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RISK FACTORS FOR ATRIAL SEPTAL DEFECT

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The possible effect of environmental factors during pregnancy on the occurrence of atrial septal defect (ASD-secundum) in the offspring was studied in 50 cases and 756 controls. The cases represented all verified ASDs in Finland during 1982-1983. The controls were randomly selected from all infants born during the same period. Case and control mothers were interviewed by midwives using a structured questionnaire approximately three months after delivery. Congenital heart disease was more prevalent among parents of cases than those of controls. Maternal alcohol consumption during the first trimester of pregnancy appeared to double the risk of atrial septal defect (OR = 1.9, CI_{95} = 1.1 - 3.4). Maternal exposure to chemicals at work during the first trimester was more prevalent among the ASD-group (40.0%) than the control group (26.2%). The risk of ASD was not associated with maternal smoking, or coffee, tea or acetosalicylic acid consumption.

Maternal exposure to video display terminals, microwave ovens, organic solvents, anesthetic gases, pesticides or wood preservatives during the first trimester of pregnancy were not associated with the risk of an atrial septal defect. It is concluded that some common physical and chemical exposures during early pregnancy should not necessarily be considered risk factors for atrial septal defect.

INTRODUCTION

Among all cardiac malformations approximately 4-10% are cases of ASD (2, 3, 6, 8, 10, 11, 14, 20), the causes of which are unknown in the majority of cases (4, 5, 23, 25). The few known risk factors for ASD, including family history of congenital heart disease and viral infections, explain few cases (16, 25).

Since the classical works of Campbell and Polani (4, 5) very little attention has been paid to the etiology of congenital heart disease, especially ASDs. A study of the etiology of cardiovascular malformations was therefore initiated in Finland in 1981 (26, 27, 28, 29, 30).

The aim of the overall survey was to investigate the effect of genetic and environmental factors on the occurrence of congenital heart disease as widely as possible. The present study covered all reported cases of ASD (secundum) verified by paediatric cardiologists from among all births in Finland over a two year period (1982-1983).

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MATERIALS AND METHODS

Cardiovascular malformations

The material was derived from all infants born in Finland during 1982-83 (132,993 births) who had a congenital cardiovascular malformation diagnosed between the 20th week of gestation and one year of age. Information on infants with a cardiovascular malformation was obtained from the Children's Cardiac Register and the Finnish Register of Congenital Malformations. Both receive notifications of infants born with a congenital cardiovascular malformation diagnosed at a university central hospital on the basis of distinct auscultation findings, cardiac catheterization, ultrasound, surgery or autopsy (26, 27, 28).

In 1982-83, a total of 492 infants with various cardiovascular anomalies were reported to the registers. Thirty-one per cent of the cases were reported only to the Finnish Register of Malformations and 34% only to the Children's Cardiac Register. Both were notified in 35% of cases.

After scrutinising all these records, the paediatric cardiologist in this study declared that 22 of these infants had not had a clinically clear cardiovascular malformation. Sixty-two cases with chromosomal anomalies or a known genetic syndrome, as well as cases with extracardiac anomalies, were excluded from the data. Thus, 84 children were removed from the study.

The 408 remaining infants had a total of 583 diagnosed cardiovascular anomalies classified as follows (9): ventricular septal defect (VSD, n = 150), conus arteriosus syndrome (CAS, n = 90), atrial septal defect (ASD, n = 50), hypoplastic left ventricle (LHHS, n = 34), endocardial cushion defect (ECD, n = 22) and other defects (O, n = 237). Classification of these malformations according to their embryologic nature has been recently provided elsewhere (25, 28, 29, 30).

Atrial septal defects

In this data, atrial septal defect was defined as an opening in the atrial septum not covered by a valve. In accordance with the above classification, only patients with atrial septal defects are included in the ASD category (9, 25).

For 38 of the ASD-patients, the diagnostic method (e.g. catheterization) had been reported to the register, while for the remaining 12 patients the method had not been recorded. In all the latter cases the ASD diagnosis was found by the paediatric cardiologist by checking through the hospital records of these patients.

In 28 (56%) of 50 babies the diagnosis had been made during the first month of life, in 8 (16%) during the second month and in 2 (4%) during the third month.

The mean age of all ASD-babies at the time of diagnosis was 70.7 days, with a range of 1-345 days. If several diagnostic methods were used on different dates the time of diagnosis was taken as the date of the latest examination.

Controls

The controls were randomly selected from all deliveries in Finland during 1982-1983 (approximately 133,000 births). For each year, 400 non-malformed infants were selected from all 52 hospitals on the basis of their rate of deliveries in 1981 (26, 27, 28).

Dates were chosen at random and the first infant with no anomaly in any organ born on each date was included in the study. Forty-four (5.5%) of the mothers could not be contacted or refused to participate. Thus, the final control group consisted of 756 infants.

Interview of the mother

The mothers were interviewed by a midwife, using a structured questionnaire, at maternity welfare centers. The mothers of the affected infants were interviewed approximately 84 days (range 14-360), and those of normal infants 96 days (range 21-154), after delivery. In the ASD-group, only 76 per cent of the infants had been diagnosed within three months of delivery, so the remaining 24% of the interviews were carried out later. The interviews in both case and control groups lasted approximately one hour (26, 27, 28).

At the beginning of the interview the mothers were asked about drug consumption during the first trimester of pregnancy. First came a yes/no question on their drug consumption, followed by medications used for some common diseases and those most frequently used during pregnancy in Finland. However, only the intake of acetylsalicylic acid was considered in this study.

Working conditions and occupational exposures during the first trimester of pregnancy formed the second part of the interview. The mother was asked about specific physical or chemical exposures at work. The following exposures were noted: employed or not, organic solvents, dyes, lacquers, paints, glues, disinfectants, plastic raw materials, wood preservatives, pesticides, anesthetic gases, textile dusts, other dusts, microwave ovens and other equipment.

If the mother reported any exposure to these chemical or physical factors the interviewer noted the frequency (often, occasional). Only exposures during the first trimester were included in the study.

The third part of the interview related to disorders in the family, illness during the pregnancy and selected habits of the mothers during the first trimester. Anomalies in the following organs were noted: cardiovascular, central nervous, musculoskeletal, pulmonary, alimentary, urino-genital and lip and palate. Details of maternal smoking and coffee, tea and alcohol consumption during pregnancy were also recorded.

Obstetric data such as birthweight, length of gestation and stillbirth were derived from the mothers' maternal health care card postnatally filled at the maternity hospital. These cards are identical throughout Finland.

Statistical methods

The chi-square test was used to test the hypothesis that mothers of ASD-infants somehow differed from those of normal ones (1). Odds ratios and their 95% confidence intervals were calculated for some factors (1) (Tables 1, 2 and 3) to enable evaluation of whether lack of a difference in percentage distribution is due to small numbers of exposures.

Logistic regression analysis was also applied to the data (12). Only environmental factors which associated in cross-tabulation ($P < 0.05$) with ASD and a potential confounding factor (maternal age) were dichotomized and included in the logistic model. The adjusted point estimates of the odds ratios and their 95% confidence intervals were computed from the estimates of model parameters and their standard errors (12).

TABLE 1. - Familial anomalies among the ASD-group and control group in 1982-1983.

Characteristic	ASD-group (n = 50) %	Control group (n = 756) %	Odds ratio and 95% confidence interval
Familial anomalies*			
- cardiovascular malformation in the mother	2.0	0.4	5.1 (0.5-50)
- cardiovascular malformation in the father	4.0	0.4	10 (1.6-61)
- anomaly in mother's mother	8.0	1.7	5.0 (1.6-16)
- anomaly in mother's father	2.0	0.8	2.6 (0.3- 8.5)
- anomaly in mother's sister or brother	14.3	6.1	2.5 (1.1- 5.9)
- anomaly in father's sister or brother	10.4	5.1	2.0 (0.8- 5.3)

* = Any anomaly in the following organ or tissue: Central nervous system, musculoskeletal, pulmonary, alimentary, genito-urinary and lip and palate.

TABLE 2. - Maternal characteristics, disorders and medical examinations during the first trimester of pregnancy in 1982-1983.

Maternal characteristics, disorder, or medical examination	ASD-group (n = 50) %	Control group (n = 756) %	Odds ratio and 95% confidence interval
Maternal age $\geq$ 30 years	48.0	33.9	1.8 (1.0- 3.2)
Upper respiratory infection (no fever)	25.0	17.7	1.5 (0.8- 2.9)
Fever $\geq$ 38° C	8.0	6.4	1.3 (0.4- 3.7)
Vaginal bleeding	16.0	9.3	1.9 (1.3- 2.8)
Emesis gravidarum	50.0	50.2	1.0 (0.6- 1.8)
High blood pressure (systolic > 140 mmHg) or/and (diastolic < 90 mmHg), but < 160/110)	4.0	1.3	3.1 (0.7- 15)
Proteinuria	2.0	1.9	1.1 (0.1- 85)
Sex of the child (male)	46.0	51.9	0.8 (0.5- 1.4)
Stillbirth	26.0	0.1	265 (34 -546)
Twin birth	4.0	0.5	7.8 (1.4- 44)
Length of gestation $\leq$ 37 weeks	16.0	6.1	2.9 (1.3- 6.5)
Birth weight < 2 500 g	14.0	2.0	8.0 (3.1- 21)
Placental weight < 600 g	64.0	40.1	2.7 (1.5- 4.9)
X-ray examination	4.0	4.7	0.9 (0.2- 3.7)

TABLE 3. - Selected maternal habits and exposures at work during the first trimester of pregnancy in 1982-1983.

Habits or exposure	ASD-group (n = 50) %	Control group (n = 756) %	Odds ratio and 95% confidence interval
Maternal smoking			
1-14 cigarettes per day	14.0	18.9	0.7 (0.3- 1.6)
15-29 cigarettes per day	2.0	2.7	0.8 (0.1- 5.7)
Exposure to passive smoking			
at home	24.0	24.9	1.0 (0.5- 1.9)
at work	8.0	14.1	0.5 (0.2- 1.5)
Alcohol consumption			
(at least a single drink) proportion of users	56.0	39.0	2.0 (1.1- 3.6)
regular use (every week)[1]	0.0	3.3	
at least 2-3 drinks per occasion	8.0	8.1	1.0 (0.4- 2.9)
Coffee consumption			
proportion of users	76.0	81.1	0.7 (0.4- 1.5)
cups per day (mean)	4.0	3.3	1.2 (0.3- 5.2)
Drug consumption	13.3	14.6	1.0 (0.4- 2.2)
Use of acetosalicylic acid	2.0	5.8	0.3 (0.0- 2.4)
Use of deodorants	51.0	46.5	1.2 (0.7- 2.2)
Work attendance	78.0	75.0	1.2 (0.6- 2.4)
High temperature ($\geq$ 20° C)			
at work	22.0	23.2	0.9 (0.5- 1.9)
Sauna bathing	93.0	95.4	0.8 (0.2- 2.5)
Exposure to chemicals at work	40.0	26.2	1.9 (1.1- 3.4)
Regular exposure to organic solvents at work	6.0	2.4	2.6 (0.7- 9.1)
Regular exposure to dyes, lacquers or paints at work	2.0	0.9	2.2 (0.3-18)

[1] = Not calculable because of zero in cell frequency.

RESULTS

In 1982-1983, 408 infants with congenital heart disease were reported to the registries, 50 of whom had an ASD. During the same period 132,993 infants were born in Finland. Thus the registered prevalence of atrial septal defect was 0.4 per 1 000 births.

The relatives of ASD-infants had more congenital anomalies than those of the controls (Table 1). One mother and two fathers of ASD-patients had had a cardiovascular anomaly. The mother did not know the type of her heart defect more specifically; one father had an aortic stenosis and another some defect which was operated on.

Neither maternal upper respiratory infection nor fever during the first trimester were significantly associated with the risk of atrial septal defect (Table 2). Some conditions, such as vaginal bleeding, short gestation, twin birth, stillbirth, low birth weight and low placental weight, were significantly more common among the case mothers than controls. Maternal X-ray examination was not associated with the risk of atrial septal defect.

TABLE 4. - Environmental risk factors for atrial septal defects in Finland in 1982-1983.

Factors*	Adjusted relative risk	95% confidence interval
Maternal alcohol consumption during the first trimester	1.9	1.1 - 3.4
Maternal exposure to chemicals at work during the first trimester	1.9	1.1 - 3.4
Maternal age $\geq$ 30 years	1.2	0.6 - 2.4

* = Dichotomization of the factors for the logistic regression model: Alcohol consumption (at least one drink during the first trimester, yes/no), exposure to chemicals at work (yes/no), maternal age ($\geq$ 30 / < 30).

Maternal alcohol consumption during early pregnancy was more common (56.0%) among the ASD-group than controls (39.0%) ($p < 0.05$, X^2 -test) (Table 3). However, most mothers in both groups consumed only one alcoholic drink per occasion.

Maternal smoking, coffee consumption and intake of acetylsalicylic acid were not found to be connected with the risk of atrial septal defect (Table 3). The mean tea (1.0 cup), cocoa (0.1 cup) and cola (0.03 bottles) consumptions per day were also similar in the ASD and control groups.

Maternal employment during the first trimester of pregnancy was not associated with the risk of atrial septal defect per se (Table 3). Maternal exposure to chemicals at work during the first trimester was more prevalent among the ASD-group than among the control group ($p < 0.05$, X^2 -test). However, no marked differences were found between groups in exposures to specific chemicals such as dyes, lacquers or paints (Table 3).

Maternal occupational exposures to video display terminals, microwave ovens, pesticides, wood preservatives, anesthetic gases, glues and plastics were rare and failed to indicate a risk for atrial septal defect ($p > 0.05$, Chi-square test).

Paternal age was not associated with the risk of ASD. Mean paternal age in both groups was 30.1 years.

Environmental factors associated with the risk of ASD, and maternal age as a confounding factor, were selected for regression analysis (Table 4). Maternal alcohol consumption showed an adjusted odds ratio of 1.9 (95% confidence interval 1.1-3.4). The other significant risk factor for ASD was maternal exposure to chemicals during the first trimester of pregnancy.

DISCUSSION

The epidemiologic study of cardiovascular malformations is subject to a variety of sources of error. Low detection rate of cases, incomplete reporting of defects, difficulty of recalling events in early pregnancy and selective memory mechanisms are all potential sources of bias. There are also difficulties in controlling for confounding factors, as well as problems of chance associations (26). All these issues recently have been discussed elsewhere (13, 29, 30, 33, 34), and are therefore not dealt with here in detail.

This study material is limited in size. For example, in our data only 21 out of 806 mothers had been exposed regularly to solvents during the first trimester of pregnancy. Thus the power of this study is weak for testing the teratogenicity of specific chemicals. This is particularly true for effects of rare exposures. Therefore, conclusions about the negative findings of this investigation must be drawn very carefully.

Numerous classifications and diagnostic coding systems have been proposed for congenital heart disease. Thus far, none have found universal acceptance (32). In this data cardiovascular malformations were classified into ontogenetic categories according to a method developed for epidemiological studies of congenital heart disease (9, 28). This segmental approach has been regarded as a logical (31) and reliable method in epidemiological studies because it takes account of the different embryologic nature of defects. However, in spite of this classification the case-group consisted of only 50 patients.

In this study controls were randomly selected from all deliveries in Finland. Dates were chosen at random and the first non-malformed infant born on each date was selected as control. In spite of this randomization only 2% of the control infants had a birthweight below 2,500 g and the stillbirth rate among controls was only 1:1000, which suggests a minor selection bias. The reason for this is not known. The obstetric data for this study was derived from the mother's maternal health care card, which is standardized in Finland and therefore considered very reliable. No other criteria which might explain this bias, such as normal length of gestation, were used in selection of controls.

The interview of the mothers also included some potential sources of error. They were performed among the ASD-group a little later after delivery than among

the control group, thus the range between delivery and interview was 213 days wider in the case than in the control group. This is because only 76% of the ASD-infants had been diagnosed by the age of three months, the remaining 24% of mothers of ASD-infants being interviewed later than three months after delivery. Moreover, the possible biases due to the use of many interviewers should also be considered. Nevertheless, the interviews were performed by experienced and well-educated midwives, using structured and pre-tested questionnaires (25).

Some surveys have established an increase in the occurrence of congenital heart disease among parents and siblings of ASD children (2, 17, 18). Other near relatives of ASD children also have a higher risk of cardiovascular malformation than the general population (9, 15). In this data, however, only a few mothers knew the type of familial anomaly. Therefore, this information can only provide pointers to the true genetic background of the case and control infants.

Some other studies have also shown an excess of complications in pregnancy (e.g. vaginal bleeding and short gestation) to be associated with atrial septal defect (9, 15). Mechanisms linking ASD and these complications are not known. However, the similarity of the risks in this data with the results of Heinonen (9) suggests that these associations are highly consistent.

Some papers have focused attention on environmental contamination with teratogenic chemicals (25, 30) and one recent estimate suggests that at least 180 chemicals may be teratogenic in humans (25). In this data, overall maternal exposure to chemicals was more prevalent among the ASD-group than the controls, but no specific chemicals were associated with the risk of ASD. Therefore, the association between the whole group of chemicals and atrial septal defect is hardly causal and may be due to such things as maternal selective memory bias, chance, or confounding factors (22).

Maternal alcohol consumption during the first trimester of pregnancy was slightly more prevalent among the ASD group mothers than the controls. This association should be interpreted with caution, however, because of the notorious problem of obtaining reliable estimates of alcohol consumption during pregnancy. The consumptions reported by the mothers are probably underestimates (24). The association between maternal alcohol consumption and atrial septal defect is not very convincing because the finding is based on sporadic alcohol use. It is very unlikely that sporadic use of alcohol causes atrial septal defects. The finding may be due to most heavy drinkers being classified as sporadic users. It is also possible that the difference in alcohol consumption between case and control groups is an expression of recall or interviewer bias.

On the other hand, in experimental animals, alcohol has been found to cause congenital abnormalities (19), and some epidemiological studies (7, 21) have shown increased rates of FAS-children born to women who consumed abundant alcohol. In these studies, the cardiovascular malformations most commonly associated with alcohol were atrial and ventricular septal defects (21, 24).

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REFERENCES

1. *Armitage P.* (1985): Statistical methods in medical research - Blackwell Scientific Publications - Oxford.
2. *Boughman J.A., Berg K.A.* and *Astemborski J.A.* (1987): Familiar risks of congenital heart defect assessed in a population-based epidemiologic study - Am. J. Med. Genet. *26:* 839-849.
3. *Bound J.P.* and *Logan W.F.W.E.* (1977): Incidence of congenital heart disease in Blackpool 1957-1971 - Br. Heart J. *39:* 445-450.
4. *Campbell M.* (1965): Causes of malformations of the heart - Br. Med. J. *2:* 895-904.
5. *Campbell M.* and *Polani P.E.* (1961): Factors in the etiology of atrial septal defect - Br. Heart J. *23:* 477-493.
6. *Carlgren L.E.* (1969): Kongenitala hjärtfel hos barn födda i Göteborg 1941-1960 - Läkartidningen *66:* 4883-4888.
7. *Clarren S.K.* and *Smith D.W.* (1978): The fetal alcohol syndrome - N. Engl. J. Med. *298:* 1063-1067.
8. *Ferencz C., Rubin J., McCarter R.J.* and *Boughman J.A.* (1987): Cardiac and non-cardiac malformations: Observations in a population-based study - Teratology *35:* 367-378.
9. *Heinonen O.P.* (1976): Risk factors for congenital heart disease. A prospective study. Ketty S., Hook E.B., Janerich D.T., Porter I.H., eds. Birth Defects: Risks and consequences - Academic Press, New York, 221-264.
10. *Henriksen J.B.* (1974): Congenital heart defects in children born in Norway 1967-1968 - Tidsskr. Nor. Laegeforen *94:* 624-627.
11. *Kenna A.P., Smithless R.W.* and *Fielding D.W.* (1975): Congenital heart disease in Liverpool: 1960-1969 - Q. J. Med. *44:* 17-44.
12. *Lemeshow S.* and *Hosmer D.W. Jr.* (1984): Estimating odds ratios with categorially scaled covariates in multiple logistic regression analysis - Am. J. Epidemiol. *119:* 147-151.

13. *MacKenzie S.G.* and *Lippman A.* (1989): An investigation of report bias in a case-control study of pregnancy outcome - Am. J. Epidemiol. *129:* 65-75.

14. *Mitchell S.C., Korones S.B.* and *Berendes H.W.* (1971): Congenital heart disease in 56,109 births. Incidence and natural history - Circulation *43:* 323-332.

15. *Mäkinen L.* (1981): Severe congenital cardiovascular malformations in infancy - Thesis. Helsinki.

16. *Nadas A.S.* and *Fyler D.C.F.* (1972): Pediatric Cardiology. WB Sounders Company - Third edition - Philadelphia - London - Toronto.

17. *Nora J.J., McGill C.W.* and *McNamara D.G.* (1970): Empiric recurrence risk in common and uncommon congenital heart lesions - Teratology *3:* 325-329.

18. *Nora J.J., Nora A.H.* and *Wexler P.* (1971): Hereditary and environmental aspects as they affect the fetus and newborn - Clin. Obst. and Gynecol. *24:* 851-861.

19. *Randell C.L., Taylor J.* and *Walker D.W.* (1977): Ethanol induced malformations in mice - Alcoholism *1:* 219-244.

20. *Richards M.R., Merritt K.K., Samuels H.M.* and *Langmann A.G.* (1955): Congenital malformations of the cardiovascular system in a series of 6053 infants - Pediatrics *15:* 12-28.

21. *Sandor G.G.S., Smith D.F.* and *Maclead P.M.* (1981): Cardiac malformations in the fetal alcohol syndrome - J. Pediatr. *98:* 771-773.

22. *Saxén L.* (1983): Twenty years of study of the etiology of congenital malformations in Finland. In: Kalter H. ed. Issues and Reviews in Teratology. New York - Plenum Press Corporation 73-100.

23. *Stoll C., Alembik Y., Roth M.P., Dott B.* and *De Geeter B.* (1989): Risk factors in congenital heart disease - Eur. J. Epidemiol. *5:* 382-391.

24. *Tikkanen J.* (1984): Smoking and alcohol consumption during pregnancy in Finland. Publications of the National Board of Health - Series Original Reports 4/1984 - Helsinki.

25. *Tikkanen J.* (1986): Risk factors for congenital heart disease - Thesis. Health services research by the National Board of Health in Finland - Helsinki.

26. *Tikkanen J.* and *Heinonen O.P.* (1988): Cardiovascular malformations and organic solvent exposure during pregnancy in Finland - Am. J. Ind. Med. *14:* 1-8.

27. *Tikkanen J., Kurppa K.* and *Timonen H.* (1988): Cardiovascular malformations, work attendance, and occupational exposures during pregnancy in Finland - Am. J. Ind. Med. *14:* 197-284.

28. *Tikkanen J., Heinonen O.P., Kurppa K.* and *Rantala K.* (1989): Cardiovascular malformation and maternal exposure to video display terminals during pregnancy - Eur. J. Epidemiol. *6:* 61-66.

29. *Tikkanen J.* and *Heinonen O.P.* (1990): Risk factors for cardiovascular malformations in Finland - Eur. J. Epidemiol. *6:* 348-356.

30. *Tikkanen J.* and *Heinonen O.P.* (1991): Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring - Teratology *43:* 591-600.

31. *Tynan M.J., Bercker A.E., Macartney F.J., Jimènez M.O., Shinebourne E.A.* and *Andersson R.H.* (1979): Nomenclature and classification of congenital heart disease - Br. Heart J. *41:* 544-553.

32. *Van Mierop L.H.S.* (1984): Diagnostic code for congenital heart disease - Pediatr. Cardiol. *5:* 331-362.

33. *Werler M.A., Pober B.R., Nelson K.G.* and *Holmes L.B.* (1989): Reporting accuracy among mothers of malformed and nonmalformed infants - Am. J. Epidemiol. *129:* 415-421.

34. *Workshop to Guidelines to the Epidemiology of Weak Associations* (1987): Prev. Med. *16:* 139-212.