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An epidemiologic approach to the study of possible teratogenic effects of chemical and physical environments

by Peter C Holmberg MD, Kari Kurppa, MD¹

HOLMBERG PC, KURPPA K. An epidemiologic approach to the study of possible teratogenic effects of chemical and physical environments. *Scand j work environ health* 8 (1982): suppl 1, 89—91. The paper describes the general outlines of a cohort-based case-referent study on possible associations between selected congenital defects and physical or chemical exposures during the first trimester of pregnancy.

Key terms: congenital defects, case-referent study, methodology, occupation.

An epidemiologic study on chemical and physical exposures during the organogenesis of children born with congenital defects has been in progress in Finland since 1976. Initially the data collection considered only exposures during the pregnancy of mothers of children born with central nervous system defects. Successively, other types of congenital defects (ie, oral clefts, selected malformations of the skeletal system, and selected malformations of the cardiovascular system) have been included in the study. The approach is a continuous cohort-based case-referent one.

The Finnish Register of Congenital Malformations

Compulsory notification of all malformations detected in children during the first year of life was introduced in Finland in 1963, the same year in which the Finnish Register of Congenital Malformations was established (3). In addition to these

notifications, a death certificate of every stillborn child must be sent to the Register. Combined data from the notification cards and the death certificates are recorded.

Since 1964 further information has been collected on the prenatal history of children with certain marker defects (oral clefts, skeletal defects, central nervous system defects). A questionnaire is sent to the local maternity welfare center of the mother selected for the study. Each mother of a child born with a marker defect is interviewed according to a standardized schedule. The completed questionnaire and a photocopy of the antepartum record are returned to the Register.

The mother whose delivery preceded that of the case mother in the same maternity welfare district serves as a referent mother, and she is interviewed in an identical manner. As a result, the referents are matched according to the season of birth and the domicile of the mother, but, for reasons described elsewhere (2), not with respect to parity, maternal age, or other factors. Possible differences in the distributions of the nonmatched modifying variables among the case and referent mothers are taken into consideration during the analysis of the data.

The questionnaire of the Register consists of 80 items, the filling out of which

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does not require an unreasonable work load. The routine questionnaire gathers information on, eg, the consumption of drugs and alcohol during pregnancy, and smoking habits. The only occupational factors included are parental occupations and whether or not the mother worked outside the home during pregnancy. Yet, more comprehensive and more specifically focused data can be collected for specified periods and selected target groups, and such data enable the undertaking of special projects and ad hoc studies.

Data collection of the present study

The investigation of associations between congenital defects and environmental exposures uses the Register as its source of primary information. The notification cards and death certificates sent to the Register are checked and selected by a pathologist with experience in teratology. Registry material of the accepted cases is photocopied and filed by the study group of the present special project.

Two experienced interviewers from the Institute of Occupational Health travel around the country and gather the data related to different occupational and domestic exposures during pregnancy. After receiving a monthly list of the names of the case and referent mothers from the Register, they contact the respective maternity welfare centers, which arrange the personal interviews with the case and referent mothers. These special interviews usually take place at the mother's first postdelivery visit to the maternity welfare center. More than 95 % of the mothers have agreed to participate in the study.

A particularly designed questionnaire is used (1). It consists of open and fixed questions and was tested as to its general comprehensibility prior to the start of the study. The fixed questions include information concerning possible exposures to organic solvents, pesticides, and ionizing and nonionizing radiation. The questionnaire starts with an open question which requests the mother to describe in detail the activities of her usual workday. This description is completely registered by the interviewer. Thus, the questionnaire is not restricted as to particular hypotheses

but registers exposures as they come from the mothers without paying attention to a priori biological meaningfulness of the exposure. The interviewer codes the questionnaires for later recognition.

Analysis of the exposure data

The validity of the quantitative estimation of the exposure is a crucial point in the present study. Because of the limits of the number of pairs that accumulate in the Register within a reasonable length of time, we cannot restrict the analysis only to pairs with definitely heavy exposure, say, levels above hygienic standards. On the other hand, the inclusion of quantitatively insignificant exposures would result in the dilution and possible masking of association. Therefore, it is mandatory to make a compromise between these two extremes of quantitation.

The information gathered on environmental exposures is first analyzed by two industrial hygienists. The hygienists are unaware of whether the information comes from a case or a referent mother. Chemical composition of the commercial products that appear in the answers as tradenames (eg, pesticides, paints) is clarified. The categorization of the exposure (none / minor / substantial / strong) is often a matter of an educated guess, though it is largely based on the long industrial hygienic expertise of our institute. When necessary, the hygienist requests further information on exposures through personal contacts with employers and may visit the workplaces.

After the primary estimation of the exposure data, the hygienist classifies the material, still blindly and with two experts in occupational medicine, into the final exposure categories. Quantitatively minor exposures are ignored. Mothers are considered "substantially" exposed (eg, to organic solvents) if their estimated exposure has been approximately one-third of the current threshold limit value of the American Conference of Governmental Industrial Hygienists (ACGIH). We have also included point exposures that probably exceeded the respective ceiling values for a few hours. Pairs in which the exposure occurred after the termination of the first

trimester are deleted from the analysis. Thereafter the codes are broken, the exposure frequencies between the cases and the referents are compared, and the differences are statistically tested.

Accumulation of pairs with discordant exposures

The accumulation of pairs is naturally restricted by the annual rate of reporting to the Register. Each year there will be approximately 60 new pairs with congenital defects of the central nervous system, 110 pairs with oral clefts, 110 pairs with selected skeletal malformations, and 80 pairs with selected cardiovascular defects. The final figure for cardiovascular defects will become even lower since we have not yet checked the reliability of these findings from hospital records.

We have roughly estimated that, for most exposure groups (eg, organic solvents), a maximum of some 5 % (and often less) of the pairs has reported a quantitatively interesting exposure during pregnancy. Restriction of the analysis to the first trimester of pregnancy will produce still lower figures. A glance at the rather low percentage of pairs with substantial exposure and the annual accumulation rate of pairs in different malformation groups suggests that material must be collected a minimum of a few years before any meaningful statistical analyses will be possible.

Comment

A study that includes retrospective collection of exposure data has limitations and shortcomings as to the validity of the results. There is a potential risk that the interviewer, who cannot be blinded as to the case-referent status, will inadvertently register exposure data more effectively from the case mothers than from the referent mothers. We have tried to minimize this bias by categorizing the exposure quantities blindly and by considering exposures as "substantial" only when they can be judged as reasonably founded in light of industrial hygienic experience. Thus, even exposures that the mother herself may have considered heavy are deleted if deemed insignificant. Other validity problems involved with the kind of approach used in the present study have been more extensively discussed earlier (2).

References

1. Holmberg PC, Nurminen M. Congenital defects of the central nervous system and occupational factors during pregnancy: A case-referent study. *Am j ind med* 1 (1980) 167—176.
2. Saxén L. Population surveillance for birth defects. In: Motulsky AG, Lenz W, ed. *Birth defects. Excerpta Medica*, Amsterdam 1974, pp 177—186.
3. Saxén L, Klemetti A, Härö AS. A matched-pair register for studies of selected congenital defects. *Am j epidemiol* 100 (1974) 297—306.