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Central nervous defects in two children of mothers exposed to chemicals in the reinforced plastics industry

Chance or a causal relation?

by PETER C. HOLMBERG, M.D., M.Sc.¹

HOLMBERG, P. C. Central nervous defects in two children of mothers exposed to chemicals in the reinforced plastics industry: Chance or a causal relation? *Scand. j. work environ. & health* 3 (1977) 212—214. With the use of a specially designed questionnaire, with the emphasis on occupational exposure to chemical agents at work, a case-referent study was started on 1 June 1976. The series comprised mothers of all children with central nervous defects notified to the Finnish Register of Congenital Malformations and their matched-pair referents. Information was gained by personal interview. By 1 March 1977 information had been gathered from 43 cases and their referents. Two case mothers had been employed in the reinforced plastics industry and had been exposed at work to a combination of styrene, polyester resin, organic peroxides, and acetone. When the number of fertile women in this industry is considered (some 250), along with the low rate of anencephaly and hydrocephalus in the general population — diagnoses made of the children of these case mothers (0.5/1,000 live births in Finland) — this occupational group is strongly overrepresented in the material. The paper is a more-detailed report regarding the two cases. Moreover a third case is mentioned in which the pregnant mother, a juvenile diabetic, had been exposed at home to styrene, polyester resin, and organic peroxides.

Key words: central nervous defects, pregnancy, occupational exposure, reinforced plastics industry.

On 1 June 1976 in Finland an investigation was started concerning the possibility of mothers of children with central nervous defects having been exposed during pregnancy to noxious influences at work. The investigation was designed as a semipro prospective case-referent study and was to cover 12 months.

MATERIAL AND METHODS

The series comprised mothers of all children with central nervous defects notified to the Finnish Register of Congenital Malformations (notification is compulsory). Their matched-pair referents were the mothers whose delivery immediately preceded that of the case-mother in the same maternity welfare district (5). In addition to the information obtained through the Register, supplementary information was collected on exposure of the mother to noxious influences at work. For this purpose the same person personally inter-

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viewed each mother (both case and referent). The interviewer completed a specially designed questionnaire (19 main questions). Furthermore, copies were obtained of all documents relating to the course of pregnancy and delivery of the case mothers.

By 1 March 1977 the series comprised 45 cases, and information had been gathered from 43 of them and their matched-pair referents. (Two case mothers refused to be interviewed.) Two case mothers had been employed in the reinforced plastics industry and had been exposed at work to a combination of styrene, polyester resin, organic peroxides, and acetone. Exposure was further verified by visits to the industries concerned. No similar exposure could be demonstrated for any of the referents.

Case histories

Case 1 was a 19-year-old woman who had worked in the reinforced plastics industry and whose husband was a 26-year-old carpenter employed in the same factory. She was a *primigravida*, *primapara* whose last menstruation before the pregnancy in question began on 20 August 1975. The estimated time of delivery was 27 May 1976. She began her maternity leave on 30 April 1976 and on 12 May 1976 she delivered a boy (weight 3,900 g, length 54 cm).

The child received the following diagnosis: congenital hydrocephalus, anomaly of the right ear, bilateral malformations of the thoracic vertebral column and ribs.

The results of the laboratory tests were the following: (a) Antibodies of the child: rubella (12 May 1976); complement fixation 8; hemagglutinin inhibition 80; rubella (15 June 1976); hemagglutinin inhibition 40; toxoplasma (12 May 1976); complement fixation 4; immunofluorescence 4; listeria (12 May 1976) negative. (b) Antibodies (complement fixation) of the mother (15 June 1976): rubella 4; parotitis 4; herpes simplex 16; toxoplasma 4.

In the third month of pregnancy the mother experienced bronchitis and was given three days of sick-leave and put on penicillin. Otherwise her pregnancy was normal, and she had taken no drugs apart

from iron and vitamin preparations. The mother attended work regularly during pregnancy. At work she grinded, polished and mended reinforced plastic products and was exposed at work to styrene, polyester resin, organic peroxides, acetone, and polishes. In the winter of 1976 she was heavily exposed to styrene for about three days when she cleaned a mold without a face mask.

Case 2 was a 24-year-old woman worker in the reinforced plastics industry whose husband was a 22-year-old welder-plater in the metal industry. She was a *primigravida*, *primapara* whose last menstruation before the pregnancy began on 1 May 1976. The estimated time of delivery was 8 February 1977. On 26 November 1976 she left work at her own request. The child's delivery occurred on 27 December 1976. The child was a girl weighing 2,200 g and 47 cm in length.

The child died during delivery, and anencephaly was diagnosed.

The results of the laboratory tests were the following: Antibodies of the mother: toxoplasma (29 December 1976); complement fixation < 4; listeria (O-agglutination) (29 December 1976) 80; listeria (7 February 1977) 80; listeria culture (placenta) (27 December 1976) negative.

The mother was A Rh negative and the child A Rh positive; the Rh antibodies had been negative when the mother attended the maternity welfare center on 5 August, 16 October and 16 December 1976. The karyotype of both parents was normal.

The pregnancy had been normal with the exception of contractions in the second month of pregnancy. At that time 10 mg of isoxuprin (Duvaldilan®) was prescribed three times a day for one week. Slight edema occurred in the seventh month of pregnancy, and 500 mg of chlorthiazid (Salutrid®) per day was prescribed for one week. The mother worked during most of her pregnancy. In the third month of pregnancy she did manual laminating (hand-rolling) for about three weeks with no face mask and was then exposed to styrene, polyester resin, organic peroxides, and acetone. After this period she did needlework in the same workshop for about one month and then laminated again at varying intervals.

DISCUSSION

In 1974 and 1976 the reinforced plastics industry in Finland employed some 1,800 workers, of whom about 400 were women (4). In 1974 about 60 % of the total female labor force (16 to 64 years of age) belonged to the age group 18 to 44 years. In this group the fertility rate (births per year) was 65 births per 1,000 women (1).

In Finland the reinforced plastics industry does not select female workers by age. Hence it may be concluded that the age group 18 to 44 years is represented in the reinforced plastics industry by approximately 250 women with an annual fertility rate (births per year) of 16. Thus in the nine-month period during which information has been collected from the Register of Congenital Malformations (1 June 1976 to 1 March 1977), about 12 births would be expected among these women.

The rate of anencephaly and hydrocephalus is 0.5 per 1,000 live births in Finland (0.2 and 0.3 per 1,000 live births, respectively) (7). Thus in the group of births concerned the rate was increased more than 300-fold during the nine-month period of the investigation (0.5/1,000 versus 2/12).

In the same series a third suggested case was found, but drawing conclusions about it is even more difficult because of a confounding risk factor. The mother, a 20-year-old *primigravida*, had not worked during her pregnancy, but she had been exposed some six times during her pregnancy to styrene, polyester resin, and organic peroxides when her husband did repair work with reinforced plastic at home in their kitchen. A stillborn child with anencephaly was born in the seventh month of pregnancy. The mother suffered from juvenile diabetes, however, and was receiving insulin therapy. According to recent investigations such an occurrence could be another risk factor with an estimated risk ratio of 10 (3).

Styrene (vinyl benzene) is metabolized to styrene oxide, a substance which has

proved to be mutagenic in bacteria (6, 8). Styrene is structurally related to vinyl chloride. An excess of chromosome aberrations in lymphocytes has been reported among workers exposed to the vinyl chloride monomer (2). In man, as far as is known, no teratogenic activity has been reported for styrene or its metabolites.

I am well aware that the "witch hunt" for teratogens has already led to many overhasty warnings and conclusions. Yet, since the majority of malformations in human subjects remains without a causal explanation (9), every lead towards their clarification seems worth reporting.

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