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Possible association of first and high birth order of pregnant women with the risk of isolated congenital abnormalities in Hungary – a population-based case-matched control study

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ABSTRACT

Objective: In epidemiological studies at the estimation of risk factors in the origin of specified congenital abnormalities in general birth order (parity) is considered as confounder. The aim of this study was to analyze the possible association of first and high (four or more) birth order with the risk of congenital abnormalities in a population-based case-matched control data set.
Study design: The large dataset of the Hungarian Case-Control Surveillance of Congenital Abnormalities included 21,494 cases with different isolated congenital abnormality and their 34,311 matched controls. First the distribution of birth order was compared of 24 congenital abnormality groups and their matched controls. In the second step the possible association of first and high birth order with the risk of congenital abnormalities was estimated. Finally some subgroups of neural-tube defects, congenital heart defects and abdominal wall's defects were evaluated separately.
Results: A higher risk of spina bifida aperta/cystica, esophageal atresia/stenosis and clubfoot was observed in the offspring of primiparous mothers. Of 24 congenital abnormality groups, 14 had mothers with larger proportion of high birth order. Ear defects, congenital heart defects, cleft lip ± palate and obstructive defects of urinary tract had a linear trend from a lower proportion of first born cases to the larger proportion of high birth order. Birth order showed U-shaped distribution of neural-tube defects and clubfoot, i.e. both first and high birth order had a larger proportion in cases than in their matched controls.
Conclusions: Birth order is a contributing factor in the origin of some isolated congenital abnormalities. The higher risk of certain congenital abnormalities in pregnant women with first or high birth order is worth considering in the clinical practice, e.g. ultrasound scanning.

Introduction

Just 100 years ago, i.e. in 1914, Pearson published a book to demonstrate that the first-born child to be liable to physical and mental handicaps [1]. This idea stimulated Penrose to investigate the effect of birth order and maternal age for birth outcomes [2] and his study showed that advanced maternal age associated with a higher risk of Down syndrome and he postulated: "mongolism and some others malformations may have their origin in chromosome anomalies" in the 1930s.

Thus at the estimation of association between different risk factors and the higher risk of structural birth defects, i.e. congenital abnormalities (CAs), maternal socio-demographic data such as age, birth order (parity), socio-economic status and ethnicity as confounders are considered. The possible association of birth order, namely first or high birth order with higher risk of preterm birth, low birthweight, small for gestational age, perinatal mortality was evaluated frequently [3]. Later, the effect of birth order was shown as confounder in the origin of some specified CAs, e.g. esophageal atresia had more than 30% decreased risk for mothers delivering their second (OR, 0.68; 95% CI, 0.56–0.83) or third child (OR, 0.64; 95% CI, 0.49–0.83) compared to primiparous mothers [4]. Recently the association of risk for autism with higher birth order was also observed [5]. This topic is important because there is drastic birth control in most developed countries,

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including Hungary, therefore a robust increase was observed in the proportion of first birth.

However, as far as we know, the effect of birth order has not been evaluated systematically in all different CA-groups compared to their matched controls. Thus, the aim of this study was to evaluate the birth order of pregnant women who had index patients affected with isolated CA in the population-based large data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [6]. Syndromic and multiple CAs will be evaluated in another study.

Materials and methods

Study groups

Index patients, as cases affected with CA were selected from the data set of the Hungarian Congenital Abnormality Registry (HCAR) for the HCCSCA. The HCAR is based on the mandatory reporting of cases with CA by physicians, mainly obstetricians and pediatricians [7,8]. In Hungary the autopsy was also mandatory for all infant deaths and frequent in stillborn fetuses, and pathologists sent a copy of the autopsy report to the HCAR if defects were identified. Since 1984 prenatal diagnostic centers were also asked to report malformed fetuses diagnosed prenatally to the HCAR. In the HCAR two main categories of cases with CA are differentiated strictly: isolated (only one organ is affected) and multiple-syndromic (concurrence of two or more CAs in the same person affecting at least two different organ systems) CAs. The recorded total (birth + fetal) prevalence of cases with CA was 35 per 1000 informative cases (live-born infants, stillborn fetuses and electively terminated malformed fetuses) between 1980 and 1996 [7] and about 90% of major CAs were recorded in the HCAR [9].

The staff of the HCAR organized annual meetings of parents with cases affected with different CAs by the request of families in our institute between 1980 and 1996 [10]. First the staff of the HCAR informed parents on the characteristics of CAs in their children and the possible causes of CAs, after this invited experts examined children and, if parents requested, advised on further examinations, treatments, and prevention of recurrence risk. One of the major benefits of these parental meetings was that the physical examination of cases by experts improved the quality of CA-diagnoses in the HCAR.

Only those cases were selected from the HCAR for the HCCSCA, who were reported during the first three months after births or pregnancy terminations (77% of all cases). In addition cases with congenital dislocation/dysplasia of the hip, congenital inguinal hernia, large hemangioma and CA-syndromes caused by gene mutations or chromosomal aberrations with preconception origin were excluded. The exception was Down syndrome because cases with this CA were used as malformed controls.

The controls were defined as newborn infants without CA. The source of these controls was the National Birth Registry of the Central Statistical Office for the HCCSCA on the basis of case lists for each quarter of the years from the staff of the HCAR. In general two controls were matched to every 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.

Collection of maternal socio-demographic data

(i) Maternal age and birth order were recorded in the Notification Form of Cases with CA reported by medical doctors to the HCAR.

(ii) A letter and printed informed consent were mailed continuously to the address of the mothers of cases and controls immediately after their selection for the HCCSCA and they were requested to send us the discharge summary of their delivery and every medical record concerning their child's CA. The latter helped us to improve the quality of CA-diagnoses further. These documents were sent back within four weeks.

(iii) A structured questionnaire was also mailed to the mothers of cases and controls asking them to give – among others – their socio-demographic data (maternal age, birth and pregnancy order, employment status as indicator of their socio-economic status).

The mean ± S.D. time elapsed between the end of pregnancy and return of the "information package" (including discharge summary, questionnaire and informed consent) in our prepaid envelope was 3.5 ± 2.1 and 5.2 ± 2.9 months in cases and controls, respectively.

(iv) There was a supplementary data collection as well. Regional district nurses were asked to visit all mothers of cases who did not respond and to 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, because the ethics committee considered this follow-up to be disturbing for the parents of all healthy children [6].

Thus, finally the confirmed maternal data were 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) in the HCCSCA. The signed informed consent was available in 98% of mothers; the name and address were deleted in 2% of subjects without signed informed consent.

Here only the 17 years' data set of the HCCSCA, 1980–1996 are evaluated [6] because the method of data collection was changed in 1997 and the recent data have not been validated at the time of this analysis.

Statistical analysis

The software SPSS, version 15.0 (SPSS Inc., Chicago, IL, USA) was used. Mean birth order (and maternal age) was compared using Student's *t*-test. The birth order distribution was first evaluated at the comparison of mothers of cases with different CA and their matched controls. After this the proportion of first birth order was compared with the proportion of two or more birth orders between the mothers of cases with different CA and their matched controls. In the next step high, i.e. four or more birth order was analyzed compared to the 1–3 birth orders in different CA-groups. The relative risk (OR with 95% CI) of different CAs was estimated on the basis of comparison of cases and their matched controls using conditional logistic regression model. At the calculation of adjusted OR for birth order, maternal age was considered as confounder. If OR less than 1.00, there is a higher risk for the given CA while if OR larger than 1.00, there is a lower risk.

Results

The case group consisted of 22,843 malformed newborns or fetuses ("informative cases") with CA and among them 21,494 (94.1%) had isolated CA in the HCCSCA, 1980–1996. Of these 21,494 cases, 21,056 (98.0%), 335 (1.5%) and 103 (0.5%) were live-born babies, stillborn fetuses (late fetal death after the 28th gestational week) and elective termination of malformed fetuses after prenatal diagnosis, respectively.

The total number of births in Hungary was 2,146,574 during the study period between 1980 and 1996. Thus the 38,151 live-born