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# Pregnancy Outcome Following Gestational Exposure to Organic Solvents

## A Prospective Controlled Study

Sohail Khattak, MD, FRCPC

Guiti K-Moghtader, BSc

Kristen McMartin, MSc

Maru Barrera, PhD

Debbie Kennedy, MD

Gideon Koren, MD, FRCPC

**M**ANY WOMEN OF CHILD-bearing age are occupationally exposed to organic solvents. The most important women-dominated occupations with potential chemical exposures are health care professions and work tasks in the clothing and textile industries, all of which involve exposure to organic solvents.<sup>1,2</sup>

Many industrial solvents are teratogenic in laboratory animals. There are reports of limb and central nervous system defects in mice, marked developmental toxic effects and retardation of skeletal growth in rats, and congenital malformations in rabbits.<sup>3-10</sup> However, the animal studies typically use high doses of single solvents and a variety of routes of administration. In the occupational setting, exposure usually occurs to a multitude of solvents at much lower doses by inhalation, making extrapolation from animals to humans problematic.

A recent meta-analysis of studies in humans detected an apparent increased risk of major malformations and a trend toward increase in rates of miscarriage<sup>11</sup> in women who self-reported occupational exposures to solvents. However, all available published experience is based on retrospec-

**Context** Numerous women of childbearing age are exposed occupationally to organic solvents. Previous retrospective studies have reported conflicting results regarding teratogenic risk.

**Objective** To evaluate pregnancy and fetal outcome following maternal occupational exposure to organic solvents.

**Design** A prospective, observational, controlled study.

**Setting** An antenatal counseling service in Toronto, Ontario.

**Patients** One hundred twenty-five pregnant women who were exposed occupationally to organic solvents and seen during the first trimester between 1987 and 1996. Each pregnant woman who was exposed to organic solvents was matched to a pregnant woman who was exposed to a nonteratogenic agent on age ( $\pm 4$  years), gravidity ( $\pm 1$ ), and smoking and drinking status.

**Main Outcome Measure** Occurrence of major congenital malformations.

**Results** Significantly more major malformations occurred among fetuses of women exposed to organic solvents than controls (13 vs 1; relative risk, 13.0; 95% confidence interval, 1.8-99.5). Twelve malformations occurred among the 75 women who had symptoms temporally associated with their exposure, while none occurred among 43 asymptomatic exposed women ( $P < .001$ ). (One malformation occurred in a woman for whom such information was missing.) More of these exposed women had previous miscarriage while working with organic solvents than controls (54/117 [46.2%] vs 24/125 [19.2%];  $P < .001$ ). However, exposed women who had a previous miscarriage had rates of major malformation that were similar to exposed women who had no previous miscarriage.

**Conclusions** Occupational exposure to organic solvents during pregnancy is associated with an increased risk of major fetal malformations. This risk appears to be increased among women who report symptoms associated with organic solvent exposure. Women's exposure to organic solvents should be minimized during pregnancy. Symptomatic exposure appears to predict higher fetal risk for malformations.

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tive studies.<sup>12-14</sup> The present study is the first to prospectively evaluate pregnancy and fetal outcome following maternal occupational exposure to organic solvents.

### METHODS

The study group consisted of all pregnant women occupationally exposed to

**Author Affiliations:** The Motherisk Program, Division of Clinical Pharmacology and Toxicology (Drs Khattak, Kennedy, and Koren, Mr Moghtader, and Ms McMartin), and the Department of Psychology (Dr Barrera), The Hospital for Sick Children, and the University of Toronto, Toronto, Ontario.

**Corresponding Author and Reprints:** Gideon Koren, MD, FACCT, FRCPC, Division of Clinical Pharmacology and Toxicology, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8.

organic solvents and counseled between 1987 and 1996 by the Motherisk Program at the Hospital for Sick Children in Toronto, Ontario. Each mother who was occupationally exposed to organic solvents was paired with a pregnant woman who was exposed to a nonteratogenic agent, attended the Motherisk clinic, and matched the index woman on age ( $\pm 4$  years), gravidity ( $\pm 1$ ), and smoking and drinking status. A nonteratogenic agent was defined as a medicinal or environmental substance that has been proved not to increase the baseline risk for major malformations or miscarriages. Organic solvents to which women were occupationally exposed included aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene, vinyl chloride, acetone, and related compounds.

During the initial assessment (at or up to several weeks after the point at which pregnancy was determined), we collected all available data on exposure during pregnancy to medicinal and recreational drugs, smoking, alcohol, lifestyle, medical and nutritional status, and sexually transmitted diseases. Other reproductive hazards were elucidated by taking a detailed medical, genetic, and obstetric history. Although we recorded the medical history of the father of the child and his use of drugs, most fathers did not work with organic solvents and were not exposed to medications. Details concerning the time of exposure to organic solvents were recorded for determination of temporal relationship between exposure and conception. The details on chemical exposure were recorded, including occupation, chemicals involved, duration of exposure, type of protective equipment used, and other safety features, including ventilation fans. Adverse effects were defined as those known to be caused by organic solvents (eg, irritation of the eyes or respiratory system, breathing difficulty, headache). Temporal relationship to exposure was investigated to separate these symptoms from those associated with pregnancy.

The postnatal assessment occurred between 6 and 9 months after the expected date of confinement. During this interview,

the mother was questioned about the course of her pregnancy subsequent to the first meeting. This included verification of length of exposure to organic solvents during pregnancy. Possible medical or obstetric complications and details about the birth and the prenatal period were collected. All major malformations were recorded and corroborated by a written report from the physician caring for the child. The attainment of developmental milestones was recorded with the use of the Denver Scale from the maternal reports.

The following cases were excluded from the cohort of organic solvent exposure: paternal exposure only; short-term maternal exposure that did not occur in an occupational setting (eg, household painting); women whose main task at work included heavy lifting, which might increase the rate of miscarriages; cases in which during the first interview it became apparent that the exposure to organic solvents had occurred only before conception; any case in which during the first interview (ie, during the first trimester) or the second interview (postnatally) it became evident that the woman was exposed to known teratogen(s) or neurotoxin(s) during the index pregnancy; and any case in which the mother refused to give consent for participation in our follow-up program. The time of conception was verified by identification of the last menstrual period. When the time of the last menstrual period was questionable, an ultrasonographic examination was performed following the counseling session.

The primary outcome of interest was the rate of major malformations. A major malformation was defined as any anomaly that has an adverse effect on either the function or the social acceptability of the child. The expected rate is 1% to 3%. Secondary outcomes of interest were the rates of minor malformations, miscarriages or therapeutic abortions, and premature births ( $<37$  weeks' gestation); birth weight and gestational age at delivery; and presence of fetal distress or other neonatal complications. A minor malformation was defined as a structural anomaly that does not pose any significant health or social burden. Fetal dis-

tress was defined as the presence of meconium and/or abnormal fetal heart rate monitoring during delivery or the requirement of resuscitation or a neonatal intensive care unit. Neonatal complications were defined as health complications that were not structural in nature. This analysis was approved by the hospital's research ethics board. The physician who counseled the woman, as well the consultation letter sent to her physician, introduced the planned follow-up program. At the time of follow-up, subjects were asked for their consent for the follow-up interview. Rates of major malformations in the study group were compared with those in the matched control group by  $\chi^2$  analysis. Relative risk was calculated with 95% confidence intervals. Secondary end points (ie, rates of miscarriage, prematurity, and birth weight) were compared by  $\chi^2$  or Mann-Whitney rank sum test whenever appropriate. All data are expressed as mean (SD).

## RESULTS

Between 1986 and 1996, 256 women were seen in the Motherisk Program because of occupational exposure to organic solvents. Of these, 42 women (16.4%) were not pregnant at the time of the study, 26 (10.2%) were lost to follow-up, 18 (7%) refused to consent to participation in the study, and 45 (17.6%) were excluded from the study, based on our exclusion criteria. The remaining 125 women were matched to 125 control women. All exposed women worked with organic solvents for at least the entire first trimester of pregnancy. The most common occupations were factory worker ( $n = 37$ ), laboratory technician ( $n = 21$ ), professional artist/graphic designer ( $n = 16$ ), and printing industry worker ( $n = 14$ ) (TABLE 1). The organic solvents most commonly involved were aliphatic and aromatic hydrocarbons, phenols, trichloroethylene, xylene, vinyl chloride, acetone, and related compounds.

The characteristics of subjects in the 2 groups are shown in TABLE 2. There was a statistically significant difference in the rates of previous miscarriage between women in the exposed vs control groups. Subanalysis revealed that in most wom-

en, the previous miscarriages occurred during occupational exposure to organic solvents. Previous miscarriage occurred prior to such work in only 8 cases, yielding a significantly higher rate of previous miscarriage among those working with organic solvents (Table 2). As a result, women exposed to organic solvents had a lower parity prior to the index pregnancy despite similar gravidity (Table 2). However, for the rest of the characteristics, there were no differences between the 2 groups (Table 2). During the index pregnancy, there were significant differences in the birth weight and rates of fetal distress and neonatal complications (mainly eczema) (TABLE 3).

There were significantly more major malformations among the exposed women compared with the control group (Table 3). The relative risk of major malformation among the exposed women was 13.0 (95% confidence interval, 1.8-99.5). The major malformations in the study group are detailed in TABLE 4. Rates of major malformations did not differ between women who had a previous miscarriage while working with organic solvents vs those who did not have a previous miscarriage.

Among the 125 women occupationally exposed to organic solvents, 75 reported symptoms temporally associated

with their exposure, 43 were asymptomatic, and in 7 cases, such information was missing. Twelve of the 13 major malformations occurred among the symptomatic women vs 0 among the 43 asymptomatic women ( $P < .001$ ). In a further subanalysis, women exposed to organic solvents were stratified according to whether they were exposed to organic solvents for more than 7 months or for 3 to 7 months. Sixteen women who were exposed for more than 7 months had labor with fetal distress requiring resuscitative measures vs only 1 among those with shorter exposures ( $P = .002$ ). Also, birth weights were lower among those with longer exposure (mean [SD], 2975.2 [976.2] g vs 3431.4 [579.3] g;  $P = .03$ ). Gestational age was also lower, although differences were not significant (mean [SD], 38.0 [7.41] weeks vs 40.0 [1.86] weeks;  $P = .60$ ).

**Table 1.** Breakdown of Various Occupations in Organic Solvent-Exposed Group

Occupations	No. of Women	Description
Factory worker	37	Wide variety of industry, including manufacturing, cosmetics, tooling, automotive, paint manufacturing
Laboratory technician	21	Also included some researchers and research students
Artist	16	Wide variety of graphic designers, including lithographers and screen printers (all were working in business setting, not as a hobby)
Printing industry	14	Various jobs dealing with printing process (ie, handling ink and other printing-related jobs)
Chemist	13	Chemists dealing with various chemicals in variety of chemical industries
Painter	8	Various painting-related jobs not in a factory setting
Office worker	4	Included only those workers who were working in direct presence of chemicals and were reporting symptoms
Car cleaning service	3	Only workers exposed to organic solvents
Veterinary technician	3	Only workers exposed to organic solvents
Orthotist	2	Manufacturing orthotics
Funeral home service	2	Only workers exposed to organic solvents
Carpenter	1	Only workers exposed to organic solvents
Social worker	1	Only workers exposed to organic solvents

**Table 2.** Characteristics of Subjects Exposed to Organic Solvents During Pregnancy and Pregnant Control Subjects\*

Characteristics	Exposed Women (n = 125)	Control Women (n = 125)	P Value
Age at conception, y	29.4 (3.97)	29.5 (3.76)	.51†
Gravidity	1.98 (1.24)	1.94 (1.03)	.60†
Previous parity	0.36 (0.6)	0.6 (0.7)	.04†
Previous miscarriages, %	51	19.7	<.001‡
Previous miscarriages while working with organic solvents, %§	46.2	19.2	<.001‡
Previous induced abortions	0.1 (0.05)	0.2 (0.5)	.25‡
Alcohol use during pregnancy	34 (27.2)	34 (27.2)	>.99‡
Smoking during pregnancy	27 (21.6)	27 (21.6)	>.99‡

\*Data are expressed as mean (SD) except where otherwise noted.

†Data were calculated using the Mann-Whitney rank sum test.

‡Data were calculated using the  $\chi^2$  test.

§In this group (n = 117), we exclude women and their controls who had had miscarriages prior to starting occupations with organic solvents.

**COMMENT**

There are controversial reports regarding fetal outcome following prenatal exposure to organic solvents. Among them are increased rates of miscarriage, central nervous system and cardiovascular malformations, fetal solvent/gasoline syndrome, and perinatal mortality; in addition, maternal fertility is reduced.<sup>2,3,10,13,15-19</sup> Fat-soluble organic solvents can pass through biological membranes, including the placenta.<sup>10</sup> There is a paucity of information regarding the impact of in utero exposure to organic solvents on the developing brain. Animal studies have clearly shown that a variety of solvents readily cross the placenta and that maternal inhalation of organic solvents results in neurodevelopmental deficits in neonatal rodents.<sup>3-8</sup>

Our recent meta-analysis has found that occupational exposure to organic solvents is associated with increased risk of major malformation.<sup>11</sup> We have also shown a trend toward more miscarriages, although it failed to reach statistical significance.<sup>11</sup> Yet, none of the eligible studies was prospective. Recall bias may affect the accuracy of assessment of fetal outcome in such studies. Moreover, the retrospective design of these studies does not allow validation of crucial details regard-

**Table 3.** Pregnancy Outcome in Subjects Exposed to Organic Solvents During Pregnancy and Control Subjects Exposed to Nonteratogenic Agents\*

Characteristics	Exposed Women (n = 125)	Control Women (n = 125)	P Value
Live births	113	115	.64†
Miscarriages	8	6	.78†
Induced abortions	4	4	>.99†
Major malformations	13	1	<.001†
Minor malformations	5	1	.71†
Fetal distress	17/113	6/116	.02†
Gestational age, mean (SD), wk	38.8 (2.7)	39.8 (1.6)	.38‡
Premature births	9/113	3/116	.12†
Birth weight, mean (SD), g	3368 (795)	3536 (542)	.01‡
Birth weight <2500 g	8/113	3/116	.21†
Neonatal complications (eczema)	12/113	2/116	.01†

\*Data are expressed as number except where otherwise noted.

†Data were calculated using the  $\chi^2$  test.

‡Data were calculated using the Mann-Whitney rank sum test.

ing the nature or extent of the exposure; or of symptoms associated with the exposure. Also, most available retrospective studies did not match patients for smoking, alcohol use, and other potentially confounding reproductive risks.

The Motherisk protocol has allowed us to record in a systematic manner all exposure data and other maternal and paternal medical details at the time of exposure during the first trimester of pregnancy and to follow up pregnancy outcomes prospectively in this cohort. The control group was assessed in an identical manner.

This prospective study confirms the results of our recent meta-analysis.<sup>11</sup> Women exposed occupationally to organic solvents had a 13-fold risk of ma-

ior malformations as well increased risk for miscarriages in previous pregnancies while working with organic solvents. Moreover, women reporting symptoms associated with organic solvents during early pregnancy had a significantly higher risk of major malformations than those who were asymptomatic, suggesting a dose-response relationship. Other factors (eg, type of solvent) might have accounted for the presence of symptoms in some women.

Although some human teratogens have been shown to cause a homogeneous pattern of malformation(s), in other cases no specific syndrome has been described.<sup>19</sup> No homogenous pattern of malformations is obvious from the present study. However, organic solvents, although tra-

**Table 4.** Major Malformations in the Organic Solvent-Exposed Group

Aortopulmonary window, tethered umbilical cord, hemivertebrae
Ventricular septal defect
Laryngomalacia (required multiple hospitalizations)
Congenital deafness and bilateral pelvic-ureter junction obstruction requiring nephrostomy
Clubfoot requiring correction
Diaphragmatic hernia
Neuronal migration defect and focal cortical dysplasia heterotopia
Laryngotracheomalacia (patient required hospitalizations with every episode of cold)
Neural tube defect
Congenital hydronephrosis (required nephrectomy)
Left inguinal hernia requiring surgery
Cloacal extrophy, spina bifida; or pregnancy terminated because of these anomalies
Micropenis

ditionally clustered together, are a diverse group of compounds that should not be expected to cause similar patterns of reproductive toxic effects.

Although more prospective studies will be needed to confirm the present results, it is prudent to minimize women's exposure to organic solvents during pregnancy. Moreover, symptomatic exposure appears to confer an unacceptable level of fetal exposure and should be avoided by appropriate protection and ventilation. Health care professionals who counsel families of reproductive age should inform their patients that some types of employment may influence reproductive outcomes.

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## REFERENCES

- Hemminki K, Axelson O, Niemi M-L, Ahlborg G. Assessment of methods and results of reproductive occupational epidemiology: spontaneous abortions and malformations in the offspring of working women. *Am J Ind Med.* 1983;4:293-307.
- Tikkanen J, Heinonen O. Cardiovascular malformations and organic solvent exposure during pregnancy in Finland. *Am J Ind Med.* 1988;14:1-8.
- Andrew FD, Mahlum DD, Peterson MR. Developmental toxicity of solvent refined alcohol-related hydrocarbons [abstract]. *Toxicol Appl Pharmacol.* 1979;48:A27.
- Green JD, Leong BKG, Laskin S. Inhaled benzene fetotoxicity in rats. *Toxicol Appl Pharmacol.* 1978;46:9-18.
- Hemsworth BN. Embryopathies in the rat due to alkane sulphonates. *J Reprod Fertil.* 1968;17:325-334.
- Hudak A, Ungvary G. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. *Toxicology.* 1978;11:55-63.
- Doe J, Hart D, Wickramaratna S. The teratogenic potential of diethylene glycol mono methyl ether (DOME)

as assayed in the postnatal development test by subcutaneous route in rats. *Toxicologist.* 1983;3:70.

8. John JA, Quest JF, Murray FJ, et al. Effect of inhaled epichlorohydrin on fertility and fetal development in rats and rabbits [abstract]. *Toxicol Appl Pharmacol.* 1980;49:A88.

9. Andrew FD, Montgomery LF, Sikov MR, Hardin BD. Effects of inhalation exposure to ethoxy ethanol on pregnant rats and rabbits. *Toxicologist.* 1981;1:30.

10. Schardein JL. Chemical exposure in pregnancy. In: *Chemically Induced Birth Defects*. New York, NY: Marcel Dekker; 1993:751-775.

11. McMartin KI, Liao M, Kopecky E, Koren G. Pregnancy outcome following maternal organic solvent exposure: a meta-analysis of epidemiological studies. *Am J Ind Med.* 1998;34:288-292.

12. Tikkanen J. Cardiovascular malformations, work attendance and occupational exposures during pregnancy in Finland. *Am J Ind Med.* 1988;14:197-204.

13. Kurppa K. Screening for occupational exposures and congenital malformations. *Scand J Work Envi-*

*ron Health.* 1983;9:89-93.

14. Valciukas JA. The effects of exposure to industrial and commercial solvents on the developing brain and behavior of children's prenatal exposure to toxicants. In: Needleman HL, Ballinger D, eds. *Developmental Consequences*. Baltimore, Md: John Hopkins University Press; 1994:213-232.

15. Lindbohm M-L, Taskinen H, Sallmen M, Hemminki K. Spontaneous abortions among women exposed to organic solvents. *Am J Ind Med.* 1990;17:449-463.

16. Holmberg P. Central nervous system defects in children born to mothers exposed to organic solvents during pregnancy. *Lancet.* 1979;2:177-179.

17. Hanson JVV, Oakley GP. Spray adhesives and birth defects [letter]. *JAMA.* 1976;236:1010.

18. Silberg SL, Ransom DR, Lyon JA, Anderson PS. Relationship between spray adhesive and congenital malformations. *South Med J.* 1979;72:1170-1173.

19. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med.* 1998;338:1128-1137.