Maternal hypertension with nifedipine treatment associated with a higher risk for right-sided obstructive defects of the heart: a population-based case–control study

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ABSTRACT

Objective To establish possible aetiological factors contributing to congenital heart defects (CHD) overall and separately for different types of CHD, as causes are unknown for the vast majority of patients.

Design To estimate a possible association with maternal diseases and related drug treatments as exposures in the mothers of cases with right-sided obstructive defects of the heart (RSODH).

Setting A large population-based Hungarian Case-Control Surveillance of Congenital Abnormalities data set.

Patients Newborn infants with four types of RSODH based on autopsy or surgical records.

Interventions Comparison of 200 live-born cases with RSODH including 72 (36.0%) with pulmonary valve stenosis, 13 (6.5%) with tricuspid atresia/stenosis, 7 (3.5%) with Ebstein's anomaly and 108 (54.0%) with pulmonary atresia, with 304 matched controls and 38 151 population controls without any defects.

Main outcome measures Risk of any RSODH and risk of each type of RSODH.

Results High blood pressure, particularly chronic hypertension with nifedipine treatment, was associated with a risk for RSODH (OR 7.03, 95% CI 3.13 to 13.84). High doses of folic acid reduced the birth prevalence of pulmonary atresia (OR 0.29, 95% CI 0.16 to 0.53).

Conclusions The multifactorial threshold model provides the best explanation for the origins of RSODH. Genetic predisposition may be triggered by maternal hypertension with nifedipine treatment, while the risk for pulmonary atresia is reduced by high doses of folic acid in early pregnancy.

INTRODUCTION

Congenital heart defects (CHD) are structural birth defects, or congenital abnormalities (CAs), of the heart and great vessels. CHD are the most common CAs. The birth prevalence of CHD ranges from 4 to 50 per 1000 live-births in different studies because diagnosis depends on age at examination, the sensitivity of the examination technique, case definition and the types of CHD cases included.[1–3] The birth prevalence of CHD was 7.06±0.91 per 1000 in Budapest in 1963–1965 according to the Hungarian Congenital Abnormality Registry (HCAR), which is based on the records of all paediatric and pathology institutions.[4] However, a birth prevalence of CHD of 10.2±2.1 per 1000 was found in 1971–1972 in a Hungarian population-based study conducted in a country region, where each individual child was examined by a paediatric cardiologist or the autopsy report was evaluated.[5]

Despite recent medical and surgical advances,[6] CHD still causes much perinatal and infant mortality and morbidity.[3 7] The contribution of possible environmental factors to CHD is unclear in the vast majority of patients,[8] although this information would help prevent CHD.

CHD encompasses various CAs with different manifestations, severity and aetiology.[6] Thus, the objective of our project was to differentiate CHD entities and evaluate their possible risk factors.[9 10] As the recently proposed CHD classifications are based on pathogenesis rather than anatomic location,[11–13] we followed the CHD categorization in the Baltimore-Washington Infant Study.[12] The category of right-sided obstructive defects of the heart (RSODH) includes pulmonary valve stenosis, pulmonary atresia, tricuspid atresia and Ebstein's anomaly.

The aim of this study was to investigate a possible association between maternal diseases and related drug treatment exposures and the risk of RSODH based on the diagnosis noted in the autopsy or surgical report in patients with different types of RSODH recorded in the population-based Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) database.[14]

PATIENTS AND METHODS

Patients with CAs including RSODH recorded in the HCCSCA were selected from the HCAR.[15] It is mandatory for physicians to report cases with CAs to the HCAR, and most are reported by obstetricians (in Hungary most deliveries occur in inpatient obstetric clinics with obstetricians in attendance) and paediatricians (who work in the neonatal units of inpatient obstetric clinics and various general and specialised clinics). An autopsy was mandatory for all infant deaths and common (about 80%) for stillborn fetuses during the study period. Pathologists sent a copy of the autopsy report to the HCAR if defects were identified in stillbirths and infant deaths. However, only those cases reported within the first 3 months after birth or pregnancy termination (77% of all cases) were selected from the HCAR for the HCCSCA. In addition, cases with CA syndromes caused by preconception gene mutations or chromosomal aberrations were excluded.

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Controls were defined as newborn infants without CAs and were selected from the National Birth Registry of the Central Statistical Office for the HCCSCA on the basis of HCAR case lists for each quarter of the year. In general, two controls were matched to each case according to sex, birth week in the year when the case was born and district of parents' residence. If controls were twins, only one of these twin-pairs was randomly selected for the HCCSCA.

Three sources of exposure data were recorded in the HCCSCA:

1. *Prospectively recorded medical data*. Letters were sent to the mothers of cases and controls immediately after their records were selected from the HCCSCA and they were requested to send us their prenatal maternity logbook, the discharge summary of their delivery and all medical records covering any illnesses during the study pregnancy and their child's CAs. These documents were returned to them within 4 weeks. As prenatal care is mandatory for pregnant women in Hungary (if a woman does not visit prenatal care, she did not get a maternity grant or maternity leave), nearly all pregnant women visited prenatal care for an average of seven times during their pregnancy. The first visit was between the 6th and 12th gestational week calculated from the first day of the last menstrual period. Obstetricians in prenatal care recorded all maternal diseases and related medicinal products for women during the study pregnancy in the logbook.
2. *Retrospective maternal self-reported information*. A structured questionnaire with a list of drugs and diseases and a printed informed consent form were also sent to the mothers of cases and controls. The questionnaire requested information on, among other things, maternal diseases, medicine (drug and pregnancy supplements) intakes during the study pregnancy by gestational month, and family history of CAs. In order to standardise the answers, mothers were asked to read the enclosed lists of medicinal products and diseases as a memory aid before they filled in the questionnaire and returned it with the signed informed consent form. The mean ± SD length of time between the end of the pregnancy and the return of the information package (including the logbook, discharge summary, questionnaire and informed consent form) in our prepaid envelope was 3.5 ± 2.1 and 5.2 ± 2.9 months in cases and controls, respectively.
3. *Supplementary data collection*. Regional district nurses were asked to visit all case mothers who did not respond and help them to fill in the questionnaire and evaluate the available medical documents. Unfortunately, district nurses could visit only 200 non-respondent and 600 respondent control mothers as part of two validation studies[14] because the ethics committee considered this follow-up to be disturbing for the parents of healthy children. Thus, exposure information was available for 96.3% of cases (84.4% from replies and 11.9% from visits) and 83.0% of controls (81.3% from replies and 1.7% from visits). The signed informed consent form was returned by 98% of mothers; names and addresses were deleted in the 2% of subjects without signed informed consent.

The method of data collection was changed in 1997 (after the retirement of AEC) and all case and control mothers are now visited and questioned at home by regional nurses. As these later data had not been validated at the time of this analysis, only the 17 years of HCCSCA data from 1980 to 1996 are evaluated.

The major problem concerning cases with CHD was that about 50% of cases were reported to the HCAR as unspecified CHD because the exact CHD diagnosis needed further time-consuming investigation. However, as collection of the medical data of cases with CA in the HCCSCA took place 3.5 ± 2.1 months later, we were able to obtain specific CHD diagnoses in a further 20% of cases. However, the remainder (ie, nearly 30% of our CHD cases) had no specific diagnosis in the HCCSCA. We presumed that most surviving cases with CHD were cared for or had undergone surgical interventions in one of the paediatric cardiology institutions in Hungary. Therefore, one of us (MC-S) visited these clinics in 2008. Medical records were reviewed and the previous diagnosis of a specific CHD was checked (and corrected if necessary) and previous unspecified CHD diagnoses were modified to specific CHD diagnoses. We corresponded with the mothers of any cases still without a specific CHD diagnosis to determine the outcome and/or diagnosis of these cases in 2009 and 2010. Cases were excluded from the study if: (i) they were not found; (ii) a specific CHD diagnosis could not be made based on autopsy or surgical records; (iii) a specific CHD diagnosis could not be confirmed; or (iv) mothers refused collaboration.

Three steps were used to select cases with RSODH:

A. Cases with syndromic RSODH due to major mutant genes (eg, Williams-Beuren syndrome) or chromosomal aberrations (eg, Down syndrome) were excluded from the HCCSCA. Cases with unclassified multiple CAs including RSODH were also excluded from the study.
B. Among cases with isolated RSODH, four groups were evaluated using the following criteria:
    1. Congenital stenosis of the pulmonary valve (CSPV). Only cases with an intact ventricular septum were included in the study. CSPV covers a wide spectrum of clinical severity and most infants are asymptomatic. This condition is therefore common but often undiagnosed. Cases with no pulmonary valve, pulmonary valve regurgitation, or infundibular or supravalvular pulmonary valve stenosis were excluded.
    2. Congenital atresia/stenosis of the tricuspid valve (ASTV) results in failure of communication between the right atrium and the right ventricle and may develop in mid and late pregnancy. The great vessels are normal.
    3. Ebstein's anomaly (EbA) is a CA of the tricuspid valve, characterised by downward displacement of the attachment of the tricuspid valve into the inflow portion of the right ventricle. The severity spectrum of EbA is very wide, from severe disturbances in fetal and neonatal life to virtually symptomless survival throughout a long and active adult life. Only cases with EbA diagnosed after birth were included in the study.
    4. Congenital atresia/stenosis of the pulmonary artery (ASPA). Cases with an intact ventricular septum were included in this study, while cases with a ventricular septal defect were excluded.
C. The four types of RSODH exhibit a very wide spectrum of severity, from mild forms of CSPV (the very mild manifestations of this developmental disturbance may constitute normal anatomic variants, ie, minor anomalies) to severe forms of EbA (sometimes with fatal outcome). Therefore, in order to evaluate groups as evenly as possible, only severe cases who underwent surgical management or died (as indicated by autopsy reports) were included in the study.

First we evaluated cases with different types of RSODH together due to their limited numbers. However, if a specific

exposure seemed to be associated with a higher risk of RSODH, different groups were evaluated separately in the second step.

The critical periods for the four types of RSODH are different (table 1), but when RSODH cases were evaluated together, the critical period was considered to span the third to ninth gestational months.[16]

The software GNU R V.2.14 and RStudio V.0.97 were used for statistical analysis of data. Different maternal exposures during pregnancy were compared in the mothers of cases with RSODH and in population controls using an unconditional logistic regression model to estimate the relative risk (OR, 95% CI). A multivariate conditional logistic regression model was used to compare cases and their matched controls. Confounders considered were maternal age, birth order (parity) and employment status of the mother as an indicator of socio-economic status.[14]

RESULTS

Our population-based data set included 200 live-born cases with severe RSODH based on autopsy or surgical reports. The numbers in the different RSODH groups and their 304 matched controls are shown in table 1. In addition, we evaluated 38 151 population controls without CA and in the first step cases with RSODH and population controls were compared.

No association with a higher risk of RSODH was found when the incidence of acute maternal disease was evaluated during any time in pregnancy and in the third to ninth gestational months in the mothers of cases and population controls.

Among chronic maternal diseases (table 2), only chronic (essential) hypertension occurred more frequently in the mothers of cases than in the mothers of population controls. Blood pressure was measured at each prenatal visit, and any previous hypertension was recorded in the prenatal maternity logbook, allowing for differentiation between chronic and pregnancy-related hypertension. Pre-eclampsia and gestational hypertension occurred in the mothers of 19 cases (9.5%) and 11 matched controls (3.6%) (OR 2.63, 95% CI 1.15 to 6.31). However, pregnancy-related hypertension and chronic hypertension did not cluster in any RSODH group (table 1).

The 32 most frequently used drugs (used by at least by five case mothers) were also evaluated during any time in pregnancy and in the third to ninth gestational months, but only the antihypertensive drug nifedipine showed higher use during the critical period for RSODH in case mothers (5.0%, 10) than in population control mothers (0.9%, 342) (OR 5.82, 95% CI 2.72 to 11.06). In the 10 case mothers taking nifedipine, four received monotherapy, while in six nifedipine was combined with methyldopa, oxprenolol, prazosin, metoprolol, dihydralazine, aminophylline or verapamil. However, none of these drugs were associated with a higher risk for RSODH. Nine of 10 case women receiving nifedipine had chronic hypertension, while the 10th had gestational hypertension. The eight nifedipine treatments administered to case mothers during the critical period for RSODH were associated with a higher risk for RSODH (OR 4.45, 95% CI 1.19 to 11.79). The distribution of nifedipine treatment in the four groups of RSODH cases and their matched controls is shown in table 1.

Of 20 case mothers with chronic hypertension, 11 (5.5%) did not receive nifedipine. When this subgroup (hypertension without nifedipine treatment) was compared with population control mothers with chronic hypertension but without nifedipine treatment (3.5%), the association with RSODH was not significant (OR 1.62, 95% CI 0.79 to 2.11). On the other hand, when the nine (4.5%) case mothers with hypertension and

Table 1 Characteristics of RSODH cases and their matched controls

Right-sided obstructive defects of the heart (RSODH)	Critical period Month	Cases		Chronic hypertension*		Pregnancy hypertension*		Nifedipine		Folic acid*		Matched controls		Chronic hypertension*		Pregnancy hypertension*		Nifedipine		Folic acid*	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Congenital stenosis of the pulmonary valve (CSPV)	6th–9th	72	36.0	7	9.7	5	6.9	3	4.2	17	23.6	121	39.8	7	5.8	5	4.1	2	1.7	23	19.0
Congenital atresia/stenosis of the tricuspid valve (ASTV)	6th–9th	13	6.5	2	15.4	2	15.4	2	15.4	5	38.5	19	6.3	4	21.2	1	5.3	1	5.3	3	15.8
Ebstein's anomaly (EbA)	6th–9th	7	3.5	0	0.0	2	28.6	0	0.0	1	14.3	12	3.9	1	14.3	0	0.0	0	0.0	3	25.0
Congenital atresia/stenosis of the pulmonary artery (ASPA)	3rd–7th	108	54.0	11	10.2	10	9.3	5	4.6	21	19.4	152	50.0	9	5.6	5	3.3	3	2.0	69	45.4†
Total	3rd–9th	200	100.0	20	10.0	19	9.5	10	5.0	44	22.0	304	100.0	21	6.9	11	3.6	6	2.0	98	32.2

Pregnancy hypertension includes gestational hypertension and pre-eclampsia.
*Medically recorded.
†OR 0.29 (95% CI 0.16 to 0.53) or bivariate analysis: p<0.0001; other associations did not reach a level of significance in the four different RSODH groups.

Table 2 Prevalence of medically recorded chronic diseases during the study pregnancy in at least 2 case mothers and population control mothers

	Case mothers (N=200)		Population control mothers (N=38 151)		
Chronic diseases	No.	%	No.	%	OR (95% CI)
Diabetes mellitus	4	2.0	229	0.6	3.38 (0.90 to 8.91)
Panic disorder	2	1.0	210	0.6	1.83 (0.22 to 6.76)
Migraine	4	2.0	725	1.9	1.05 (0.28 to 2.75)
Hypertension, chronic	20	10.0	1592	4.2	2.55 (1.52 to 4.07)*
Haemorrhoids	6	3.0	1624	4.3	0.70 (0.25 to 1.55)
Varicose veins†	4	2.0	566	1.5	1.36 (0.36 to 3.54)
Hypotension, essential	6	3.0	1265	3.3	0.90 (0.33 to 2.00)
Allergic rhinitis	2	1.0	509	1.3	0.75 (0.09 to 2.75)
Dyspepsia/reflux	3	1.5	135	3.7	4.29 (0.87 to 12.99)
Constipation	5	2.5	799	2.1	1.20 (0.38 to 2.86)
Skeletal system	2‡	1.0	193	0.5	1.99 (0.24 to 7.37)
Congenital abnormalities	2§	1.0	155	0.4	2.48 (0.30 to 9.22)

*p<0.0001, bivariate analysis.
†In the lower extremities.
‡Pain in joint: 1; pain in limb: 1.
§Without CHD; vaginal atresia: 1; clubfoot: 1.
CHD, congenital heart defects.

nifedipine treatment were compared with a similar subgroup of population control mothers (0.7%), a significant association was found (OR 7.03, 95% CI 3.13 to 13.84). Thus, the higher risk for RSODH after nifedipine treatment in hypertensive pregnant women may be due to an interaction between maternal hypertension and this antihypertensive drug. Other antihypertensive drugs evaluated in this study were not associated with a higher risk for RSODH, nor was nifedipine associated with a higher risk for other CHD entities.

Angiotensin-converting enzyme inhibitors and angiotensin-II receptor inhibitors/antagonists with human teratogenic potential were not used for the treatment of our pregnant women during the study period.

Only medically recorded pregnancy supplements were evaluated in the study, and folic acid use showed an association with RSODH. Forty-four of 200 case mothers (22.0%) and 13 632 of 38 151 population control mothers (35.7%) had used folic acid during pregnancy (OR 0.51, 95% CI 0.35 to 0.71). Of 304 matched controls, 98 (32.2%) were born to mothers with folic acid supplementation (OR 0.58, 95% CI 0.38 to 0.90). Folic acid supplementation usually began after the first prenatal visit. Only one type of folic acid tablet was available during the study period and this tablet contained 3 mg. The daily dose of folic acid varied between 3 and 9 mg in the study, with about 60% of women taking 6 mg. Evaluation of the different RSODH groups showed that folic acid had some protective effect only for ASPA (table 1). Folic acid supplements containing multivitamins were medically recorded only in six case mothers.

DISCUSSION

The objective of this study was to analyse the possible role of maternal diseases and related drug treatments in the origin of different types of RSODH. An association was found between high blood pressure, particularly chronic hypertension in pregnant women treated with nifedipine, and a higher risk of RSODH in their children.

Our previous study[17] showed a higher risk of CAs in the offspring of pregnant women with chronic hypertension, but the different entities of CHD were not differentiated. Unfortunately, current antihypertensive drugs cannot protect the fetus from maternal hypertension.[18 19] The association of chronic hypertension with a greater risk for RSODH is supported by the higher incidence of gestational hypertension and pre-eclampsia in the mothers of cases with RSODH.

Among the drugs evaluated, only nifedipine (Cordaflex, EGIS; Corinfar, ADW 'R' V, K'; Nifedipin, Pharmavit), a calcium channel-blocking agent, was associated with a higher risk for RSODH. Our previous study did not suggest nifedipine had teratogenic potential,[20] but different entities of CHD were not differentiated. This finding was in agreement with the results of another study.[21] Only Scott *et al*[22] reported a higher risk for cardiac defects, mainly in the aortic outflow tract, after nifedipine treatment in pregnant rats. The findings of our study suggest that the higher risk for RSODH in the newborn infants of hypertensive women may be due to an interaction between maternal disorders and nifedipine.

The role of maternal diabetes in the origin of CHD is well known,[12] but its role in RSODH has not been recognised.

A previous Hungarian randomised controlled trial indicated that a folic acid-containing multivitamin supplement in early pregnancy in addition to providing protection against neural-tube defects also protected against some CHD,[23 24] and this was confirmed in another Hungarian intervention trial[25] and in some observational studies.[26 27] Folic acid may be protective against CHD.[28–31] Evaluation of medically recorded high doses of folic acid supplementation showed some preventive effect for ASPA in this study. The recommended daily dose of folic acid is 0.4 mg in pregnant women with a low risk for neural-tube defects. However, only one type of folic acid tablet containing 3 mg was available in Hungary during the study period, and obstetricians tended to recommend two tablets per day.

The multifactorial threshold model provides the best explanation for the origin of common CHD including RSODH.[32] This study showed that maternal hypertension with nifedipine treatment may trigger a genetic predisposition for RSODH.

Our study has several strengths. We used the large HCCSCA population-based data set including 200 cases with RSODH, and 304 matched and 38 151 population controls without CA in the ethnically homogeneous Hungarian (Caucasian) population in Hungary. The validity of CHD diagnoses is good due to follow-up of our cases in cardiology institutions or reference to autopsy records. As we wanted to work with a homogeneous RSODH group, syndromic/multiple cases were excluded and only severe cases who underwent surgical intervention or died were included in the study. Exposure data were mainly collected from prospective medically recorded data. Exposure time and potential confounders were measured.

However, there were some weaknesses in our study. The ascertainment of some RSODH groups is incomplete due to late diagnoses and the mild manifestations of these CHD, although our sample included only severe cases. Furthermore, the limited number of pregnant women in the different RSODH groups was a drawback. Finally, cases with RSODH were born between 1980 and 1996 and so the impacts of recent progress in medical care cannot be evaluated.

In conclusion, our findings showed maternal hypertension with nifedipine treatment had a possible aetiological role in the origin of RSODH, while high doses of folic acid were protective against ASPA.

Contributors AV checked the data of the Hungarian Case-Control Surveillance of Congenital Abnormalities and evaluated birth outcomes, maternal socio-demographic characteristics, maternal diseases and related drug treatments, and pregnancy complications. MC-S visited cardiology institutions and checked and/or revised (if necessary) the diagnoses of cases with congenital cardiovascular abnormalities. BG performed the statistical analysis. AEC established the Hungarian Case-Control Surveillance of Congenital Abnormalities, and prepared and completed (with the help of Erika Varga) the data of cases and controls for analysis. The paper was written and approved by all authors.

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