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Stillbirth and chemical exposure of pregnant workers

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GOULET L, THÉRIAULT G. Stillbirth and chemical exposure of pregnant workers. *Scand J Work Environ Health* 1991;17:25—31. A case-referent study was conducted among women in health, personal services, agriculture, and manufacturing industries. Stillbirths (N = 227) were matched with live births (N = 227) on mother's age, gravidity, and socioeconomic status. Exposure was assessed by workplace visits, telephone calls, or estimations. Conditional logistic regression analyses were used which controlled for maternal education, race, cigarette and alcohol consumption, and previous stillbirths. The results showed a significant decreased risk of stillbirth for hairdressers [odds ratio (OR) 0.1, 95 % confidence interval (95 % CI) 0.0—0.3] and garment workers (OR 0.2, 95 % CI 0.1—0.8). Women in metal-electrical-chemical industries (OR 5.1, 95 % CI 1.0—26.4) and those with low-level exposure to pesticides or germicides (OR 3.1, 95 % CI 1.1—8.6) had an increased risk. Ergonomic factors could be related to some of these findings.

Key words: ergonomic factors, occupation.

In 1985 the Province of Quebec in Canada had an incidence of stillbirth (≥ 20 weeks of gestation) of 5.3 per 1000 total births (1). Along with neonatal deaths, stillbirths ranked fourth among causes of potential years of life lost, after cancer, cardiovascular diseases, and accidents (2). The growing number of women who choose to continue their professional activities during pregnancy justifies the concern as to what burden the work environment may put on the life of the fetus. Of all occupational exposures, chemicals are particularly suspect of potential fetotoxic effects. Their use is widespread, most of them cross the placenta, and many have caused fetal damage in laboratory experiments.

Several maternal occupations have been associated with an increased risk of stillbirth, for example, manufacturing (3), pharmaceutical laboratory work (4), and leatherwork (5). McDonald et al (6) reported an excess risk of stillbirth for saleswomen, sports-women and dancers, and agriculture, horticulture, leather and textile industry workers. Specifically, exposure to the following five chemicals has been associated with an excess of stillbirth in human studies: solvents (chlorinated hydrocarbons and petroleum products) (7), lead (8—10), butiphos (a herbicide) (11), formaldehyde (12), and hexachlorobenzene (13).

These observations have led us to address the following question: Does occupational exposure to certain chemicals, during pregnancy, increase the risk of stillbirth?

Methods

In 1986 we conducted a case-referent study using data from a large study, the Montreal survey on pregnancy and work (14). In the Montreal survey, 56 067 women were interviewed over a two-year period (May 1982—May 1984), after delivery or spontaneous abortion, in 11 hospitals of the metropolitan area of Montreal. Interviews were conducted by trained nurses, and questions were asked about personal, social, and occupational factors for both current and previous pregnancies. Information was collected on 104 649 pregnancies.

Our case-referent study was conducted among women working full-time (> 30 h/week) for at least two weeks at the beginning of their pregnancy in the four occupational sectors of health services, personal services, agriculture, and manufacturing industries. Twin pregnancies were excluded from the study. A total of 227 stillbirths of 20 weeks of gestation or more without major malformations were matched with 227 live births without major malformations on mother's age (± 2 years), gravidity (1, 2, 3, ≥ 4), socioeconomic status, hospital, and period of birth (prior to May 1982 or between May 1982 and May 1984). As a control for socioeconomic status, the reference mothers were selected from the same occupational sector as the cases. The occupational sectors were divided into three groups, namely, health services, personal services and agriculture, and manufacturing industries.

During the study period, two subjects had more than one stillbirth which fit the eligibility criteria. Only one stillbirth was selected at random for each subject.

Pregnancies dated back as far as 1961. More than 50 % were recorded after 1980 (57.7 % for cases and 55.9 % for referents). Compared with the referents,

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more cases were observed before 1970 (3.5 versus 0.9 %).

The mother's occupational exposure was defined by her occupation and by her specific exposure to chemicals. Occupations during pregnancy, recorded as for the Canadian census, were coded by an experienced clerk (6). The standard occupational classification (15) and the standard industrial classification (16) were used for the coding. For the purpose of our project, the mothers' occupations were categorized into 20 groups.

Chemical exposure was assessed blindly according to the name of the employer and the job description given by the mother during the interview. Field inquiries were made by visits to the workplace or by telephone calls for 71 % of the subjects. (See table 1.) Telephone calls were used in the assessment of the exposure of nurses and nurse's aids working on acute care wards and sewing machine operators in garment industries. Estimations by extrapolation were required for 29 % of the subjects because the workplaces could not be found or because the women had worked outside Quebec during the index pregnancy. The methods used to assess the exposure of the cases and referents were comparable.

Chemical exposure assessment was performed by two industrial hygienists and one occupational health physician. The commercial products to which the subjects were occupationally exposed were recorded, and their chemical compositions determined. For the purpose of the analysis, chemical exposures were classified into 10 categories: aliphatic solvents, aromatic solvents, detergents, plastics, pesticides or germicides, oils, metals, gas, other potentially fetotoxic chemicals, and nonfetotoxic chemicals (eg, fabric dust).

The maximal intensity reached during the period of use of each chemical was determined. The intensity of chemical exposure was expressed as light [less than or equal to one-third of the threshold limit value (TLV) (17)], moderate (more than one-third of the TLV but less than the TLV), and high (equal to or more than the TLV). This classification, based on the assumption that exposure to at least one-third of the TLV may have important biological consequences for the development of the fetus, has been proposed by Holmberg et al (18). It was then used by Eskenazi et al (19) and has recently been refined by McDonald et al (20).

The frequency of chemical exposure was also recorded and categorized as frequent (at least once a day), occasional (less than once a day but at least once a week), or rare (less than once a week). The timing and duration of the exposure could not be assessed. Exposure was recorded as it occurred on a typical workday. It is important to bear in mind, as Battaglia (21) suggested, that exposure to a chemical pollutant at any time during pregnancy could lead to effects that can be observed only at the perinatal period, depending on the mechanism of action of the substance.

The grading of all the exposures was based on subjective judgments. The hygienists and the occupational health physician discussed the findings in order to standardize their grading. They were unaware of the case-referent status of the subject during the grading process. Estimations were carried out with the use of job titles and descriptions and chemical exposure profiles developed by McDonald et al (22).

Conditional logistic regression analyses were performed which controlled for the following potential confounding variables: maternal education (elementary school, high school, college, university), race (Caucasian, black, other), cigarette smoking (0, 1–9, 10–19, ≥ 20 cigarettes/d) and alcohol consumption (0, 1, 2–3, > 3 drinks/week) during pregnancy, and previous stillbirths (yes, no). Odds ratio (OR) estimates and 95 % confidence intervals (95 % CI) were calculated with the use of the standard errors of the regression coefficients. Statistical significance was tested with the likelihood ratio statistic. For each maternal chemical exposure, the base-line category was the absence of exposure. In a matched case-referent study with a polytomous independent variable, odds ratios for a specific level of exposure are calculated as a weighted sum of all discordant pairs involving that level of exposure (23). All of the analyses were done with EPIC (epidemiological computing package) (24, 25).

Separate analyses were carried out for two groups of stillbirths defined according to their gestational age [20–27 weeks of gestation (124 cases), ≥ 28 weeks of gestation (103 cases)]. This decision was guided by the findings of Shapiro & Bross (26), who observed that, for stillbirth, the strength and interactive effect of some risk factors differ from one gestational age to the other. Fetuses of 28 weeks of gestation or more had higher risk levels when compared with those of 20–27 weeks of gestation.

Table 1. Case and reference mothers according to the method used to assess chemical exposure.

Method	Cases		Referents		Total	
	N	%	N	%	N	%
Visits	84	37.0	89	39.2	173	38.1
Telephone calls	70	30.8	79	34.8	149	32.8
Estimations	73	32.2	59	26.0	132	29.1
Total	227	100.0	227	100.0	454	100.0

Results

As far as maternal occupation is concerned (table 2), the decreased risk of stillbirth observed for hairdressers in both gestational age groups was statistically significant when all stillbirths were combined (adjusted OR 0.1, 95 % CI 0.0–0.3, $P=0.01$). For stillbirths of 20–27 weeks of gestation, none of the results were significant. A decreased risk of stillbirth of ≥ 28 weeks

of gestation was observed for garment workers (adjusted OR 0.2, 95 % CI 0.1–0.8, $P=0.02$). Working in metal, electrical, or chemical industries increased the risk of stillbirth of ≥ 28 weeks of gestation with an adjusted OR of 5.1 (95 % CI 1.0–26.4, $P=0.049$).

Table 3 shows the risk of stillbirth associated with the maximal intensity of chemical exposure by gestational age. When all stillbirths were combined, exposure to a low level of metals decreased the risk (adjusted OR 0.3, 95 % CI 0.1–0.8, $P=0.02$). For stillbirths of 20–27 weeks of gestation, none of the results were significant. For stillbirths of ≥ 28 weeks of gestation, exposure to a low level of pesticides or germicides increased the risk (adjusted OR 3.1, 95 % CI 1.1–8.6, $P=0.03$).

Discussion

With respect to maternal occupation, the decreased risk of stillbirth observed for hairdressers (≥ 20 weeks of gestation) and garment workers (≥ 28 weeks of gestation) has been reported by Schilling & Lallich in an-

other study (3). Hairdressers are exposed to low and moderate levels of solvents and to low levels of metals (found in some hair dyes). None of these exposures can explain the protective effect observed in this category of pregnant workers. On the other hand, among garment workers, no subject was exposed to moderate or high levels of chemicals, compared with 59 % for other manufacturing workers with whom they were matched. As long as exposure to certain chemicals is associated with an increased risk of stillbirth, the fact that garment workers are not exposed to a substantial level of any chemical could have resulted in a decreased risk of stillbirth.

In our study, 80 % of the metal-electrical-chemical workers were exposed to a moderate or high level of solvents and metals, mainly in soldering activities. Only 11 % of their matched pairs were exposed to the same levels of chemicals. No specific solvent could be identified, but inorganic lead and cadmium were the main metals used. Both metals have been associated with stillbirth in studies of animals (27) and humans (8–10). Recently, Savitz et al (28) found an increased risk of

Table 2. Odds ratios (OR) and 95 % confidence intervals (95 % CI) by maternal occupation and gestational age.

Maternal occupation	Stillbirth								
	20–27 weeks of gestation			≥ 28 weeks of gestation			≥ 20 weeks of gestation		
	Discor- dant pairs	OR ^a	95 % CI	Discor- dant pairs	OR ^a	95 % CI	Discor- dant pairs	OR ^a	95 % CI
<i>Health services</i>									
Physicians, dentists' nurses and nurse's aids	4/7	2.0	0.3–15.8	6/7	0.7	0.2–3.1	10/14	1.0	0.4–3.1
Operating room nurses	1/1	0.6	0.0–30.2	1/0	-	-	2/1	0.7	0.0–11.7
Therapists	2/3	0.2	0.0–4.4	3/2	1.7	0.2–14.2	5/5	1.3	0.3–5.7
Laboratory technicians	1/0	-	-	3/3	1.2	0.2–8.2	4/3	2.8	0.5–16.5
Radiology technicians	2/0	-	-	0/2	-	-	2/2	0.2	0.0–2.4
Dental hygienists	3/1	1.3	0.1–28.2	0/0	-	-	3/1	1.2	0.1–14.9
Others	1/2	0.3	0.0–7.3	4/3	1.5	0.3–9.4	5/5	0.6	0.1–2.9
<i>Personal services</i>									
Food preparation and service	8/6	5.7	0.3–10.7	5/4	1.3	0.3–6.9	13/10	2.6	0.7–9.4
Hairdressers	2/6	0.3	0.1–1.7	1/6	0.1	0.0–1.4	3/12	0.1	0.0–0.3*
Cleaners and janitors	3/4	0.8	0.2–1.7	5/5	1.2	0.2–7.1	8/9	1.1	0.3–4.4
Laundry and dry cleaning	2/0	-	-	2/0	-	-	4/0	-	-
Child care workers	2/3	1.1	0.1–21.4	3/3	1.3	0.1–24.0	5/6	0.5	0.1–3.0
<i>Agriculture</i>									
Agriculture/horticulture	2/0	-	-	4/2	4.2	0.3–61.8	6/2	3.9	0.5–31.9
<i>Manufacturing</i>									
Food and beverages	1/1	0.3	0.0–7.8	1/2	0.4	0.0–4.9	2/3	0.5	0.1–3.5
Rubber and plastics	2/0	-	-	1/1	0.9	0.1–17.2	3/1	3.0	0.3–30.8
Leather	3/5	1.4	0.2–8.8	5/2	2.6	0.5–14.3	8/7	1.6	0.5–4.9
Textile	3/5	0.5	0.1–2.4	5/2	2.6	0.4–15.4	8/7	1.1	0.4–3.2
Clothing	15/13	0.9	0.4–2.2	5/17	0.2	0.1–0.8*	20/30	0.6	0.3–1.1
Metal — electrical — chemical	6/8	0.8	0.2–2.9	9/2	5.1	1.0–26.4*	15/10	1.9	0.8–4.6
Others	8/6	1.7	0.5–6.2	5/5	1.1	0.3–3.8	13/11	1.2	0.5–2.8

^a Adjusted for maternal education, race, cigarette smoking, alcohol consumption, and previous stillbirths.

* $P<0.05$.

Table 3. Odds ratios (OR) and 95 % confidence intervals (95 % CI) by maternal exposure and gestational age.

Maternal exposure	Stillbirth								
	20—27 weeks of gestation			≥ 28 weeks of gestation			≥ 20 weeks of gestation		
	Discor- dant pairs	OR ^a	95 % CI	Discor- dant pairs	OR ^a	95 % CI	Discor- dant pairs	OR ^a	95 % CI
Aliphatic solvents									
Low level	18/21	0.8	0.4—1.7	21/22	0.9	0.5—1.8	39/43	0.9	0.6—1.5
Moderate level	16/15	1.0	0.5—2.4	8/6	0.9	0.4—2.2	24/21	1.0	0.6—1.9
High level	2/2	0.9	0.1—7.0	3/0	.	.	5/2	2.5	0.5—13.3
Aromatic solvents									
Low level	11/6	1.3	0.4—4.1	11/6	1.5	0.5—4.3	22/12	1.4	0.7—3.1
Moderate level	6/7	1.1	0.3—4.1	5/5	1.2	0.3—4.3	11/12	1.1	0.4—2.6
High level	2/2	1.0	0.1—8.0	3/0	.	.	5/2	2.6	0.5—13.7
Plastics									
Low level	14/16	0.6	0.3—1.4	16/12	1.3	0.6—2.9	30/28	0.8	0.5—1.4
Moderate level	1/4	0.2	0.0—2.1	4/4	0.9	0.2—3.9	5/8	0.6	0.2—1.9
High level	1/0	.	.	1/0	.	.	2/0	.	.
Pesticides/germicides									
Low level	16/10	1.6	0.6—4.1	16/8	3.1	1.1—8.6*	32/18	1.8	0.9—3.4
Moderate level	5/3	1.7	0.4—8.0	2/2	2.7	0.2—29.9	7/5	1.5	0.4—5.3
High level	.	.	.	1/0	.	.	1/0	.	.
Oils									
Low level	12/16	0.6	0.3—1.4	18/16	1.1	0.5—2.3	30/32	0.9	0.5—1.5
Moderate level	2/1	2.7	0.1—87.8	2/1	3.2	0.2—44.9	4/2	2.1	0.3—15.1
Metals									
Low level	4/8	0.3	0.1—1.1	1/5	0.2	0.0—1.5	5/13	0.3	0.1—0.8*
Moderate level	4/3	0.9	0.2—5.1	4/0	.	.	8/3	2.3	0.6—9.1
High level	1/0	.	.	.	.	.	7/0	.	.
Gas									
Low level	2/3	0.3	0.0—2.3	.	.	.	2/3	0.5	0.1—2.9
Moderate level	3/4	0.6	0.1—2.9	2/2	0.9	0.1—8.0	5/6	0.8	0.2—2.8
Detergents									
Low level	13/14	1.0	0.4—2.3	13/11	1.0	0.4—2.4	26/25	1.1	0.6—2.0
Other fetotoxic chemicals									
Low level	17/17	1.0	0.5—2.3	16/15	1.3	0.6—2.7	33/32	1.2	0.7—2.0
Moderate level	11/8	1.1	0.4—3.2	7/7	1.1	0.4—3.1	18/15	1.0	0.5—2.1
High level	2/0	.	.	2/0	.	.	4/0	.	.
Nonfetotoxic chemicals									
Low level	18/23	0.7	0.4—1.4	12/22	0.5	0.3—1.2	30/45	0.7	0.4—1.1
Moderate level	1/1	0.7	0.0—12.7	1/1	1.9	0.1—63.1	2/2	1.3	0.1—10.8
High level	.	.	.	1/1	0.7	0.1—22.2	1/1	1.0	0.1—16.7

^a Adjusted for maternal education, race, cigarette smoking, alcohol consumption, and previous stillbirths.* $P < 0.05$.

stillbirth among women who were occupationally exposed to lead. In human studies, occupational exposure to solvents has been associated with fetotoxic effects such as birth defects of the urinary tract (29) and the central nervous system (30—31). The excess risk of stillbirth among metal-electrical-chemical workers could have resulted from exposure to chemicals. The same hypothesis has been suggested to account for the excess of spontaneous abortion observed in this occupational group (32—36).

Clarke & Mason (5) and McDonald et al (6) have reported an excess risk of stillbirth for leatherworkers. Exposure to fetotoxic chemicals was suggested to explain the increased risk. In our study, leatherworkers showed an increased risk of stillbirth which was not statistically significant. We found that leatherworkers

were exposed to moderate and high levels of aromatic solvents (neoprene, xylene, petroleum products, and other aromatic hydrocarbon solvents), mainly in the manufacturing of shoes and handbags. A Soviet study reported that exposure to chlorinated hydrocarbons and petroleum products among pregnant workers putting glue on rubber products was associated with an excess risk of perinatal death (mainly stillbirth) (7).

Exposure to a low level of pesticides or germicides increased the risk of stillbirth. For half of the cases exposed to this category of chemicals, the specific exposure was sodium hypochlorite (Javex®). Sodium hypochlorite is an irritant, and, to our knowledge, it has never been associated with any fetotoxic effects in human or animal studies.

Since we made multiple comparisons, some of the statistically significant results that we observed may have occurred by chance. The following four series of independent tests were performed: (i) 40 tests (20 occupations and two gestational age groups), (ii) 52 tests (26 exposure categories and two gestational age groups), (iii) 20 tests [20 occupations and one gestational age group (all stillbirths)], and (iv) 26 tests [26 exposure categories and one gestational age group (all stillbirths)]. At the 5 % level of significance, some associations would be expected to be significant by chance, two in the first two series and one in each of the other. We observed two significant associations in the first series and one in the last three. The role of chance in the significant associations that were observed in our study could therefore not be excluded. However the concordance of our results with those of other studies suggests that they may not be due to chance alone.

The small number of cases in the data set used in our study ($N=227$), coupled with the low frequency of biologically significant levels of chemical exposures (ranging from 0 % for detergents to 14 % for aliphatic solvents), resulted in imprecise estimates of effects illustrated by wide confidence intervals. The adjustment for potential confounding variables added to the problem of precision in the estimates.

Selection bias was very likely of no concern in our study. Even if approximately 50 % of the mothers who gave birth to a dead fetus actually participated in the study (6), compared with about 90 % for mothers of live births (32), the main reason for the difference in the participation rates would be that mothers of stillbirths did not stay long enough in the hospital to be interviewed or that clinical nurses thought that their emotional status was not stable enough for them to participate in the interview. It therefore seems unlikely that exposure to chemical substances could have differentially motivated the case and reference mothers to participate in the study.

We tried to minimize information bias by using data that were as objective as possible (job title and description) and by performing a blind assessment of chemical exposure in the workplace. However, since half of the pregnancies were recorded before 1980, some exposures may have been identified erroneously. Moreover, our method of categorizing exposures based on subjective judgment may have resulted in some misclassifications. In both cases, we believe that the errors were random, and consequently the measured effects may be biased towards the null.

The possibility of confounding by personal factors has been taken into account in the design (matching on mother's age, gravidity, and socioeconomic status) and in the analysis (race, education, cigarette and alcohol consumption, and previous stillbirth). The selection of referents in the same occupational sector as that of the case raises the issue of overmatching. Overmatching occurs when one matches for a variable that

is not a confounding variable. In such a situation, matching results in a loss of study efficiency. In our study, socioeconomic status as measured by mother's occupation met the definition of a confounding variable in that it has been identified in the literature as an independent risk factor for stillbirth, and, on the basis of *a priori* observations, the nature and the intensity of the chemical exposures varied from one occupational sector to the other. Socioeconomic status has been qualified, with reason, as an "epidemiologic embarrassment" (37). Socioeconomic status is an amalgam of interrelated behavioral and environmental factors that influence pregnancy outcome. As far as research in perinatality is concerned, mother's occupation is considered to be one of the best indicators of socioeconomic status (38). Matching on the socioeconomic status measured by the mother's occupation was one way of controlling for unmeasured risk factors such as adequacy of prenatal care and nutrition, and for unknown risk factors associated with this variable. Finally, because of the heterogeneity of chemical exposures within each occupational sector, the consequences of overmatching, if overmatching was ever present, was considerably reduced.

Exposure to other occupational factors may explain the decreased risk of stillbirth observed for hairdressers and the increased risk of stillbirth found for mothers exposed to sodium hypochlorite. In this study, hairdressers were compared with women working in the same occupational sector, specifically with agricultural workers, with laundry and dry-cleaning workers, with food preparation and service workers, with cleaners and janitors, and with child care workers. These jobs all seem to be more physically demanding than hairdressing. Likewise, the women exposed to sodium hypochlorite were almost exclusively found in the following jobs: nurses and nurse's aids, waitresses, laundry workers, and cleaners, all of which are physically demanding jobs. Therefore, we suggest as an explanatory hypothesis that ergonomic factors could explain the association between exposure to a low level of pesticides or germicides and stillbirth. This hypothesis could partly account for the decreased risk of stillbirth observed for hairdressers. Physically demanding jobs have been associated with spontaneous abortion (<28 weeks of gestation) (39) and stillbirth among rural women (40).

The possibility that the response to chemical exposure varies with gestational age could not be verified. Even if odds ratios calculated for stillbirths of 28 weeks of gestation or more were larger, the overlapping of the confidence intervals could indicate that risks are actually similar in both groups.

In conclusion, the results of this study suggest that exposure to metals and solvents among metal-electrical-chemical workers and leatherworkers could increase the risk of stillbirth. Because of the small proportion of pregnant workers exposed to biologically significant levels of chemicals, further epidemiologic studies in

that field must include more subjects. Studies looking at the association between ergonomic factors, especially physically demanding jobs, and stillbirth are also indicated. The possibility of an interaction between chemical exposures, or between chemical exposures and ergonomic factors, would also be important to examine in further research.

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