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ORIGINAL ARTICLE

POSSIBLE ASSOCIATION OF MATERNAL HAEMORRHOID WITH CONGENITAL ABNORMALITIES IN THEIR CHILDREN – A POPULATION-BASED CASE-CONTROL STUDY

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ABSTRACT

Objectives: To look for a possible association of maternal haemorrhoid during pregnancy with a risk of congenital abnormalities in their children.

Methods: Comparison of the prevalence of medically-recorded haemorrhoid in pregnant women who had fetuses/newborns (cases) with congenital abnormalities and healthy babies (controls) in the population-based Hungarian Case-Control Surveillance System of Congenital Abnormalities.

Results: Of 22,843 cases with congenital abnormalities, 798 (3.49%), while of 38,151 controls, 1,624 (4.26%) had mothers with recorded and usually treated severe haemorrhoids. We found a higher risk for exomphalos (OR with 95% CI: 4.9, 1.7-7.9), and malposition-malrotation of gut (OR with 95% CI: 17.2, 2.1-142.0) which were present in 14 and 8 children of pregnant women with haemorrhoid, respectively. These associations could not be explained by teratogenic effect of maternal haemorrhoid or by drug treatments, so we hypothesized a possible common genetic background.

Conclusions: The higher frequency of exomphalos and malposition-malrotation of gut found in the children of mothers with haemorrhoid during pregnancy requires further study.

Key words: Haemorrhoid; Related drug treatment; Pregnancy; Maternal effect; Congenital abnormalities; Exomphalos; Malposition-malrotation of gut; Population-based case-control study.

INTRODUCTION

Our ongoing project is the systematic analysis of the possible association of maternal diseases in pregnant women with adverse birth outcomes in their newborns babies based on the large population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [1]. Our motivation is that: (i) the possible teratogenic-fetotoxic effect of drugs has been frequently studied but the reasons of these treatments, i.e. underlying maternal diseases sometimes were neglected; and (ii) the association of some maternal diseases, such as diabetes and epilepsy with pregnancy outcomes is well-known, but some other pathological conditions, e.g. haemorrhoid were not studied in controlled epidemiological studies [2, 3].

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Haemorrhoid is a common pathological condition [4] particularly in females and in pregnant women [5]. There are two main manifestations of haemorrhoid. External haemorrhoid consists of a cluster of veins and the overlying, redundant squamous integument at the external brim of the rectal outlet. Secondary aggregates may be found flanking these primary sites to increase the number of external and internal haemorrhoid complexes from the usual three to as many as six. Pain without bleeding is the characteristic symptom of these external redundancies. With injury by abnormal bowel movements (diarrhoea or constipation), bleeding and painful oedema may develop in the overlying skin with or without thrombosis within one or more of the subintegumental haemorrhoidal veins. Internal haemorrhoid consists of a cluster of submucosal veins adjacent to the dentate line. Redundancy of the overlying mucosa produces a prominence immediately within the rectal outlet.

We have studied the possible association between maternal haemorrhoid and related drug treatments with congenital abnormalities (CAs) in their offspring in the population-based data set of the HCCSCA on the basis of a "no association" hypothesis.

MATERIALS AND METHODS

Study Subjects: *Cases* with CA were selected from the data set of the Hungarian Congenital Abnormality Registry (HCAR), 1980-1996 [6] for the HCCSCA. Notification of cases to the HCAR is compulsory for physicians from the birth until the end of first postnatal year. Most cases were reported by obstetricians and paediatricians since practically all deliveries took place in inpatient obstetric clinics and were attended to by obstetricians. Paediatricians worked in the neonatal units of inpatient obstetric clinics, or in various inpatient and outpatient paediatric clinics. Autopsy was mandatory for all infant deaths and was suggested for stillborn fetuses, thus autopsy was done in nearly 100% of infant deaths and in about 80% of stillborn fetuses (i.e. fetal death after 28th gestational week) during the study period. Pathologists sent a copy of the autopsy report to the HCAR if defects were identified in stillbirths and infant deaths. Since 1984 fetal defects diagnosed in prenatal diagnostic centres with or without termination of pregnancy have also been included into the HCAR.

CAs were differentiated into three groups: (i) lethal, if defects cause stillbirth or infant death or pregnancies were terminated due to fetal defect in more than 50% of cases; (ii) severe, if without medical intervention CAs cause handicap or death; and (iii) mild, these CAs require medical intervention but life expectancy was good. The first two groups together constituted major CAs. Two main categories of CAs were also differentiated: isolated (only one organ is affected) and multiple (if two or more CAs were present in the same person in at least two different organ systems).

The total (birth + fetal) prevalence of cases with CA diagnosed from the second trimester of pregnancy through the age of one year was 35 per 1000 *informative offspring* (live-born infants, stillborn fetuses and selectively -terminated malformed fetuses) in the HCAR, 1980-1996, although 65.3 per 1000 was expected [7]. However, about 90% of major CAs were recorded in the HCAR during the 17 years of the study period [6].

Three exclusion criteria were used for the selection of cases with CAs from the HCAR for the data set of the HCCSCA: (i) cases reported after three months of birth or elective pregnancy termination (23% of cases which were mainly mild CAs), (ii) three mild CAs (congenital dysplasia of hip and inguinal hernia, large haemangioma), and (iii) CA syndromes caused by major mutant genes or chromosomal aberrations with preconceptional origin.

Controls were newborns without CA and were derived from the National Birth Registry of the Central Statistical Office for the HCCSCA. Controls were defined as newborn infants without CA. Two controls were matched to every case according to sex, birth week in the same year when cases were born, and district of parents' residence.

The case group consisted of 22,843 malformed newborns or fetuses ("informative offspring"). The total births numbered 2,146,574 in Hungary during the study period, thus the control group containing 38,151 newborns represented 1.8% of all these births.

Exposure Data and Possible Confounders

1. Prospective data recorded by medical doctors. Mothers were asked, in an explanatory letter, to send us the prenatal maternity logbook and other medical records particularly discharge summaries. Since prenatal care was mandatory and non-attendance carried serious penalty, nearly 100% of pregnant women visited prenatal care clinics, on average 7 times. The first visit was between the 6th and 12th gestational week when obstetricians recorded all pregnancy complications, maternal diseases and related drug prescriptions in the prenatal maternity logbook.

2.Retrospective self-reported maternal information. A structured *questionnaire,* a list of drugs and vitamin supplements, a list of diseases, and a printed informed consent form for signature were also mailed to the mothers immediately after the selection of cases and controls. The list of diseases (including haemorrhoid) and of drugs/supplements that were enclosed was used as a memory aid before the questionnaire was filled in.

The mean $\pm$ S.D. time elapsed between the birth or pregnancy termination and the return of the "information package" (questionnaire, logbook, etc) in the prepaid envelope was 3.5 $\pm$ 1.2 and 5.2 $\pm$ 2.9 months in the case and control groups, respectively

3. Supplementary data collection. Regional nurses were asked to visit all non-respondent case mothers at home and to help them filling in the questionnaire, to evaluate available medical records, particularly prenatal maternity logbook**. In addition they were asked to obtain data of lifestyle factors through an interview of mothers and fathers or other close relative living with them so that a 'family consensus' was recorded regarding smoking and alcohol drinking. Smoking was recorded as the number of cigarettes per day. Drinking was recorded as (i) abstinent or occasional (less than one drink per week), (ii) regular (from one drink daily to one drink per week), and (iii) hard (more than one drink per day). Regional nurses visited 200 non-respondent and 600 respondent control mothers in two validation studies [8, 9] because the committee on ethics considered this follow-up to be disturbing if required for the parents of all the healthy children. Similar methods were used for control and for case mothers.

The exposure data were available on 96.3% of cases (84.4% from reply to the mailing, 11.9% from the nurse visit) and 83.0% of the controls (81.3% from reply, 1.7% from visit). Informed consent form was obtained from 98% of mothers.

The preliminary analysis revealed one group of pregnant women who had medically-recorded diagnosis of haemorrhoid in the prenatal maternity logbook that was confirmed by the obstetrical examination and a second group who had reported haemorrhoid in the questionnaire by mothers, but that was not recorded in the prenatal maternity logbook usually because there was no treatment and/or their onset was not reported. The second group was not included in the study.

All drug treatments, medically-recorded or self-reported, were evaluated with special attention to those that were haemorrhoid related. Potential confounding factors such as maternal age, birth order, marital and employment status as indicators of socio-economic status [10], pregnancy complications, other maternal diseases, vitamin supplements particularly folic acid and multivitamins as indicators of the standard of preconceptional and prenatal care, were also considered.

Gestational time was calculated from the first day of the last menstrual period. Since the critical period of most major CAs is in the second and third gestational months, this time window was used in the study [11]. Besides birth weight (g) and gestational age at delivery (wk), the frequency of low birth weight (< 2500 g) and preterm births (< 37 weeks) as adverse birth outcomes were analyzed on the basis of discharge summaries from inpatient obstetric clinics.

Statistical Methods

SAS version 8.02 (SAS Institute Ins., Cary, North Carolina, USA) was used for statistical analyses. First the main maternal and newborn variables were evaluated in case and control pregnant women with or without haemorrhoid as reference using Student t test for quantitative chi square test for categorical variables. The occurrence of pregnancy complications, other maternal diseases and drug intakes during pregnancy, were compared between the case and the control mothers with haemorrhoid using crude odds ratios (OR) with 95% confidence intervals (CI). The occurrence of haemorrhoid in the mothers of cases with specific CA groups and in the

mothers of all matched controls was compared in conditional logistic regression models and adjusted OR with 95% CI was calculated for estimating of association of maternal haemorrhoid with CA in their children. The bias connected with multiple testing was limited by the use of the Bonferroni method [12].

RESULTS

The case group consisted of 798 (3.49%) informative offspring while the control group included 1,624 (4.26%) newborns who had mothers with medically-recorded diagnosis of haemorrhoid in the prenatal maternity logbook. Of 798 case mothers, 276 (34.6%), while of 1,624 control mothers, 543 (33.4%) had haemorrhoid before the conception and during the study pregnancy. This condition was considered as *chronic haemorrhoid,* and about 90% of them occurred multiparae. In the rest, *new-onset* haemorrhoids started usually between the seventh and ninth gestational months.

The maternal demographic variables are shown in Table 1. Mean age of case and control mothers with haemorrhoid was 26.2 and 26.7 years, respectively. These figures are higher than the mean age (25.4 years) of control mothers without haemorroid. This difference is explained by the lower frequency in those 19 years or less of age and the higher frequency in those with 30 or more years of age. The mean birth order was 1.9 in pregnant women with haemorrhoid, higher than in those without haemorrhoid (1.7-1.8). Haemorrhoid occurred more frequently in managerial (28.0% vs. 25.1%) and in mainly professional (17.2% vs. 10.2%) women. Folic acid and multivitamin supplementations were more frequent in women with haemorrhoid , both in case mothers (51.8% vs. 49.3%) and particularly in control mothers (57.1% vs. 54.3%). Nearly all other pregnancy supplements, except for vitamin D, were used more frequently by pregnant women with haemorrhoid.

Of 2,640 pregnant women visited at home, 101 (3.8%) recorder haemorrhoids, and 16 (18.8%) smoked during the study pregnancy. Of 2,539 pregnant women without haemorrhoids, 564 (22.2%) smoked. Of 800 control mothers visited at home, 36 (4.5%) had recorded haemorrhoids and 6 (16.7%) smoked, while of 764 pregnant women without haemorrhoids, 146 (19.1%) were smokers. About 1% of case and control mothers were hard or regular drinkers.

Among medically-recorded pregnancy complications in the maternity logbook, only the frequency of anaemia was significantly higher in both case mothers (23.8% vs. 13.8%, OR with 95% CI: 1.9, 1.6-2.3) and control mothers (24.4% vs. 16.3%, OR with 95% CI: 1.7, 1.5-1.9) with haemorrhoid compared to pregnant women without haemorrhoid.

The incidence of acute maternal diseases and the prevalence of chronic maternal disorders are shown in Table 2. All acute diseases, especially those of digestive system and due mainly to infectious diarrhoea, were more frequent in pregnant women with haemorrhoid. About 40% of those with haemorrhoid had a recorded diagnosis of constipation. Phlebitis-thrombophlebitis (11.3% vs. 1.7%), varicose veins of lower extremities (7.0% vs. 1.2%) and migraine (3.2% vs. 2.1%) showed a higher prevalence in pregnant women with haemorrhoid. Comparison of case and control mothers with haemorrhoid showed a significantly higher occurrence of influenza-common cold (36.8% vs. 27.5%), acute diseases of digestive system (10.0% vs. 6.0%) and constipation (45.7% vs. 39.3%) in case mothers than in control mothers with haemorrhoid.

We found no significant difference in the frequency of drugs used for the treatment of haemorrhoid in case and control mothers so we have combined them as 'pregnant women with or without haemorrhoid' (percentages are shown in parentheses). Treatment mainly consisted of tribenoside (Glyvenol®) (19.0% vs. 0.0%) and dobesylicum calcium (Doxium®) (4.7% vs. 0.0%) as tablet, phenol + bacterium coli (Reparon®) (18.2% vs. 0.3%), epinephrine + ephedrine + procaine + others (Hemorid®) (6.2% vs. 0.1%) as suppository and ointment, epinephrine + chloramphenicol + tetracaine + others (Nodicid®) (4.5% vs. 1.1%), lidocaine + others (Aurobin®) (8.1 vs. 0.2%) as ointments. However, the analgesic dipyrone (10.6% vs. 5.2%) and acetylsalicylic acid (7.7% vs. 4.0%), the antispasmodic drotaverine (12.7% vs. 8.8%), the laxative senna (6.5% vs. 2.0%) and the antifungal clotrimazole (12.1% vs. 7.6%) were also

used more frequently by 2,422 pregnant women with haemorrhoid than by 58,572 pregnant women without haemorrhoid.

Only the birth outcomes of newborns without CA in the control group are shown Table 3, since CAs may have a more severe effect on gestational age at delivery and birth weight than haemorrhoid. There was no difference in sex ratio and in the mean gestational age between newborn infants born to pregnant women with or without haemorrhoid. However, the mean birth weight (3,339 vs. 3,273g) was significantly larger in the newborns of mothers with haemorrhoid, but this 67 grams excess does not seem to be clinically important. The frequency of preterm births and of low birthweight was not significantly different in the newborns of mothers with or than in those of mothers without haemorrhoid.

Table 1. Maternal variables of case and control mothers with or without haemorrhoid

Variables	Case mothers				Control mothers			
	without haemorrhoid		with haemorrhoid		without haemorrhoid		with haemorrhoid	
Quantitative	(N=22,045)		(N=798)		(N=36,527)		(N=1,624)	
Maternal age, yr.	No	%	No	%	No	%	No	%
19 or less	2,462	11.2	44	5.5	3,210	8.8	67	4.1
20 – 29	15,023	68.1	570	71.4	26,457	72.4	1,145	70.5
30 or greater	4,560	20.7	184	23.1	6,860	18.8	412	25.4
Mean, S.D.	25.4	± 5.3	26.2	± 4.9	25.4	± 4.9	26.7	± 4.8
Birth order								
1	10,388	47.1	330	41.4	17,577	48.1	632	38.9
2 or more	11,657	52.9	468	58.6	18,950	51.9	992	61.1
Mean, S.D.	1.8	± 1.1	1.9	± 1.0	1.7	± 0.9	1.9	± 1.0
Categorical	No.	%	No.	%	No.	%	No.	%
Unmarried	1,243	5.6	26	3.3	1,417	3.9	55	3.4
Employment status								
Professional	1,864	8.5	113	14.2	4,120	11.3	303	18.7
Managerial	4,880	22.1	217	27.2	9,804	26.8	462	28.4
Skilled worker	6,271	28.4	230	28.8	11,451	31.3	457	28.1
Semiskilled worker	4,070	18.5	127	15.9	5,921	16.2	239	14.7
Unskilled worker	1,742	7.9	34	4.3	2,118	5.8	69	4.3
Housewife	2,342	10.6	64	8.1	2,291	6.3	63	3.9
Others	876	4.0	13	1.6	822	2.3	31	1.9
Pregnancy supplements								
Iron	14,180	64.3	562	70.4	25,596	70.1	1,175	72.4
Calcium	1,715	7.8	88	11.0	3,386	9.3	197	12.1
Folic acid	10,866	49.3	413	51.8	19,847	54.3	928	57.1
Vitamin B6	1,928	8.7	85	10.7	3,869	10.6	217	13.4
Vitamin D	5,920	26.9	181	22.7	9,776	26.8	374	23.0
Vitamin C	857	3.9	55	6.9	1,590	4.4	95	5.8
Vitamin E	1,357	6.2	61	7.6	2,205	6.0	102	6.3
Multivitamins	1,273	5.8	57	7.1	2,385	6.5	124	7.6

Table 2. Incidence/prevalence of maternal disease of case and control mothers with and without haemorrhoid

Maternal diseases	Case mothers					Control mothers					Comparison of cases and controls with haemorrhoid
	without haemorrhoid (N=22,045)		with haemorrhoid (N=798)		Comparison	without haemorrhoid (N=36,527)		with haemorrhoid (N=1,624)		Comparison	
	No.	%	No.	%	OR 95% CI	No.	%	No.	%	OR 95% CI	OR 95% CI
Acute disease groups											
Influenza - common cold	4,673	21.2	294	36.8	**2.2 1.9-2.5**	6,614	18.1	447	27.5	**1.7 1.5-1.9**	**1.5 1.3-1.8**
Respiratory system	2,010	9.1	108	13.5	**1.6 1.3-1.9**	3,201	8.8	254	15.6	**1.9 1.7-2.2**	0.8 0.7-1.1
Digestive system	661	3.0	80	10.0	**3.6 2.8-4.6**	835	2.3	98	6.0	**2.7 2.2-3.4**	**1.7 1.3-2.4**
Urinary tract	1,513	6.9	76	9.5	**1.4 1.1-1.8**	2,195	6.0	113	7.0	1.2 0.9-1.4	1.4 1.0-1.9
Genital organs	1,602	7.3	74	9.3	**1.3 1.0-1.7**	2,732	7.5	159	9.8	**1.3 1.1-1.6**	0.9 0.7-1.2
Others	361	1.6	25	3.1	**1.9 1.3-2.9**	482	1.3	30	1.8	1.4 0.9-2.0	1.7 1.0-2.9
Chronic diseases											
Diabetes mellitus	76	0.3	4	0.5	1.5 0.5-4.0	68	0.2	6	0.4	2.0 0.9-4.6	1.4 0.4-4.8
Epilepsy	79	0.4	5	0.6	1.8 0.7-4.3	85	0.2	3	0.2	0.8 0.3-2.5	3.4 0.8-14.3
Essential hypertension	984	0.9	46	5.8	1.3 0.9-1.8	1,491	4.1	88	5.4	**1.3 1.1-1.7**	1.1 0.7-1.5
Migraine	533	2.4	32	4.0	**1.7 1.2-2.4**	668	1.8	45	2.8	**1.5 1.1-2.1**	1.5 0.9-2.3
Phlebitis-thrombophlebitis	256	1.1	65	8.1	**7.5 5.7-10.0**	731	2.0	208	12.8	**7.2 6.1-8.5**	0.6 0.5-0.8
Varicose veins of lower extremities	281	1.3	51	6.4	**5.3 3.9-7.2**	448	1.2	118	7.3	**6.3 5.1-7.8**	0.9 0.6-1.2
Constipation	100	0.5	365	45.7	**185.0 145.4-235.3**	158	0.4	639	39.3	**149.3 124.1-179.7**	**1.3 1.1-1.5**

Bold numbers show significant association

The possible risk of maternal haemorrhoid for CAs in their offspring was estimated by comparing medically- recorded haemorrhoid in the mothers of cases with different CA groups (including at least 3 cases) and in those of their *all matched controls* (Table 4). There was no higher risk for the total group of CAs and for the multiple CA group, the upper limit of confidence interval not reaching 1. However, of the 22 groups of isolated CAs, exomphalos/gastroschisis was distinctive. Of the 238 cases, 172 had exomphalos/omphalocele and 66 had gastroschisis. (Umbilical hernia and exomphalos or gastroschisis as component of multiple CAs were excluded from this CA-group). Of 172 cases with isolated exomphalos, 14 (8.14%) had mothers with haemorrhoid during the study pregnancy (OR with 95% CI: 4.9, 1.7-7.9), while of 66 cases with gastroschisis, only one had a mother with haemorrhoid (1.52%; OR with 95% CI: 0.4, 0.1-1.2). After Bonferroni correction, the association of maternal haemorrhoid with a higher risk of exomphalos remained significant (p=0.03). The critical period for exomphalos is in the second and third gestational month, but of 14 cases with exomphalos, 13 had mothers with new-onset haemorrhoid that appeared after the third gestational month. All cases with exomphalos were diagnosed live-born infants and had no familial occurrence of this CA.

We also evaluated the different entities in the group of "Other isolated CAs". Of these 868 cases, 31 had mothers with haemorrhoid, of which 8 cases had malposition/rotation of digestive organs, i.e., transposition of small intestine in 4 and malrotation of colon in 3. All were males and had no familial history of these CAs of gut. There were 53 (0.23%) cases with malposition/malrotation of gut in the total group of 22,843 CAs, of which 8 (1.00%) were born to 798 mothers with haemorrhoid (chi square: 17.8, p=0.0001). In addition, of the above 53 cases 8 (15.5%) had malposition/malrotation of gut, while of their 98 matched controls, 3 (3.1%) had mothers with haemorrhoid. This difference also shows a significant association with maternal haemorrhoid (OR with 95% CI: 17.2, 2.1-142.0, after Boferroni correction p=0.03). Of these 8 cases, 6 had mothers with chronic haemorrhoid.

DISCUSSION

The above results made us reject the "no association" hypothesis because of the higher risk of exomphalos and malposition-malrotation of gut in children of mothers with haemorrhoid during pregnancy.

We confirmed that pregnant women with haemorrhoid are older and comprise a higher

Table 3. Birth outcomes of newborn without any defect born to mothers with or without haemorrhoid

Birth outcomes	Pregnant women without haemorrhoid (N=36,527)		with (N=1,624)		Comparison			
					Crude		Adjusted	
Quantitative	Mean	S.D.	Mean	S.D.	t =	p =	t =	p =
Gestational age (wk)*	39.4	2.0	39.4	2.0	0.3	0.76	0.1	0.94
Birth weight (g)**	3,273	511	3,339	516	5.1	<0.0001	**4.4**	**<0.0001**
Categorical	No.	%	No.	%	OR (95% CI)		OR (95% CI)	
Preterm birth*	3,3587	9.2	139	8.6	0.9 (0.8-1.1)		1.0 (0.8-1.2)	
Low birthweight**	2,090	5.7	77	4.7	0.8 (0.7-1.0)		0.8 (0.6-1.1)	

*adjusted for maternal age, birth order, use of folic acid, and maternal socio-economic status

**adjusted for maternal age, birth order, maternal socio-economic status, some maternal disease and related drug treatments, use of folic acid and gestational age

Bold number shows significant association

Table 4. Matched analysis to estimate the association between maternal haemorrhoid any time during pregnancy and different CAs in their offspring

Study groups	Grand total No	During pregnancy No.	%	Adjusted OR** (95% CI)
Controls	38,151	1,624	4.26	reference
Isolated CAs				
Neural-tube defects	1,202	48	3.99	1.1 (0.8-1.7)
Cleft lip ± palate	1,375	46	3.46	0.8 (0.6-1.2)
Cleft palate	601	17	2.83	0.7 (0.4-1.2)
Oesophageal atresia/stenosis	217	7	3.23	0.6 (0.2-1.4)
Cong. pyloric stenosis	241	10	4.15	1.2 (0.5-2.8)
Intestinal atresia/stenosis	158	4	2.53	0.4 (0.1-1.4)
Rectal/anal atresia/stenosis	231	11	4.76	1.4 (0.6-3.6)
Renal a/dysgenesis	126	5	3.97	0.6 (0.2-2.6)
Obstructive CAs of urinary tract	343	11	3.21	0.6 (0.2-1.4)
Hypospadias	3,038	111	3.65	1.0 (0.7-1.2)
Undescended testis	2,052	66	3.22	0.8 (0.6-1.1)
Exomphalos/gastroschisis	238	15	6.30	**3.0 (1.3-6.9)**
Microcephaly, primary	111	3	2.70	0.7 (0.2-2.9)
Cong. hydrocephalus	314	8	2.55	0.6 (0.2-1.4)
Ear CAs	354	14	3.95	0.7 (0.3-1.3)
Cardiovascular CAs	4,480	147	3.28	0.8 (0.7-1.0)
Clubfoot	2,424	88	3.63	0.9 (0.7-1.1)
Limb deficiencies	548	18	3.28	0.7 (0.4-1.3)
Poly/syndactyly	1,744	57	3.27	0.9 (0.6-1.2)
CAs of musculo-skeletal system	585	25	4.27	0.9 (0.5-1.4)
CAs of diaphragm	244	14	5.74	1.1 (0.5-2.5)
Other isolated CAs	868	31*	3.57	0.7 (0.5-1.2)
Multiple CAs	1,349	42	3.11	**0.6 (0.4-0.9)**
Total	22,843	798	3.49	**0.85 (0.78 – 0.93)**

* porencephaly 1, CAs of eyes 2 (ocular albinism, complex CA of eye), branchial cysts/sinus 2, bronchial stenosis 2, lung a/hypoplasia 2, cong. cystic lung 1, macroglossia 1, dilatation of oesophagus 1, malposition/rotation of gut 8 (see text), Hirschsprung's disease 1, horseshoe kidney 3, accessory kidney 2, giant kidney 1, exstrophy of urinary bladder 1, CA of spine 1, pectus excavatum 1, spleen agenesis 1

**adjusted for maternal age and employment status, birth order, some maternal diseases and related drug treatments, and use of folic acid.

Bold numbers show significant associations

proportion of multiparae [3]. About two-thirds of pregnant women had new-onset haemorrhoid during the study pregnancy, suggesting that pregnancy itself (not only delivery) is a predisposing factor for haemorrhoid. Haemorrhoid was more frequent in women with higher socioeconomic status and healthier lifestyle (who had a lower proportion of smokers), and higher standard of prenatal care including more frequent folic acid/multivitamin supplementation. These factors may explain a somewhat larger mean birth weight in children born to such mothers.

Anaemia is a common complication of haemorrhoid because of the frequently associated bleeding. Acute diseases of digestive system (mainly diarrhoea) and constipation were also more frequently associated with haemorrhoid. The more frequent phlebitis-thrombophlebitis, varicose veins of the lower limbs and migraine may be explained partly by advanced maternal age, but may also have some common genetic and/or environmental background with haemorrhoid.

Two important characteristics of pregnant women with haemorrhoid in this study were that the diagnosis of haemorrhoid was based on medically- recorded data in the maternity logbook and that most pregnant women were treated with drugs indicating the severity of their condition.

Our major finding was the possible association of maternal haemorrhoid with exomphalos and malposition/malrotation of gut in their newborn infants. The question is whether these possible associations are connected with the effect of maternal haemorrhoid itself, the causes of haemorrhoid, related drug treatments or other confounders and chance effect .

Exomphalos (or omphalocele) is a pathologically expanded umbilical hernia in which fetal liver and frequently bowel extrude (sometimes with malrotation of intestines), covered by a membrane which may or may not remain intact prior to, during or after delivery [13]. Approximately 25-40% of infants with exomphalos have other CAs and most of these multimalformed cases involve abnormal karyotypes or may be the component of other CA-syndromes with Mendelenian origin such as Beckwith-Wiedemann syndrome [14]. However, multiple CAs including exomphalos and umbilical hernia were excluded from our cases of exomphalos. The prevalence of isolated exomphalos was 0.2 per 1000 births in Hungary [15], and sometimes exhibited familial clustering [16-18].

An important argument against a causal association of the exomphalos in our cases with maternal haemorrhoid being an environmental factor is that all but one such case occurred in pregnant women with new-onset haemorrhoid, i.e. after the critical period of this CA, between the 6th and 11th gestational weeks.

Malposition/malrotation of gut occured more frequently in newborns of mothers with haemorrhoid. Atresia and stenosis of pylorus, small and large intestines, rectum/anal canal are well-known CAs of gut, but malposition/malrotation of gut is much less-known [3]. The mechanism of these CAs was described as a failure of the bowel to undergo normal migration and attachment on returns from physiological omphalocele to the celomic cavity and to simultaneously rotate in a counter clockwise direction around the superior mesenteric pedicle. Eventually the caecum and right colon become fixed to the posterior abdominal wall by the Toldt fusion fascia. If the rotation does not proceed to completion, fixation of the right colon does not occur and the entire intestine will have a narrowed pedicle. These defects may follow arrest of development during the 12th and 13th gestational week. However, reports regarding the etiology of transposition/malrotation of stomach, small intestine, colon are very limited but may be autosomal dominantly inherited CA [19, 20]. None of our cases were familial.

The relationship of exomphalos and malposition/malrotation of gut suggests a possible causal association with maternal haemorrhoid, because this “triad” may have a common genetic background and this hypothesis merits further study.

The drugs used in treatment of our pregnant women showed no causal association with haemorrhoid. This agrees with the scarce data on these drugs [2, 21]. Supplementary drugs such as drotaverine [22], dipyrone [23], acetylsalicylic acid [24, 25], senna [26] and clotrimazole [27] also do not increase risk for CAs.

The value of folic acid/multivitamin supplementation in prevention of exomphalos is debatable [28, 29], nevertheless, folic acid supplementation as confounder was evaluated in

the study, because mothers with hemorrhoid used folic acid more frequently in the early pregnancy as well.

When a large number of statistical tests are performed, a significant difference ($p<0.05$) is expected in every 20th calculation by chance alone. However, associations found in the study remained significant after the Bonferroni adjustment [12].

Since only women with severe, treated medically-recorded haemorrhoid were evaluated in our study, we cannot extrapolate the findings to mild haemorrhoid. Recent studies have shown an association of maternal obesity with exomphalos [29-31], but prepregnancy body mass index (BMI) of our pregnant women was not known.

In conclusion, we found a higher risk for exomphalos and malposition-malrotation of gut in the offspring of pregnant women with haemorrhoid. Further studies are needed to check these possible associations with the maternal haemorrhoid.

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