ORIGINAL ARTICLE

Spontaneous abortions in female populations occupationally exposed to ionizing radiation

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Abstract

Objective Exposure to radioisotopes of metals and halogen elements occurring in medical practice may cause spontaneous abortions. The potential role of occupational exposure to X-rays and internal radioisotopes on pregnancy outcome in childbearing age women employed in hospital departments were analyzed in order to estimate miscarriage risk.

Methods Over a period of 16 years, the occurrence of miscarriages in 61 women exposed to radioisotopes was compared to that reported in 170 X-ray exposed women. Chromosomal aberrations (CA) were measured in both radiation-exposed groups and in 53 non-exposed women.

Results Women exposed to radioisotopes experienced at least a threefold higher rate of spontaneous abortions than those exposed to X-ray (OR = 3.68, 95% CI = 1.39–9.74, $P < 0.01$). Although X-ray and radioisotopes exposed women had significantly higher levels of chromosome type frequency (0.51 ± 0.82, and 0.63 ± 0.99, respectively) than referents (0.17 ± 0.34), there was no clear difference between radiation-exposed women.

Conclusions For exposure levels within standard recommended guidelines, radioisotopes are far more likely to play a role in the occurrence of spontaneous abortions than X-rays. Such biological effect is not detectable by deviations in CA frequency.

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Introduction

Physical monitoring of medical staff occupationally exposed to ionizing radiation is mainly limited on X-rays while beta emission is measured much more rarely and with less precision. Nuclear medicine and endocrinology departments apply radioactive sources that have both gamma and beta emissions. According to recent reports (Phipps et al. 2001; Barber et al. 2003; Mountford and Steele 1995), even in routine work at nuclear medicine departments, the dose to which pregnant medical staff may be exposed could exceed the limit for a fetus. Moreover, given that intakes by the mother occurring before pregnancy can lead to significant doses to the fetus, protection for female workers is of particular relevance to fetal safety (Phipps et al. 2001). Therefore, for radiological protection of the fetus, occupational intake of some radionuclides by women in their fertile age (who are or may become pregnant) should be lower than the recommended dose limit for workers (1 mSv, HSE 2000; ICRP 2001). Radioisotopes of metals and halogen elements are used in medical practice; thus, the mechanism of action of these agents can be both as chemical carcinogens and an ionizing radiation source. Ionizing radiation

causes spontaneous abortions in humans (Auvinen et al. 2001; Russell et al. 1997a, b), but also certain metals have also been shown to cause fetal deaths in animals (ICRP 2003). The aims of this study were to investigate whether young women in the radioisotope workplace face an increased risk of miscarriage compared to those working with pure radiation sources such as X-rays and to contrast chromosome aberration frequency in radioisotope and X-ray-exposed women and in women not occupationally exposed to any source of radiation.

Methods and subjects

A total of 231 women occupationally exposed to ionizing radiation during their childbearing years were identified over a period of 16 years (1986–2001) and were included in an historical miscarriage the study. A total of 170 women were exposed to X-rays in radiological hospital departments and 61 to radioisotopes in nuclear medicine and biochemical diagnostics hospital departments from all public hospitals in Croatia in which such departments exist. We administered a standardized questionnaire form to investigated pregnancies and their outcome over the study period of observation. The form included items concerning smoking and drinking habits, recent history of infectious diseases (last 2 months), exposure to diagnostic or therapeutic radiation exposure (last 6 months), exposure to petroleum products, pesticides or solvents (including benzene) at work as well as at home, drug intake such as oral contraception and vaccination was recorded. Trained person blinded of the women's exposure status conducted face-to-face interviews. To be included in the study women had to be in their childbearing age, working as a professional in the medical field with registered exposure to either X-rays or to radioisotopes, had more than 1 year of employment before pregnancy and not exposed to any kind of radiation source in diagnostic or therapeutic purposes, without hormonal treatment and vaccination 6 months before pregnancy. Occupational data were gathered from the hospitals' personnel historical records and were not collected during the interview to prevent the interviewers from becoming aware of the women's exposure status. Spontaneous abortion (SA) was defined as a pregnancy terminated before 26th week of gestation.

Croatian—and former Yugoslavian—legislation (Republic of Croatia 1986) requires all persons working with ionizing radiation to undergo periodic medical examinations prior and during employment where, among other diagnostic procedures and tests, the chromosomal aberration analysis is required. Therefore, a group of 53 women not occupationally exposed to any known occupational source of radiation were randomly selected from the same

hospitals to serve as referents in the chromosome aberration component of the study. Only women (exposed and referents) without infectious diseases, not taking medications, and without a history of SA prior to employment, and women not exposed to diagnostic or therapeutic ionizing radiation 6 months prior to blood sampling for chromosome aberration assay were included in the study.

All the assays were performed at the Institute for Medical Research and Occupational Health, Zagreb, by one of the author (A.F.).

Monitoring of occupational exposures was performed on regular basis (twice per year) using survey meters (Thermo-Eberline FH 40G), with probes for gamma and beta, and wipe tests of working surfaces (appropriate spectrometry method). The levels of beta emission were in accordance with international recommendations (HSE 2000). Radiation levels estimated over the period studied were below 10 mSv per year and none of the 231 exposed women received a radiation dose that exceeded the international regulation limit of 20 mSv per year or 100 mSv in the period of 5 years.

All women achieved the level of education required to be employed as professional in the medical field, belonged to the same occupational level, and received the same salary through the Ministry of Health of the Republic of Croatia.

The Ethics Committee of the Institute for Medical Research and Occupational Health, Zagreb, Republic of Croatia, approved the study as part of a national project funded by Croatian Ministry of Science, Technology and Sport. All women agreed to participate in the study and signed a study specific informed consent form.

Chromosome aberration assay

An independent physician performed blood sampling. Samples of heparinized blood were taken from each woman, and cell cultures were initiated within a few hours. Upon receipt of the specimens, standard 48 h lymphocyte cultures were made and fixed following accepted protocols (IAEA 1986). From each sample, 200 metaphases were Giemsa block-stained and scored for conventional unstable aberrations, dicentrics, chromatid breaks and acentric fragments.

Statistical methods

The effect of individual covariates on the number of SA was evaluated through a multiple logistic regression model where each woman represented a cluster of allegedly correlated pregnancy outcomes. Given the non-independence of the outcomes, a generalized estimating equation (GEE) was applied to account for within-subject correlation (Diggle et al. 1994). Two regression models were run: Model A

assuming an equal within-subject correlation and Model B—applied to women with two or more pregnancies—allowing for the possibility that a woman who had a spontaneous abortion is more likely to experience a second one. Specifically, the latter model was based on an autoregressive correlation structure where the closer the events the higher the correlation. Differences in the frequency of chromosome aberrations were tested by the analysis of variance and non-parametric Kruskal Wallis univariate test statistics. Bonferroni's adjustment was used to account for multiple comparisons. Multiple Poisson regression analysis (Lindsey 1995) was used to investigate the effect of radiation exposure (X-ray, radioisotope) while accounting for the effect of age, smoking, and drinking habits at blood sampling. Poisson regression allows the computation of the mean ratio (MR), i.e., the ratio of the mean level of chromosome aberrations measured in radiation exposed relative to referent women. Analysis of the frequency of dicentrics, that were absent among referent women, was carried out by fitting a linear regression model to the data which permits estimation of the difference between means. Standard diagnostic procedures were carried out to inspect the applied statistical models. Statistical analyses were performed using STATA statistical software.

Results

The numbers of self-reported spontaneous abortions and pregnancies reported by X-ray and radioisotope-exposed women are shown in Table 1. In both exposed groups, all abortions happened within the first trimester of pregnancy.

The results of the two multiple regression models (Model A and B, Table 1) revealed that radioisotope exposed had a higher risk of SA than X-ray-exposed women. The age, smoking, and drinking adjusted odds ratio estimates (OR) ranged between 3.68 (95% CI = 1.39–9.74, $P < 0.01$) and 4.89 (95% CI = 1.99–11.98, $P \leq 0.001$) according to the regression model. This finding suggests that radioisotopes could be far more effective in causing SA compared to X-rays. Duration of employment in both groups was similar for X-ray and radioisotope exposed women: 11.2 (SD = 8.9) and 10.4 (SD = 8.4) years, respectively (data not shown).

The mean frequency of chromosome type aberrations (Table 2) was significantly higher ($P < 0.05$) in exposed than in referent women (0.17%, SD = 0.34), but failed to show any difference between radioisotope- (0.63%, SD = 0.99) and X-ray- (0.51%, SD = 0.82) exposed women. The frequencies of dicentric chromosomes were similar for X-ray and radioisotope-exposed women and were significantly increased ($P < 0.05$) in both exposed groups compared to referent women. The mean age at the time of sampling (data not shown) was 37.3 (SD = 8.8), 38 (SD = 9.2), and 32 (SD = 8.5) years for the X-ray exposed, radioisotope exposed and for referent women, respectively. Multivariate analysis (Table 3) revealed significantly higher mean levels of chromosome type aberration in X-ray (MR = 3.13, 95% CI = 1.54–6.37) and radioisotopes exposed (MR = 3.61, 95% CI = 1.69–7.71) compared to referent women. Dicentrics were also significantly increased in radiation exposed than in unexposed women (mean difference, MD = 0.11, 95% CI = 0.01–0.21, $P \leq 0.03$ and MD = 0.14, 95% CI = 0.02–0.27, $P \leq 0.02$,

Table 1 Multiple logistic regression odds ratio (OR) point estimates and 95% CI adjusted for age at pregnancy outcome for spontaneous abortion in radioisotopes exposed women

Covariate	Women no.	Miscarriages no.	Pregnancies no.	Model A		Model B	
				OR	95% CI	OR	95% CI
Exposure							
X-ray	77	13	135	1	–	1	–
Radioisotopes	45	31	104	4.89[*]	1.99, 11.98	3.68[*]	1.39, 9.74
Smoking habits							
Never smokers	70	23	136	1	0.41, 2.13	1	0.37, 2.38
Smokers	52	21	103	0.93		0.94	
Drinking habits							
Teetotalers	116	43	229	1	0.03, 10.67	–[a]	–
Drinkers[b]	6	1	10	0.59			

Limited to 122 ever pregnant women (81 = never pregnant) and with complete data for the covariates included in the multiple logistic regression models (28 women with missing data)

[a] None of the women with ≥2 pregnancies were drinkers

[b] All drinkers reported to drink one glass of wine occasionally before pregnancy

[**] $P \leq 0.001$; odds ratios are adjusted by age at pregnancy outcome

Table 2 Chromosome aberrations detected in referent, X-rays and in radioisotopes exposed women and corresponding univariate statistics

Cytogenetic endpoints	Study groups		
	Referents (no. = 53)	X-ray exposed (no. = 170)	Radioisotopes exposed (no. = 61)
Chromosome aberrations	Mean ± SD	Mean ± SD	Mean ± SD
Chromatide	1.58 ± 0.96	1.97 ± 1.41	1.98 ± 1.47
Chromosome	0.17 ± 0.34	0.51 ± 0.82[a]	0.63 ± 0.99[a]
Acentric	0.35 ± 0.46	0.60 ± 0.90	0.61 ± 1.09
Dicentrics	0.0	0.12 ± 0.36[b]	0.16 ± 0.36[b]

[a] Bonferroni adjustment for multiple comparisons: significantly different from reference mean levels ($P < 0.05$)

[b] Nonparametric Kruskal Wallis test statistics: significantly different from reference mean levels ($P < 0.05$)

respectively). The increases observed for chromatide and acentric type reached statistical significance only among X-ray-exposed women (Table 3). Smoking was significantly associated with a moderate increase of the frequency of chromosome-type aberrations (MR = 1.49, 95% CI = 1.04–2.16, $P = 0.032$).

Discussion

The occupational protection protocol for radioisotope workers has historically focused on radiation protection. However, elements that are used routinely in practice in their radioisotope forms are typically halogens (iodine, fluorine) or metals (chromium, thallium, thorium), and have been reported as toxic or suspected mutagen and teratogenic agents (Kanojia et al. 1998; Mertz 1986). Thallium is applied in injections as [201]Th chloride contaminated with approximately 0.2%, [203]Pb, which is a known teratogenic element (Wibberley et al. 1977; Baghurst et al. 1991). [99]Tc

is applied as a pharmaceutical in several forms such as ^{99}Tc-glucoheptonate or ^{99}Tc-pertechnetate. It has been shown in animal models that retention and its transmission through placenta differs for different Tc compounds (Mahon et al. 1973). The majority of Technetium 99 compounds employ the stannous reduction method by using SnCl2 2H2O, tin (II) chloride which is described as a potent DNA damaging agent via formation of reactive oxygen species and direct linkage to DNA (McLean et al. 1983; Dantas et al. 2002) and can cause post-transplantation mortality in animal models (NIOSH 2006). In sodium chromate Cr-51 injections, chromium is present as a hexavalent, which is the most potent carcinogen of the various groups of chromium compounds tested. Hexavalent chromium inhibits DNA synthesis (Bridgewater et al. 1998; Gambelunghe et al. 2003; Bagchi et al. 2002) and cause DNA damage, as has strong affinity to nucleic acid and may be involved in maintaining of the nucleic acid tertiary structure (Mertz 1986; McLean 1983). A significantly reduced number of viable fetuses implantation sites has been reported in mice exposed to hexavalent chromium (Elbetieha and Al-Hamood 1997). The increased incidence of SA observed following paternal exposure to chromium in a population of steel welders suggests the possibility that even non-radioactive isotopes of chromium have mutagenic and teratogenic potential (Hjollund et al. 2000). Tritium freely cross the placenta and is distributed approximately uniformly in maternal and in fetal tissue (Von Zallinger and Tempel 1998). Due to the high concentration of water in earlier stages of development, rats exposed on the 13th day of gestation had an increased concentration of tritium compared to those exposed on the 17th day (Takeda et al. 1994). In mice embryos ^{3}H-thymidine was found to be 1,000 times more radiotoxic than tritiated water (Streffer et al. 1978; Yamada and Yukawa 1984). Due to the high proliferation rate of embryos, ^{3}H-thymidine is rapidly incorporated into the DNA; thus, the dose to the nucleus is much higher than that to the cytoplasm. It could be

Table 3 Mean ratios (MR) for chromatide, chromosome type and acentrics aberrations and mean differences (MD) for dicentrics, X-rays and radioisotopes exposed compared to referent women estimated by using Poisson multiple regression analysis

Covariate	Women no.	Chromatide type			Chromosome type			Acentrics			Dicentrics		
		MR	95% CI	P	MR	95% CI	P	MR	95% CI	P	MD	95% CI	P
Exposure													
Referents	53	1	–		1	–			–		0	–	
X-ray	170	1.30	1.02, 1.65	0.04	3.13	1.54, 6.37	0.002	1.72	1.00, 2.97	0.05	0.11	0.01, 0.21	0.03
R-isotope	61	1.28	0.97, 1.71	0.09	3.61	1.69, 7.71	0.001	1.63	0.87, 3.06	0.13	0.14	0.02, 0.27	0.02
Smoking habits													
Never smoked	171	1	–		1	–		1	–		0	–	
Smoker	113	1.14	0.96, 1.35	0.17	1.49	1.04, 2.16	0.032	1.40	0.98, 2.01	0.06	−0.02	−0.1, 0.06	0.63

MRs and MDs are adjusted by age and drinking habits; 95% CI = 95% confidence interval; P = P value

speculated that in humans there is also accumulation of ^{3}H-thymidine due to similar proliferative activities.

As the fetus is considered to be most sensitive to radiation during the period of major organogenesis in the first trimester (Brent 1987), SA could be a relevant health outcome in evaluating exposure-related adverse effects. Despite current knowledge on the effects of radiation, there is no support on exact values of radiation dose due to transplacental crossover of radioisotopes after occupational exposure (ICRP 2001). Additionally, considering chemical substances, there is strong evidence that fetus elimination of xenobiotics is less effective than in adults and that the placenta does not act as a barrier, but instead, accumulates hazardous compounds (Schonfelder et al. 2002). Finally, considering animal experimental models, irradiation increases susceptibility to carcinogenic and teratogenic chemical agents (ICRP 2001). Thus, complex exposures are likely to lead to synergistic effects, which in human development are yet to be revealed. Human studies have reported a twofold elevated odds ratio in female research laboratory personnel in Sweden (Wennborg et al. 2000) who worked with chloroform, and a 50% higher risk of SA reported by women who worked in dry cleaning as operator compared to non-operators (Doyle et al. 1997), in pharmaceutical and nursing staff who were exposed to antineoplastic drugs during pregnancy (Valanis et al. 1999), and in farm women who were exposed to phenoxy acetic acid herbicides and/or other pesticides (Arbuckle et al. 2001). A threefold higher risk was detected in US women employed at semiconductor manufacturing plants and occupationally exposed to ethylene glycol ethers (Correa et al. 1996; Swan et al. 1995) and an increased risk of SA was reported following exposure to benzene, gasoline, and hydrogen sulfide in Chinese petrochemical female workers (Xu et al. 1998).

Our study showed that occupational exposure to radioisotopes, within regulated doses, has a clear impact on reproduction in humans by significantly increasing the risk of SA in radioisotopes compared to X-ray exposed Croatian hospital workers. This is in agreement with the few human studies investigating the association between job-related exposure to ionising radiation and the risk of miscarriage. A weak, non-statistically significant increased risk (OR = 1.3, 95% CI 0.8–2.0) was reported in US female veterinarians exposed to ionizing radiation (Steele and Wilkins 1996) and a twofold-increased risk was detected among Finnish practicing veterinarians during the 1970s (Lindbohm and Taskinen 2000). Female veterinarians who reported performing five or more radiographic examinations per week had an elevated risk of SA (Schenker et al. 1990). Conversely, similar rates of SA were reported in Canadian pregnant women who inhaled anesthetics and/or were exposed to ionizing radiation in veterinary practices (Shuhaiber et al. 2002).

Smoking was not associated with the risk of SA in our study. The available epidemiological evidence suggest an association between smoking and SA, with odds ratios ranging between 0.6 and 1.8 for women who quit smoking and those who continued to smoke during pregnancy (Henriksen et al. 2004; Wisborg et al. 2003; Chatenoud et al. 1998; Himmelberger et al. 1978; Kline et al. 1977). The lack of association in our study could be explained by the fact that we defined smoker women as those who smoked at any time during pregnancy. Therefore, we were not able to separate women who smoked during pregnancy from those who quit.

The lack of association between SA and alcohol consumption reported in our study is only apparent in contrast with the available epidemiological evidence supporting a clear link between alcohol intake and an increased risk of SA (discussed in reference Henriksen et al. 2004). Only 6 out of 122 pregnant women in our study population reported alcohol intake, and these women reported to drink only occasionally (one glass of wine) before they became aware of being pregnant. Indeed, the size of our study, the low proportion of drinkers among pregnant women, and the small amount of alcohol intake reported prevent any meaningful statistical evaluation of the association between alcohol consumption and SA.

We used the chromosome aberration assay in our study as a marker of genetic damage since women were continuously exposed at the workplace and therefore results were not affected by instability of measured genome damage over time. Chromosomal aberration frequency showed an increase for the radiation-exposed groups over referent women. Detected values of reference group were in agreement with historical values for R Croatia (Kašuba et al. 1995). Our findings revealed the interesting fact that chromosomal aberration frequency in peripheral lymphocytes failed to show any difference between radioisotopes and X-rays- exposed women. Therefore, the higher rates of spontaneous abortions detected in radioisotopes compared to X-rays-exposed women suggest that either other biological mechanisms (other than those reflected by the chromosome aberration assay) are involved in the occurrence of the adverse pregnancy outcome or that peripheral lymphocytes are not a reliable surrogate tissue for the embryo.

Reproductive health risk after occupational exposure to radioisotopes should be considered not just as a risk of exposure to low doses of ionizing radiation, but as a complex exposure to radiation and genotoxic/teratogenic chemical agents. Special emphasis should be placed on evaluation of such risk according to gestational age, time of exposure, and the amount of chemical agent that can reach the fetus in relation of its placental transmissibility and the biokinetics of the radioisotope in the conceptus. Special concern should be taken, as non-radioactive isotopes of

used elements are trace elements with significant influence on the human physiology because of their imbalanced concentrations.

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