (i) exposure: the number of nurses involved in drug preparation and administration; weekly and/or daily shifts; the average amount of drugs handled weekly and/or daily; (ii) drug storage, preparation, waste disposal; work practices, such as utilisation of the laboratory for any work other than the preparation of cytostatic drugs; use of the different rooms dedicated to their storage and preparation; restriction of access to personnel only; the amount of cyclophosphamide handled each day; to where the waste is removed from the workbench and mode of removal; (iii) cleaning: frequency of cleaning of laboratory work-surfaces and floors; methods of cleaning, and chemical agent used (sodium hypochlorite, alcohol, generic detergent). Additional information about protective measures and safety occupational training courses was also collected.

*Wipe samples*

Wipe-tests were carried out by using a 9 × 20 cm gauze (TNT, Farmac-Zabban, Italy) dampened in 2 ml of a 0.03 M sodium hydroxide solution, wiped on surfaces and placed in a 50 ml polypropylene tube. In the case of plane areas, sampling surfaces were defined by placing on them a plastic object with an open surface of 15 × 15 cm (2.25 $dm^2$); when handles were sampled, the surface area was measured by approximating the handle to a rectangle.

To avoid sample decay (Schmaus *et al.*, 2002), each sample was stored at 4°C up to the end of the whole sampling period (8 h) whereafter it was frozen at −20°C. Frozen samples were transported to the laboratory and analyzed within 10 days.

After defrosting, 18 ml of the sodium hydroxide solution was added to each test-tube and the sample divided into two aliquots. To one aliquot was added 100 µl of a freshly prepared aqueous solution of 50 ng $\mu l^{-1}$ iphosphamide (from Baxter, Germany; purity, 95%), and used as internal standard. Samples were shaken for 10 min, mixed in a vortex mixer, and centrifuged (15 min, 3000 r.p.m.). The second aliquot was used for the detection of iphosphamide: aliquots of five samples were combined and purified by the following procedure without addition of the internal standard: samples containing iphosphamide were discarded as far as the quantitative determination was concerned; the analytes were purified from matrix by liquid–liquid extraction with 30 ml of diethyl ether (twice) and the organic layers combined; residual water was removed with anhydrous sodium sulfate; samples were dried, dissolved in 100 µl of ethyl acetate and derivatized by adding 100 µl of heptafluorobutyric anhydride (Sannolo *et al.*, 1999); after 20 min at 70°C, the solvent was evaporated under a stream of nitrogen and the residue stored at 4°C. Samples were dissolved in 100 µl of isooctane and analysed by Gas Chromatography/Mass Spectrometry (TraceGC/PolarisQ, ThermoFinnigan, San Jose', CA, USA); chromatographic and instrument conditions are described elsewhere (Sannolo *et al.*, 1999). Data were elaborated by Xcalibur software, version 1.2 (ThermoFinnigan). Quantitative analyses were based on standard curves from 0.25 to 250 ng $\mu l^{-1}$ (corresponding to 0.01–10.0 µg $dm^{-2}$). Wipe samples with higher drug concentrations were diluted 1:10. When, despite the dilution, the amount of cyclophosphamide was >10.0 µg $dm^{-2}$, the result was reported as >10.

Standard curves were obtained by analyzing calibration standards samples, prepared as follows: known amounts of aqueous solutions of cyclophosphamide (from Baxter, Germany; purity, 95%) were added to clean surfaces of a chemical hood, previously cleaned with sodium hypochlorite 5%, in order to have five cyclophosphamide concentrations in the range 0.01–10.0 µg $dm^{-2}$, surfaces were then wiped and samples processed as described above. Quality control samples were also prepared with concentrations of 0.1, 1 and 5 µg $dm^{-2}$. Blank wipe samples (with neither cyclophosphamide nor iphosphamide added) and zero-point samples were prepared (by adding only iphosphamide) were used to evaluate the specificity of the method.

## RESULTS

*Working conditions*

Table 1 summarizes information about working conditions (cyclophosphamide amounts usually handled with respect to the total antineoplastic drugs used, the number of drug preparations carried out, cleaning procedures and working practices) collected by means of a questionnaire in Hospitals A and B.

The percentage ratios between the amount of cyclophosphamide and the total antineoplastic agents prepared in a day ranged from 76.2 to 89.2% and from 61.3 to 89.2%, respectively, for Hospitals A and B.

The absolute amount of cyclophosphamide handled in a day ranged from 10 800 to 21 600 mg (Hospital A) and from 33 750 to 71 550 mg (Hospital B).

The total number of daily preparations of antineoplastic drugs ranges from 9 to 15 and from 38 to 60 for Hospitals A and B, respectively. The number of daily cyclophosphamide preparations accounts for

Table 1. Summary of information about working conditions in Hospital A and Hospital B

| | Hospital A | | | Hospital B | | |
|---|---|---|---|---|---|---|
| *Amount of cyclophosphamide/total antineoplastic drugs (%) | | | | | | |
| Range | 76.2–89.2 | | | 61.3–89.2 | | |
| $X_m \pm SD$ | 82.3 ± 4.1 | | | 80.7 ± 6.4 | | |
| M | 81.1 | | | 82.2 | | |
| Total amount of cyclophosphamide handled in a day (mg) | | | | | | |
| Range | 10 800–21 600 | | | 33 750–71 550 | | |
| $X_m \pm SD$ | 15 600 ± 3320 | | | 51 525 ± 10 015 | | |
| M | 14 400 | | | 51 300 | | |
| *Number of drug preparations including cyclophosphamide/total drug preparations (%) | | | | | | |
| Range | 66.7–88.9 | | | 50.0–93.0 | | |
| $X_m \pm SD$ | 74.7 ± 8.0 | | | 76.0 ± 9.8 | | |
| M | 72.1 | | | 77.9 | | |
| Working practices | | | | | | |
| Drug supply | Lyophilized drugs | | | Lyophilized drugs | | |
| Working modality | Handled with syringes without Luer Lock device | | | Handled with syringes provided with Luer Lock device | | |
| Cleaning procedures | | | | | | |
| | Frequency | Detergent | Employed personnel | Frequency | Detergent | Employed personnel |
| Workbench | After each preparation | Benzalkonim chloride | Pharmacy technicians | After each preparation | Sodium Hypochlorite 5% | Pharmacy technicians |
| Floor and furniture | Daily | Generic detergent | Cleaning staff | Daily | Polyphenol 0.4 % | Cleaning staff |

$X_m$ = Mean value, SD = standard deviation, M = median.
*Data have been collected in a month.

66.7–88.9% and 50.0–93.0% of the total number of antineoplastic drugs preparations (Hospitals A and B, respectively).

The number of (male) nurses deployed on drug preparations was 13 for the Hospital A and 30 for the Hospital B, with a turn shift of 8 h $day^{-1}$.

In both the hospitals examined the nurses involved in drug preparations had attended a special training course and were provided with written guidelines on working practices to be adopted when handling antineoplastic drugs. They prepare drugs in a vertical laminar flow hood on 5 successive days. Work shifts are organised so that one subject is employed in drug preparation for a whole week in Hospital B, although in Hospital A one subject prepares antineoplastic drugs for 3 days a week for a maximum of 2 consecutive days. For each subject, the number of daily preparations of cyclophosphamide ranged from 1 to 5 in Hospital A, and from 5 to 12 in Hospital B.

Potential causes of contamination, such as unsuitable cleaning procedures and working practices were investigated. The cleaning of working surfaces (workbenches, storage shelves and transport boxes) is mainly assigned to the nursing staff itself, but only the workbench planes of the hood are cleaned after each preparation. The analytical procedure introduced by Guidelines, concerning the cleaning of surfaces potentially contaminated by antineoplastic drugs (G.U. 236/1999, Italy), involves the use of sodium hypochlorite as specific detergent. Hospital A does not use sodium hypochlorite for workbench cleaning; in both hospitals floors and furniture are cleaned by the cleaning staff, with detergents non-specific for antineoplastic drugs. While Hospital B adopts the Luer Lock device during drug preparation (as suggested by Guidelines), nurses of Hospital A prepare the drugs that are to be administered to patients using two needles: one to inject the physiological solution into the lyophilized drug vial, and the other to avoid the phenomenon of overpressure.

For personal protection, the (male) nurses wear latex gloves, hairnets and special clothing. As for general protective measures, Hospital A is not provided with a centralized air system; in both hospitals, the rooms are assigned to the exclusive use of drug preparation where the only indispensable article is the furniture.

*Wipe samples*

The detection limit for cyclophosphamide was measured by analysing wipe samples from clean surfaces (2.25 $dm^2$ each) previously spread with decreasing known amounts of cyclophosphamide. A ratio of signal to noise of 3:1 corresponded to 0.00135 μg per sample, hence the detection limit was fixed at 0.0006 μg $dm^{-2}$. The detection limit

for ifosphamide was 0.003 μg $dm^{-2}$. The quantification limit for cyclophosphamide was established as 10 times the detection limit (0.006 μg $dm^{-2}$). Experiments were repeated in triplicate.

Even though the literature reports many studies on the quantification of cyclophosphamide by wipe tests, there is no standardized and validated procedure. Hence the specificity of the method was evaluated by analysing blank and zero-point samples. In both cases, no peaks at the cyclophosphamide retention time were detectable. The calibration curves used for cyclophosphamide quantification reflected the latest FDA guidelines (US FDA: Bioanalytical Method Validation, 2001), which state that precision and accuracy should not deviate by >20%, with which the results obtained were in line. In fact, both within-batch and between-batch accuracy and precision were <14%, and from 5 to 15%, respectively. Moreover, the calibration curves had correlation coefficients ≥0.9949, showing good linearity in the dynamic range evaluated.

The quantification of cyclophosphamide in unknown samples implied a calibration curve for every 20 unknown samples; i.e. for every 20 unknown samples, five calibration standard samples were analysed and a calibration curve plotted. In addition, quality control samples were analysed for every 5 unknown samples. Wipe samples from 1 to 8 were collected from the two hospitals on analogous surfaces (Fig. 1). Each examined surface was monitored at three different work times. First: every day after the room was cleaned, before the work shift, over the period of a month (30 samples for each location). Second: on 15 chosen days, (male) nurses were asked not to clean working surfaces after a single preparation, and wipe samples were taken after the preparation. Third: after the shift; in this case, the (male) nurses were aware of the monitoring process but this knowledge was expected to have no effect on the study because they were asked to work as usual. Altogether, 400 wipe samples were taken. The number of samples tested positive for cyclophosphamide contamination (without ifosphamide) was 65%, 16% of samples were discarded because they contained both drugs, the others were all negative.

Surface monitoring was carried out on those days when iphosphamide was not administered, since it was used here as internal standard. Moreover, wipe samples were first analysed after mixing together 5 samples without the addition of the internal standard, in order to identify samples eventually containing iphosphamide. In some cases (5 samples) data relating to quantitative determination were discarded because of the presence of iphosphamide; the other samples were independently analysed and the cyclophosphamide amount was determined as previously described. The results obtained, for both hospitals, are as reported in Table 2. Cyclophosphamide was below the quantification limit in many samples from Hospital B, except for the amount found on the floor

Table 2. Cyclophosphamide amount in 260 wipe samples of drug preparation rooms

| Sample | Location | Before shift after room cleaning | | After a single preparation without cleaning Cyclophosphamide (μg/$dm^2$) | | After shift | |
|---|---|---|---|---|---|---|---|
| | | Median ± SD [CP] | Range | Median ± SD [CP] | Range | Median ± SD [CP] | Range |
| 1 | Hospital A | 0.21 ± 0.02 | 0.06–0.30 | 0.71 ± 0.09 | 0.60–2.23 | 0.28 ± 0.02 | 0.12–0.62 |
| | Hospital B | ND | | Trace* | | Trace* | |
| 2 | Hospital A | 2.55 ± 0.28 | 0.05–4.20 | 2.45 ± 0.01 | 1.22–6.50 | 0.10 ± 0.01 | 0.05–3.21 |
| | Hospital B | ND | | ND | | ND | |
| 3 | Hospital A | 0.18 ± 0.06 | 0.10–0.32 | 0.18 ± 0.02 | 0.12–0.50 | 0.05 ± 0.01 | 0.02–0.23 |
| | Hospital B | ND | | ND | | ND | |
| 4 | Hospital A | 0.11 ± 0.01 | 0.10–0.25 | >10 | From 0.82 to >10 | 0.33 ± 0.03 | 0.10–3.22 |
| | Hospital B | ND | | Trace* | | ND | |
| 5 | Hospital A | 4.35 ± 1.30 | 3.21–5.62 | >10 | From 3.80 to >10 | >10 | From 4.12 to >10 |
| | Hospital B | Trace* | | Trace* | | ND | |
| 6 | Hospital A | 0.38 ± 0.05 | 0.25–0.52 | >10 | From 0.86 to >10 | >10 | From 2.12 to >10 |
| | Hospital B | Trace* | | 1.23 ± 0.54 | 0.62–2.58 | 1.12 ± 0.15 | 1.10–2.22 |
| 7 | Hospital A | 0.28 ± 0.02 | 0.12–0.60 | 0.29 ± 0.01 | 0.08–1.26 | 1.34 ± 0.40 | 0.16–1.82 |
| | Hospital B | ND | | ND | | ND | |
| 8 | Hospital A | 0.08 ± 0.01 | 0.02–0.12 | >10 | From 1.22 to >10 | >10 | From 1.30 to >10 |
| | Hospital B | ND | | ND | | ND | |

[CP] = Cyclophosphamide concentration, SD = standard deviation, ND = not detectable.
*Detectable amount of cyclophosphamide greater than the detection limit (0.0006 μg $dm^{-2}$) and below the quantification limit (0.006 μg $dm^{-2}$).

Table 3. Cyclophosphamide amount on handles and surfaces

| Sample | Location | After shift without cleaning Median ± SD [CP] (μg $dm^{-2}$) |
|---|---|---|
| 9 | Hospital A | 1.33 ± 0.11 |
| | Hospital B | ND |
| 10 | Hospital A | >10 |
| | Hospital B | Trace* |
| 11 | Hospital A | 2.72 ± 0.54 |
| | Hospital B | ND |
| 12 | Hospital A | 0.45 ± 0.03 |

[CP] = Cyclophosphamide concentration, SD = standard deviation, ND = not detectable.
*Detectable amount of cyclophosphamide greater than the detection limit (0.0006 μg $dm^{-2}$) and below the quantification limit (0.006 μg $dm^{-2}$).

between the waste bin and the operator working position soon after drug preparation (Table 2, sample 6, columns 3 and 5). On the contrary, Hospital A presented high average levels of contamination—often beyond the upper limit of the quantification range (>10 μg $dm^{-2}$)—and the floor showed contamination even after the room was cleaned (Table 2, samples 6–8, first column).

Wipe samples from 9 to 12 (Table 3), corresponding to door handles, transport boxes and cabinet (the cabinet was absent in the preparation room of Hospital B), were taken after the work shift. They also showed, in this case, high contamination levels in Hospital A, ranging from 0.45 (drug cabinet) to >10 μg $dm^{-2}$ (upper plane of the transport box; Table 3, samples 12 and 10, respectively). In the case of Hospital B, detectable amounts of cyclophosphamide, greater than the detection limit and below the quantification limit, were found on the transport box (Table 3, sample 10).

## DISCUSSION

This study was intended to evaluate if organisational measures and working practices guidelines issued in Italy to prevent health hazard are adequate and/or actually implemented in order to reduce the exposure to antineoplastic agents. Two Italian hospitals were considered. From questionnaires submitted, we observed that both hospitals conformed to Italian guidelines; in fact they were provided with vertical laminar airflow hoods, personal equipment such as gloves tested for antiblastic drugs (or latex double gloves for use when preparing the drugs), hairnets and disposable coats. Nurses involved in drug preparation tasks attended special training courses and were provided with written procedures regarding drugs handling and workbench surface cleaning. The organisation of work imposes a restriction on the number of (male) nurses involved in the preparations, a weekly shift rotation and an anteroom for drug storage. These findings show that the Guidelines for the safe handling of cytotoxic drugs issued up to now are implemented both as regards protective equipment and organisational measures. Nevertheless, we found detectable levels of cyclophosphamide on many surfaces, in both hospitals. Vertical laminar flow hoods may decrease cyclophosphamide air concentrations, but the release of aerosols could not be wholly prevented, as was largely reported in the literature, and as indicated by the antineoplastic drugs detected on different surfaces. The contamination levels of floors and storage shelves show that there is a real possibility of these compounds being spread throughout the facilities even when vertical laminar flow hoods are present in the preparation room (Schmaus *et al.*, 2002). Working practices and cleaning procedures could be improved in order to reduce contamination levels, so we monitored surfaces in different locations to establish a possible correlation between cyclophosphamide contamination and working practices. Working methods were investigated by taking wipe samples soon after a shift without cleaning the surfaces. The operators are to handle the drug on the central part of the workbench and they should wrap the waste up, before depositing it from the workbench into the waste bin. However we found high contamination levels on both sides (above all on the right side) of the workbench plane, suggesting that potentially contaminated objects (flacons, gauze used for avoiding spillage, syringes etc.) are probably placed on the work surface. Also, the contamination level of the floor between the hood and the waste bin showed that wastes are discarded in the waste bin without exercising adequate care. Working practices were also investigated by sampling door handles and transport box surfaces and, in Hospital A, high contamination levels were found on such surfaces too. The presence of cyclophosphamide on handles, both of the room door and of the drug storage cabinet, should be attributed to wrong use of the gloves (not removed immediately) or to inadequate cleaning procedures. Contamination of the transport box surfaces could be on account of the wrong use of the gloves and/or to the absence of disposable papers.

Normally, it would be reasonable to assume a positive correlation between use and exposure. According to our investigation, the two hospitals examined deal with different quantities of cyclophosphamide in a month (Table 1). In Hospital B, where a higher amount of cyclophosphamide was handled daily, we found only traces of the drug. Furthermore, the comparison of the results of contamination reveals that Hospital B had lower contamination levels than Hospital A at most locations. This could be explained if it is assumed that the correct handling of cytotoxic agents rather than the quantity prepared is the more important in minimizing contamination.

Nevertheless, drug contamination was also found in particular locations, such as internal and external vertical panels of the hood, in the case of Hospital B, too. This supports the hypothesis that contamination is related not only to correct working practices but also to the adoption of Luer Lock device, that can avoid the spillage of the drug, and to the frequency of cleaning up with adequate detergents. The importance of the cleaning frequency in environmental contamination was shown by the fact that, in some cases, we found detectable amounts of iphosphamide even if this substance had not often been used during the sampling month, and had not been used at all on the days we took wipe samples. We investigated cleaning methods by sampling each surface before and after the shift performed under normal working conditions, i.e. without instructing the (male) nurses not to clean the workbench. Data relating to samples taken before the shift correspond to contamination levels that can be found after cleaning of the drug preparation room by the hospital cleaning staff; while the samples taken after the shift reflect the efficacy of cleaning procedures carried out by the (male) nurses. Figure 2 shows the trend of cyclophosphamide contamination levels in each location of Hospital A reflecting the different steps in working and cleaning up. The cleaning staff do not have to clean workbench surfaces; consequently there is no difference between contamination levels before and after cleaning (Fig. 2, samples 1–3, white and black bars, respectively). On the contrary, as expected, high levels of contamination were found after a single preparation when (male) nurses were instructed not to clean any surface (Fig. 2, samples 1–3, central bars). On the other hand, in the same three locations the amount of cyclophosphamide found in Hospital B was below the analytical detection limit. These results show that the use of the Luer Lock device actually prevent the contamination of working surfaces; moreover, when Luer Lock devices are not used and cyclophosphamide lies on workbench surface, the use of common detergents is not suitable, because they are not capable of molecular degradation. Samples 6–8 correspond to the floor below the hood. Soon after the shift, large amounts of drug are to be expected (Fig. 2, samples 6–8, grey and black bars) because cleaning of the floor is assigned to specific cleaning staff, who work early in the morning. The effect of this cleaning, which is before the beginning of the shift, is shown in Fig. 2, samples 6–8, white bars. Nevertheless, contamination levels should be reduced as much as possible, and this could be achieved if sodium hypochlorite solutions, instead of polyphenols or generic detergents, are used for floor cleaning, as they are for the workbenches. Locations numbered as 4 and 5 indicate the internal and the external panels of the hood, respectively. The cleaning of these surfaces is not assigned either to the (male) nurses or to the cleaning staff. The latter consider the external parts of the hood to be common furniture, which is why they are cleaned only periodically, and not adequately (Fig. 2, sample 5, white bar). On the other hand, the contamination levels of the internal panel hood before and after the shift are lower than those found after a single drug preparation (>10 μg $dm^{-2}$), when we specifically instructed the nurses not to clean. This suggests that the nurses do normally clean this surface after a preparation (Fig. 2, sample 4). The generally high levels of contamination found in Hospital A after a single drug preparation when (male) nurses were asked not to clean (Fig. 2, grey bars) clearly indicate inadequate case in drug handling by the (male) nurses themselves.

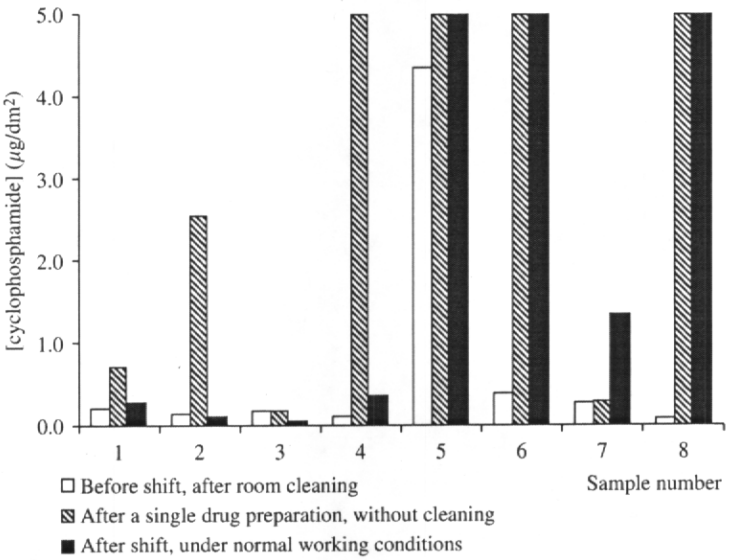


**Fig. 2.** Hospital A: cyclophosphamide surfaces contamination levels.

The results obtained from this study suggest that several improvements could be effected in working practices, leading to a considerable reduction of contamination levels. As suggested by guidelines on the handling of antineoplastic drugs, any surface in the drug preparation room should be covered with disposable papers, Luer Lock devices are highly recomended and workbenches and transport boxes should be cleaned with sodium hypochlorite on a daily basis. The inside of the hood, including not merely the work plane but also the vertical panels, should be cleaned most frequently.

Finally, environmental as well as biological monitoring analyses should be periodically carried out to verify the efficacy of the preventive and protective measures adopted and to provide a statistical base for assessment of risk and its management, aimed at preventing health hazards arising from exposure to cytotoxic drugs.

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# Use of chemotherapy during human pregnancy

Elyce Cardonick and Audrey Iacobucci

When cancer is diagnosed in a pregnant woman, life-saving chemotherapy for the mother poses life-threatening concerns for the developing fetus. Depending on the type of cancer and the stage at diagnosis, chemotherapy cannot necessarily be delayed until after delivery. Women diagnosed with acute lymphoblastic leukaemia who decline both termination and chemotherapy often die with the previable fetus in utero. Safe use of chemotherapy, especially during the second and third trimester, have been reported, and pregnant women with cancer can accept therapy without definite neonatal harm. Here, we review the use of chemotherapy in pregnancy by trimester of exposure and summarise neonatal outcomes, including malformations, perinatal complications, and oldest age of neonatal follow-up. We will also discuss the modes of action of the drugs used and look at the multiagent regimens recommended for use during pregnancy.

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Cancer develops in about one per 1000 pregnant women. The most frequent cancers are breast, cervical, lymphoma, and melanoma.[1] If chemotherapy cannot be delayed until after delivery, and if termination is not desired, chemotherapy can be considered.

The teratogenicity of any drug depends on the timing of exposure, the dose, and the characteristics affecting placental transfer. High lipid solubility, low molecular weight, and loose binding to plasma proteins favour transfer of drugs from mother to fetus.[2] Genetic predispositions to teratogenicity might explain why people given the same agents have differing susceptibility.

Use of chemotherapy during the first trimester (figure 1) increases the risk of spontaneous abortion, fetal death, and major malformations[2,3] and direct effects of the tumour sometimes confound the risks of fetal loss.[4] Malformations reflect the gestational age at exposure: the fetus is especially vulnerable when exposed during organogenesis—weeks 2–8 after conception,[5] and the heart, neural tube, and limbs are affected earlier than the palate and ear (figure 2).

After organogenesis, the eyes and genitalia, together with the haemopoietic system and CNS, remain vulnerable to continued exposure.[6] Exposure during the second and third trimesters increases the risk of intrauterine growth restriction (IUGR) and low birthweight.[3] Maternal nutritional deficiencies, caused by the tumour or by chemotherapy-induced anorexia, can also affect fetal growth and birthweight. However, studies[7] with long-term follow-up have not shown impairments in learning behaviour or haematological or immunological abnormalities. When delaying chemotherapy, the effect on maternal survival should be weighed against the risks to the fetus.

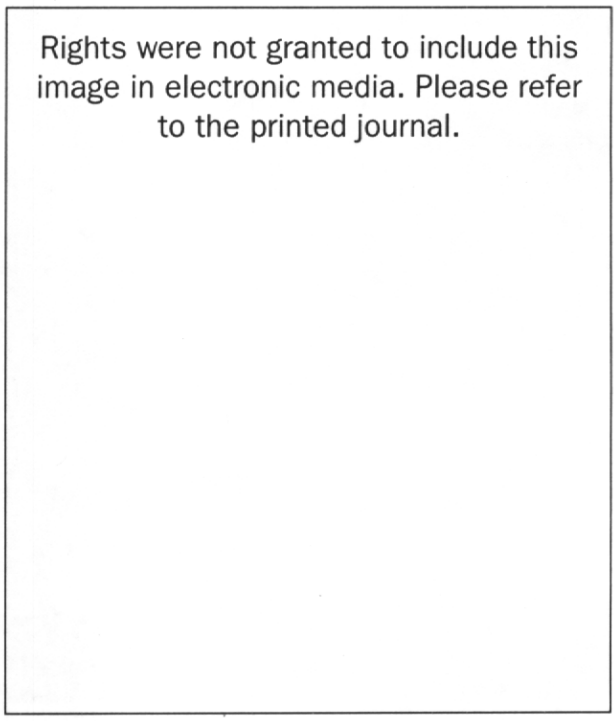




*Figure 1. Computer artwork of a human fetus developing in the uterus.*

## Chemotherapy exposure in utero

In this section, we do not discuss agents that are no longer used, such as aminopterin or melphalan, or procarbazine—a suspected teratogen. Cases that were terminated or spontaneously miscarried are included if the gross appearance or the pathological examination of the fetus was sufficiently detailed.

Almost all chemotherapeutic agents are teratogenic in animals, and for some drugs, data exists only for animals. Such data can only suggest that the drugs endanger human fetuses. The teratogenic properties of the drug depend on the type, amount, and threshold dose, and because these variables are species-specific, correlation with human development is difficult.[8] Animals with placentas that are very similar to the human placenta include mice, rats, and rabbits.[8] Therapeutic doses used in humans are often lower than the minimum teratogenic dose applied in animals and

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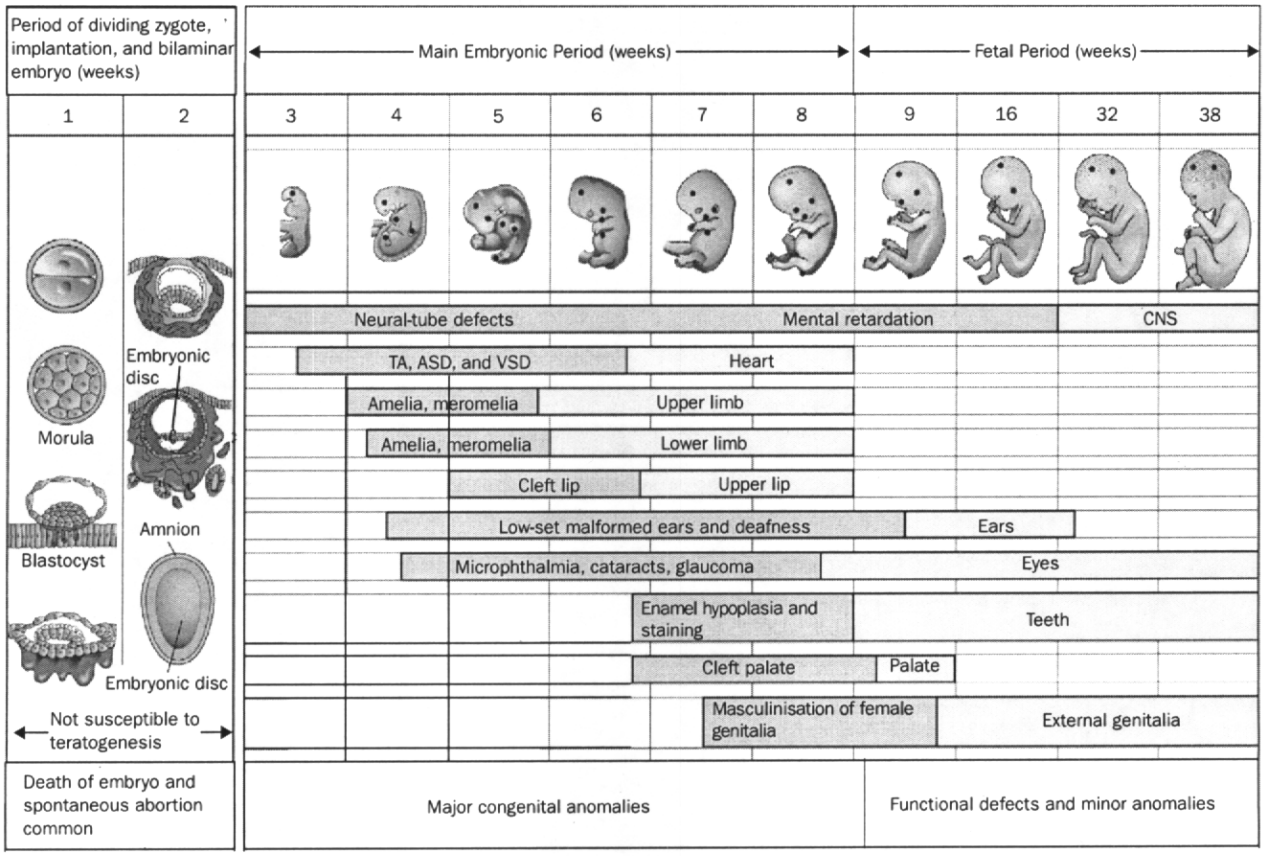


*Figure 2. Crucial periods in prenatal development. Dots on the developing fetus show common sites of action of teratogens. Horizontal bars indicate fetal development during a highly sensitive period (purple) and a less sensitive period (green). TA, truncus arteriosus; ASD, atrial septal defect; VSD, ventricular septal defect. Reproduced with permission from Moore P, ed. The developing human, 6th edition, 1998.*

animal data will apply clinically only if the teratogenic dose does not also cause maternal toxic effects.[9] Here, we discuss animal data only for agents that have no data in humans.

## Chemotherapeutic agents

Chemotherapeutic agents interrupt vital cell functions during different phases of the cell cycle. Agents are rarely used on their own; rather, drugs from different classes (see panel) are combined to increase the antineoplastic effectiveness.

### *Antimetabolities*

Antimetabolites are small, weakly acidic molecules used to treat leukaemia, lymphoma, and breast cancer. They inhibit cellular metabolism by acting as false substrates during DNA or RNA synthesis. The mechanism of these drugs is not specific to phases of the cell cycle.[10] In 42 cases of exposure to methotrexate, 23 of which were in the first trimester, no abnormalities were reported. Methotrexate can cause similar malformations to those in the aminopterin syndrome if the dose is greater than 10 mg per week in the first trimester.[11] Warkány and colleagues[12] described the aminopterin syndrome as cranial dysostosis with delayed ossification, hypertelorism, wide nasal bridge, micrognathia, and ear anomalies. Aviles and Niz[7] reported that after exposure during the first trimester, one fetus spontaneously miscarried without anomalies, and five neonates had a very low birthweight, one of whom died secondary to pancytopenia and sepsis at 3 weeks of age. This infant was also exposed to cyclosphosphamide, mercaptopurine, vincristine, cytarabine, and prednisone. At 25 weeks, the fetus died after first and second trimester exposure to cyclosphosphamide, methotrexate, and 5-fluorouracil.[13] One neonate who was given vincristine, mercaptopurine, cytarabine, and prednisone with methotrexate died at 90 days secondary to gastroenteritis.[14]

53 cases of exposure to 5-fluorouracil have been reported, including five in the first trimester. An inguinal hernia developed in one case, and one spontaneously miscarried. IUGR occurred in six (11%) of the 54 cases, when 5-fluorouracil was used with cyclophosphamide, methotrexate, doxorubicin, or mitoxantrone. One neonate had hair loss after second trimester exposure to 5-fluorouracil, doxorubicin, and cyclophosphamide. Another neonate died at 8 days after third trimester exposure to 5-fluorouracil, cyclophosphamide, and epirubicin.[15] The autopsy did not disclose the cause of death. Five other fetuses were exposed to the same regimen without complications. An intrauterine fetal death (IUFD) occurred at 25 weeks after first and second trimester exposure to 5-fluorouracil, cyclophosphamide, and methotrexate.[13] Three of the five cases exposed to this regimen had IUGR, all without anomalies.

Cytarabine has been used with several agents for treatment of acute leukaemia, but four cases had limb

malformations after first trimester exposure to cytarabine alone, in combination with tioguanine, or with doxorubicin, vincristine, and prednisone.[16–19] 89 other cases have been reported in which cytarabine was used during all trimesters, with transient cytopenia in five (5%), IUFD in six (6%),[3,20–24] IUGR in 12 cases (13%), and two neonatal deaths, secondary to sepsis and gastroenteritis.[7,14] The combination that is lethal to the fetus is unknown, since cytarabine and tioguanine were used in five of the six IUFDs, and cytarabine and daunorubicin were used in four cases. Accounting for underlying maternal leukaemia is difficult, since perinatal death is increased.[5]

49 women were exposed to mercaptopurine during pregnancy without anomalies, including 29 who were exposed during the first trimester. One fetus died at 27 weeks in a pregnancy also complicated by pre-eclampsia,[25] and a second died after second trimester exposure to mercaptopurine and daunorubicin.[23] Both of the neonatal deaths mentioned above[7,14] involved mercaptopurine in combination with several other agents. IUGR occurred in two first-trimester exposures (7%), and in two of 20 exposures after 12 weeks (10%). Of 37 exposures to tioguanine, IUGR and IUFD each occurred in four fetuses. In all IUFDs, tioguanine and cytarabine were used, with or without doxorubicin or daunorubicin.[3,20,21,23] In two of the four IUFDs, the mother had severe pre-eclampsia and severe anaemia.

### *Alkylating agents*

Cyclophosphamide is an integral part of regimens used for treatment of breast cancer, ovarian cancer and non-Hodgkin lymphoma. Malformations, including absent toes, eye abnormalities, low-set ears, and cleft palate have been reported with use of cyclophosphamide during the first trimester.[2,26,27] Reynoso and colleagues[28] reported a case of twins exposed to cyclophosphamide throughout pregnancy. The boy, born with anomalies including oesophageal atresia, right-arm deformity, and abnormal inferior vena cava, was also IUGR, and developed thyroid cancer at 11 years of age and a neuroblastoma at age 14 years. Despite the same exposure, the twin girl had no abnormalities. 16 patients were exposed to cyclophosphamide during the first trimester without malformations.

Safe use of alkylating agents during the second and third trimesters has been reported. Of 92 cases in which cyclophosphamide was used, two fetuses died, one of whom also received epirubicin, and the other who received 5-fluorouracil and methotrexate.[12,14] IUGR occurred in seven cases (7%). One neonate died secondary to pancytopenia and sepsis at 3 weeks of age after exposure to cyclophosphamide, vincristine, mercaptopurine, cytarabine, methotrexate, and prednisone.[7]

Dacarbazine is the least investigated alkylating agent, but is important for treatment of Hodgkin's disease.[28] Aviles and colleagues[7,29] reported ten cases of use of the ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) in pregnancy. Excluding one case of IUGR, there were no malformations or complications. At our institution we prospectively followed up nine patients given ABVD after 14 weeks. One minor malformation developed, which was unlikely to be secondary to chemotherapy because it was not given during organogenesis. The newborn child underwent surgical correction of syndactyly involving two fingers. All children are developing normally and meeting developmental milestones; the oldest is 5 years of age. One case of melanoma was treated with dacarbazine, carmustine, and cisplatin in the second trimester, and a healthy infant was delivered at term.[30]

Of 15 cases of busulfan use, eight were exposed during the first trimester without anomalies. Two cases had malformations, both with second trimester use: one had pyloric stenosis, and the other had unilateral renal agenesis and liver calcifications after busulfan and allopurinol.[31,32]

**Examples of chemotherapeutic agents by drug class**

**Antimetabolites**
Methotrexate, 5-fluorouracil, aminopterin, cytarabine, tioguanine, mercaptopurine

**Alkylating agents**
Cyclophosphamide, busulfan, ifosfamide, chlorambucil, carmustine, dacarbazine

**Anthracycline antibiotics**
Doxorubicin, daunorubicin, adriamycin, idarubicin, epirubicin, dactinomycin, bleomycin, mitoxantrone

**Plant alkaloids**
Vincristine, vinblastine, vinorelbine

**Taxanes**
Paclitaxel, docetaxel

**Other**
Cisplatin, carboplatin, prednisone, triamcinolone, tamoxifen, rituximab, asparaginase, etoposide, teniposide, allopurinol, mitoguazone, tretinoin

## Anthracycline antibiotics

These high-molecular-weight agents act by interposing between DNA.[10] Turchi and Villasis[33] summarised 28 pregnancies exposed to doxorubicin and daunorubicin for treatment of acute myeloid leukaemia, acute lymphoblastic leukaemia, non-Hodgkin lymphoma, sarcoma, and breast cancer. All patients were treated after the first trimester. One pregnancy was terminated and two patients miscarried; all fetuses were physically normal. One neonate had transient marrow hypoplasia. Each of a set of twins had diarrhoea and sepsis at birth but were normal at 54 months with normal T-cell function. Two patients died of their disease with the fetus in utero. 21 pregnancies were delivered without any complications.

124 cases, including 25 in the first trimester, were exposed to doxorubicin. Three malformations occurred with first trimester exposure, and two were on concomitant radiation or cytarabine, which might confound the limb abnormalities seen.[18,27,34] Our experience adds 38 cases of doxorubicin use after the first trimester. Of 162 exposures, complications included pre-eclampsia, midtrimester miscarriage, transient neonatal neutropenia and sepsis, IUGR; and IUFD.[3,35]

Daunorubicin was used in 43 cases. One malformation—adherence of the iris to the cornea diagnosed at age 2 years—developed after exposure to tioguanine, cytarabine,

and daunorubicin in the third trimester.[28] Five fetuses had IUGR and four had transient myelosuppression. Three IUFDs occurred, two of which were complicated by severe pre-eclampsia at 29 weeks or severe maternal anaemia and acute lymphoblastic leukaemia.[21,24] The third IUFD occurred after daunorubicin use with idarubicin, cytarabine, and mitoxantrone.[20]

Whether in utero exposure to anthracyclines is cardiotoxic to the developing fetus is unknown. Children and adults receiving these agents are at risk of developing dose-related cardiotoxicity.[36] Free-radical damage leads to myocardial apoptosis then hypertrophy.[37] Meyer-Wittkopf and colleagues[38] did fetal echocardiograms every 2 weeks in a pregnant patient receiving doxorubicin and cyclophosphamide, beginning at 24 weeks. Unexposed fetuses aged 20–40 weeks were controls. The left and right ventricles of the exposed fetuses grew progressively with advancing gestation, as did those of controls. The investigators identified no significant difference between exposed and unexposed fetuses in systolic function, which they assessed with fractional shortening. Postnatal echocardiograms repeated until 2 years of age showed no myocardial damage.

Cancer treatment advances more rapidly than the accumulation of safety data in human pregnancy. Caution is warranted before new agents are used, even if from the same class as agents with demonstrated safety. Four cases of neonatal cardiac effects occurred after in utero exposure to anthracycline. One electively terminated fetus, which had been exposed to doxorubicin and pelvic radiation, had only one coronary artery; the risk of congenital anomalies is higher with concomitant radiation and chemotherapy.[27] Two cases of transient right-sided cardiomyopathy occurred after second trimester exposure to idarubicin with tretinoin or with vincristine, daunorubicin, and cyclophosphamide.[37,39] Idarubicin differs from other anthracycline antibiotics in that it is more lipophilic, which favours increased placental transfer. This derivative of daunorubicin might also have a higher affinity for DNA.[20] Reynoso and Hueta[20] reported a case of IUFD 2 days after idarubicin was used for consolidation therapy for acute myeloid leukaemia. All five cases exposed to idarubicin developed complications—IUGR, IUFD, and two cases of cardiomyopathy.

Another anthracycline—epirubicin—was used in 13 women, and three fetuses were affected. One fetus died after second trimester exposure to epirubicin, vincristine, and prednisone, and another after epirubicin with cyclophosphamide.[13,15] One neonate died at 8 days, after third trimester exposure to epirubicin, cyclophosphamide, and 5-fluorouracil.[15] 23% of cases exposed to epirubicin died either as fetuses or as neonates. If doxorubicin is as effective as idarubicin or epirubicin in selected malignant diseases, doxorubicin is preferred in pregnancy.

### Plant alkaloids

Vinca alkaloids are highly protein bound, and are regarded less potent teratogens than are antimetabolites.[2,4] Of 29 patients treated during organogenesis, one delivered a baby with malformations after exposure to vincristine, doxorubicin, cytarabine, and prednisone. The baby had a defect in the atrial septum, and no radii or 5th digits.[18] 111 exposures to either vincristine or vinblastine during pregnancy have been reported. Apart from the malformations found only in first trimester use, nine cases of IUGR (8%); seven of preterm delivery (6%), and two of pre-eclampsia (2%) occurred. There were four deaths: two as a fetus and two neonates. The IUFDs occurred after doxorubicin, vincristine, prednisone, and radiotherapy in the third trimester; and vincristine, prednisone, and epirubicin in the second and third trimesters.[13,35] One of the neonates died after second trimester exposure to vincristine, ifosfamide, and dactinomycin; the second after vincristine, mercaptopurine, methotrexate, cytarabine, and prednisone.[14,40]

### Taxanes

Use of paclitaxel in human pregnancy has rarely been reported. Results of studies[41] have shown that paclitaxel is lethal to chick, rat, and rabbit embyos, but few malformations when given during organogenesis. Paclitaxel has a unique antineoplastic mode of action, inhibiting microtuble disassembly. Because microtubles have vital roles not only in cell division but also in intracellular and intercellular functions, cytotoxicity might not be restricted to the mitotic phase of the cell cycle. We identified only two cases of paclitaxel use in human pregnancy. In combination with either cisplatin, or carboplatin, paclitaxel was used after organogenesis without apparent fetal effects. In addition to these two cases, we followed up two exposures, including a case of twins without complications. At ages 2 and 7 years, both are healthy. Because of the limited human experience, and the uniqueness of taxanes' antineoplastic mode of action, the use of taxanes in pregnancy is not recommended, but this recommendation could change as more cases of exposure are published.

### Miscellaneous agents: cisplatin and carboplatin

Sensorineural hearing loss was reported in a child born with leukopenia, alopecia, and respiratory distress syndrome at 26 weeks, after exposure to cisplatin 6 days before delivery.[42] The sensorineural hearing loss at 1 year of age might have resulted from exposure to cisplatin, but prematurity and postnatal treatment with gentamycin are confounding factors.

Another patient was given cisplatin, bleomycin, and etoposide at 25 weeks for treatment of ovarian cancer. A fetal ultrasound at 19 weeks was normal, but the ultrasound was not repeated before chemotherapy. 1 week after treatment, bilateral ventriculomegaly was seen on ultrasound.[43] When born prematurely at 28 weeks, the neonate was anaemic and neutropenic, but not thrombocytopenic. Cytomegalovirus testing was negative. Cerebral atrophy present on postnatal ultrasound was presumed secondary to impaired anterior cerebral circulation. The investigators suggested that a thrombotic event had developed secondary to the platin agent.[43] Close assessment of the fetus's CNS may be warranted in exposures to cisplatin, but this was an isolated report.

We followed up four cases of cisplatin exposure with normal outcomes. 24 cases have been exposed to cisplatin, with five complicated by IUGR, IUFD, hearing loss, and ventriculomegaly.[42–46] We identified only two cases of fetal exposure to carboplatin; both neonates developed normally up to 30 months of age.

## Transplacental studies

Transplacental studies[47] have had conflicting results. Roboz and colleagues reported that doxorubicin was not detectable in amniotic fluid 4 or 16 h after maternal intravenous infusion. This absence in the amniotic fluid might not exclude transplacental passage. d'Incalci and colleagues[48] did not detect doxorubicin in amniotic fluid, fetal brain, or gastrointestinal tract 15 h after administration, but did detect this drug in fetal liver, kidney, and lung after elective termination. The fetal heart was not assessed.

By use of liquid chromatography, Karp and colleagues[35] reported that concentrations of doxorubicin were highest in placental tissue, with none in cord tissue or blood in a healthy child born 48 h after treatment. In a stillborn baby delivered 36 h after maternal treatment, a doxorubicin metabolite was present in the cord, placental tissue, and neonatal spleen.[35] 96 h after doxorubicin administration, Barni and colleagues[49] did not detect the drug in amniotic fluid. Henderson and co-workers[44] measured cisplatin-DNA adducts in amniotic cells, placental tissues, and cord blood by ELISA and spectometry. The amniotic cells and cord blood contained insufficient DNA to measure adducts with maximum sensitivity, but they did identify adducts in the placental tissue.

## Other invasive studies

Morishita and colleagues[50] sampled the umbilical blood 2 and 5 weeks after multidrug chemotherapy for maternal leukaemia. Fetal haemopoiesis was consistently normal. Patients have raised concerns about neonatal alopecia, but this disorder has been reported in only three neonates.[42,51] In these cases, the agents involved included bleomycin, etoposide, and cisplatin; or doxorubicin, cyclophosphamide, and 5-fluorouracil. Gokal and colleagues[52] did microscopic scanning of the hair of exposed neonates and showed no cytotoxic damage. None of our 55 exposed neonates were born with alopecia.

## Specific cancers treated during pregnancy

### *Breast cancer*

Webtable 1 (http://image.thelancet.com/extras/03oncl0502webtable1.pdf) summarises the 72 cases exposed to chemotherapy for breast cancer. 53 patients were exposed to cyclophosphamide and 5-fluorouracil with methotrexate or doxorubicin. Berry and colleagues[51] treated 24 patients with cyclophosphamide, 5-fluorouracil, and doxorubicin, all after 12 weeks. There were no congenital anomalies, nor growth restriction. All 29 patients in our prospective series received doxorubicin and cyclophosphamide after 12 weeks without malformations or complications, excluding IUGR and pre-eclampsia in one case. Cyclophosphamide and doxorubicin with or without 5-fluorouracil is the preferred combination during pregnancy. Because epirubicin and idarubicin have not been as extensively investigated as the combination of cyclophosphamide and doxorubicin during pregnancy, and because there were four fetal or neonatal deaths among 17 cases and two cases of transient cardiomyopathy, we do not recommend use of epirubicin and idarubicin during pregnancy.

Studies in animals have raised concerns about use of taxanes during pregnancy, and human case reports are rare. Use of tamoxifen has been reported in human series, but follow-up has been short term. A female fetus was born with ambiguous genitalia after exposure to tamoxifen during the first and second trimesters.[53] Goldenhar syndrome was reported in a fetus exposed in all three trimesters.[54] Studies in female rats and mice exposed to tamoxifen have shown metaplastic and dysplastic changes in the epithelium of the uterus and reproductive tract. Female infants that have been exposed while in utero should be followed up in the long term for genitourinary abnormalities.[55,56] Because of such concerns and the limited human experience, tamoxifen should be stopped during pregnancy.

### *Leukaemia*

The underlying malignant disease can affect perinatal outcome. Spontaneous abortion, prematurity, IUGR, and death have been associated with maternal leukaemia, despite treatment.[5] The earlier the diagnosis of leukaemia in pregnancy, the higher the perinatal mortality. Suspected causes include maternal anaemia, disseminated intravascular coagulation or leukaemia cells affecting blood flow and nutrient exchange, and oxygen delivery in the intervillous spaces of the placenta. Acute leukaemia requires treatment without delay, irrespective of gestational age. Without treatment, maternal death can occur within 2 months, even before the fetus is viable.

41 cases of acute leukaemia were treated during the first trimester. All cases with anomalies occurred with first trimester exposure to cytarabine or tioguanine, alone or in combination with an anthracycline. Cytarabine and tioguanine should be avoided in the first trimester if possible. Combinations of vincristine, mercaptopurine, doxorubicin or daunorubicin, cyclophosphamide, prednisone, and methotrexate were used in all trimesters without anomalies. Transient myelosuppression occurred in nine neonates. Two cases of transient neonatal cardiomyopathy occurred, both of which had been exposed to regimens that included idarubicin.[57,58]

Various combinations of vincristine, daunorubicin, cyclophosphamide, asparaginase, and mercaptopurine have been used during pregnancy to treat leukaemia. Of 152 patients treated for acute lymphoblastic leukaemia (63 cases) or myelogenous leukaemia (89 cases), six neonates (4%) had congenital abnormalities,[8,16–18,27,59] 12 had IUGR (8%), and 11 IUFD (7%),[3,13,20–25,59] and two neonatal deaths (1%) occurred.[7,47] Webtable 2 (http://image.thelancet.com/extras/03oncl0502webtable2.pdf) and webtable 3 (http://image.thelancet.com/extras/03oncl0502webtable3.pdf) summarise the chemotherapy exposures to treat either acute lymphoblastic leukaemia or acute myeloid leukaemia, respectively.

### *Chronic leukaemia*

Hydroxycarbamide or busulfan seem to be safe during pregnancy if necessary. Leucopheresis can also be used during pregnancy to reduce white-blood-cell count and spleen size.[60] Other agents used less frequently include mercaptopurine, tioguanine, cytarabine, vincristine, or doxorubicin (webtable 4, http://image.thelancet.com/extras/03oncl0502webtable4.pdf).

### *Lymphoma*

We reviewed 53 cases of lymphoma. The ABVD regimen for Hodgkin's lymphoma (webtable 5, http://image.thelancet.com/extras/03oncl0502webtable5.pdf) has been reported to be safe, although dacarbazine is the least investigated. One patient with stage-4 Hodgkin's disease was treated at an outside institution with doxorubicin, bleomycin, and vinblastine, deleting dacarbazine because of the scarce studies in pregnancy at that time. Unfortunately, she had recurrent disease within 1 year of delivery and is undergoing bone-marrow transplantation. Suboptimum treatment of pregnant women can place them at risk of recurrence. 35 patients with non-Hodgkin lymphoma (webtable 6, http://image.thelancet.com/extras/03oncl0502webtable6.pdf) were treated during pregnancy with multiple regimens, most of which included doxorubicin, cyclosphosphamide, and vincristine. No malformations occurred, even with first trimester treatment in 11 cases.

### *Ovarian cancer*

Because of the young age of reproductive women, and the use of pelvic ultrasound and examination during prenatal care, ovarian cancer is usually diagnosed at an early stage during pregnancy.[44,61–65] Different agents are indicated depending on the histological type; most regimens include a platin drug.

Cisplatin is preferred over carboplatin for use in pregnancy: carboplatin is more likely than cisplatin to cause thrombocytopenia[66] and it is less protein bound than other platinum agents, possibly favouring placental transfer. Our analysis showed that cisplatin has been more extensively investigated in human pregnancy with carboplatin. A neonate who had sensorineural hearing loss at 1 year was exposed to cisplatin in utero, although this case had confounding factors.[44] Transient ototoxicity has been reported for pregnant women exposed to cisplatin, but we found no other cases of hearing loss in exposed neonates.

Use of etoposide in human pregnancy is limited. One complication was reported after etoposide use with bleomycin and cisplatin: a neonate was born prematurely at 28 weeks with ventriculomegaly.[43] Etoposide is potently myelosuppressive and has been linked to transient neonatal alopecia.[44] Webtable 7 (http://image.thelancet.com/extras/03oncl0502webtable7.pdf) describes the chemotherapy regimens used to treat ovarian cancer during pregnancy and webtable 8 (http://image.thelancet.com/extras/03oncl0502webtable8.pdf) describes exposures for miscellaneous cancers seen less frequently in pregnancy, yet which expand our limited knowledge.

## Maternal risks during pregnancy

Bleomycin is associated with pulmonary toxicity, which can be exacerbated by oxygen therapy.[67] Sorosky and colleagues[67] suggested that pregnant patients exposed to bleomycin should not be given oxygen during labour because of possible aggravated pulmonary toxic effects.

Chemotherapy-induced neutropenia and the generalised immunosuppression during pregnancy place the woman and possibly the fetus at risk of infection. Granulocyte colony-stimulating factor (GCSF) given to pregnant rats stimulated granulopoiesis in the newborn bone marrow and spleen, without harm.[26] Safe use of GCSF in human pregnancy has also been reported.[26]

The dilutional and iron-deficiency anaemia during pregnancy combined with chemotherapy-induced cytopenia increases the risk of anaemia: epoietin has been used safely in this context.[26]

## Pharmacokinetic toxic effects versus subtherapeutic doses

No pharmacokinetic studies have been done in pregnant women receiving chemotherapy. Pregnant women receive similar weight-based doses as women who are not pregnant, adjusted with the continuing weight gain. The increased blood volume (by almost 50%), and increased renal clearance might decrease active drug concentrations compared with women who are not pregnant and who are the same weight. Increased drug clearance from the body can lead to a reduced area under the concentration-X time curve.[68] A faster hepatic mixed-function oxidase system might also lower drug concentrations, and changes in gastrointestinal function can affect drug absorption. The volume of distribution, peak drug concentration, and half-life of administration is also sometimes changed during pregnancy. Plasma albumin decreases, increasing the amount of unbound active drug; however, oestrogen increases other plasma proteins, which might decrease active drug fractions. Hopefully, this mechanism will not compromise the effectiveness of the drug for curing pregnant women with malignant diseases. Anecdotally, patients in our registry have reported more frequent nausea, vomiting, fatigue, alopecia, and neutropenia during postpartum chemotherapy compared with identical antenatal treatment. Whether this difference in side-effects is due to lower peak or free-drug concentrations during pregnancy is unknown. Zemlickis and colleagues[69] raised a concern for toxic effects in pregnant women undergoing chemotherapy by showing higher concentrations of free cisplatin in pregnant women compared with women who were not pregnant, but all were asymptomatic.

## Long-term neonatal follow-up

Aviles and co-workers[7,29] extensively followed up 62 children born to mothers treated during pregnancy for haematological malignant diseases. All children were normal physically and neurologically. School performance and standardised intelligence testing did not differ significantly from controls (unrelated matched children and unexposed siblings), and laboratory testing showed normal tolerance of

infections. For the older children, normal secondary sexual development was documented. Two women were menstruating normally, one gave birth to a healthy daughter.

One case of malignant disease in a child exposed in utero has been reported.[28] This child developed thyroid cancer at 11 years, then neuroblastoma at 14 years. He also had malformations at birth. His fraternal twin (exposed in utero to the same agents) was normal at birth and healthy.

## Timing of delivery and breastfeeding

Delivery should be avoided during the maternal nadir period, usually 2–3 weeks after treatment.[70] Chemotherapy should not be given after 35 weeks' gestation because spontaneous delivery can occur before the bone marrow has recovered. The delay of delivery for 3 weeks after chemotherapy also allows for fetal drug excretion via the placenta. Chemotherapy administered shortly before delivery might not have been eliminated from the fetus before delivery, and drugs might therefore persist in the newborn. This is especially true for preterm babies, who have a limited ability to metabolise drugs due to the immaturity of the liver and kidneys.[67] Iatrogenic preterm deliveries should be avoided, and preterm labour should be treated aggressively.

The ability of an agent to cross the placenta often does not correlate with the ability to pass into breast milk. The concentrations in milk are variable and related to the dose and timing of chemotherapy. Neonatal neutropenia has been reported in an infant breastfed during maternal treatment with cyclophosphamide.[71] For most agents however, no breastfeeding information is available. Breastfeeding is contraindicated while undergoing chemotherapy.

## Our experience

We followed up 55 pregnant patients receiving chemotherapy after the first trimester for: breast cancer (n=35), Hodgkin's lymphoma (ten), non-Hodgkin lymphoma (five), leukaemia (one), and ovarian cancer (four). The mean birthweight was 2642 g (SD 540) at a mean gestational age of 36·5 weeks (SD 2·56). One malformation of syndactyly of two digits occurred after exposure to ABVD, which was corrected surgically. 53 of the 55 children are meeting developmental milestones and growing well; the oldest is 7 years of age. Two neonates delivered at 35 weeks were found on neonatal CNS ultrasound to have periventricular leucomalacia—one soon after birth, the other at 2 months of age. Both were born to mothers with breast cancer undergoing therapy with doxorubicin and cyclophosphamide in the third trimester only. No thrombocytopenia was documented in either woman during therapy or postpartum. Both infants had IUGR. The timing in the first case suggests that an in utero hypoxic event occurred 16 weeks before delivery. This patient reported a hypotensive episode in the postoperative period after mastectomy at 26 weeks. Although born with a platelet count of 140 000 platelets/μL, the neonate developed thrombocytopenia and a rash on day 2 of life. Neutropenia and anaemia did not occur. A rheumatological assessment is in progress. In the second case, the neonate was iatrogenically hyperventilated to extreme hypocapnia in the newborn period. Periventricular leucomalacia was diagnosed when seizures began at 2 months of age. The occurrence of this disorder in these two newborns is concerning. Free-radical damage induced by chemotherapy that results in CNS hypoxia cannot be excluded, although both cases might have had other causes. Close observation for additional reports is necessary.

## Conclusion

The decision to use chemotherapy during pregnancy must be weighed against the effect of treatment delay on maternal survival. If possible, chemotherapy should be avoided during the first trimester, as should low-molecular-weight and highly diffusible drugs. If multidrug treatment in the first trimester is required, anthracycline antibiotics, vinca alkaloids, or single-agent treatment followed by multi-agent therapy after 12 weeks should be considered. Requena and colleagues[72] suggested using lower doses of chemotherapy during pregnancy to induce remission, followed by consolidative therapy at standard doses postpartum. However, even therapeutic doses might theoretically not be adequate for pregnant women, in view of the pharmacokinetic changes during pregnancy. We know of two pregnant patients iatrogenically given lower than standard doses of ABVD who had recurrent disease post partum.

Since 1966, adding our experience to published work, 376 fetuses have been exposed to chemotherapy in utero, most after organogenesis. 19 (5%) fetuses and four (1%) neonates died. All but three of these deaths occurred with maternal haematological malignant disease. Two of these three fetuses had been exposed to idarubicin for breast cancer. In 28 cases (7%), the neonate had IUGR, and 18 (5%) were delivered prematurely secondary to spontaneous premature rupture of membranes or preterm labour (iatrogenic cases excluded). 15 (4%) babies had transient myelosuppression. Nine of the 11 malformations occurred when chemotherapy was given in the first trimester. Two cases of transient neonatal cardiomyopathy occurred after idarubicin exposure.

Use of chemotherapy in the second and third trimesters seems to be safe. The background incidence of IUGR varies according to the population, geographic location, and standard growth curves used as a reference. In general, 4–8% of all infants born in developed countries are classified as growth restricted.[73] The mother's underlying illness might also affect perinatal complications.

Children and adults given chemotherapy for lymphoma are at risk of secondary leukaemia within 10 years.[74] The risk of secondary malignant disease after in utero exposure to chemotherapy is unknown. No cases have been reported of secondary leukaemia in exposed fetuses. Delivery should be delayed by 2–3 weeks after chemotherapy to allow the bone marrow to recover, and iatrogenic preterm deliveries should be avoided. When more than one regimen is available and effective for a particular cancer, agents should be chosen on the basis of the most extensive investigation. Placental pathology is suggested in all cases. A multidisciplinary team including specialists in oncology, perinatology, and

### Search strategy and selection criteria

Ovid, MEDLINE, and PubMed were searched from 1965 to November, 2002, with the following keywords: "pregnancy", "chemotherapy", "cancer", "breast cancer", "lymphoma", "leukemia", "cervical cancer", "ovarian cancer". Each of these terms was also combined with "pregnancy", and searches were restricted to studies published in English.

neonatology is needed to coordinate care, improve the chance of cure in the mother, and decrease neonatal harm. More women than those identified in this review have probably received chemotherapy during pregnancy, but are not included in the published case reports. We thus encourage publication of exposed cases. As we continue to follow up exposed newborns, fewer pregnant women who decline termination will not be denied treatment for cancer. Cases requiring an anthracycline should be given doxorubicin rather than idarubicin or epirubicin. Pharmacokinetic studies are indicated so that pregnant women receive adequate doses.

#### Conflict of interest

None declared.

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