

Association between bronchial asthma in pregnancy and shorter gestational age in a population-based study

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Abstract

Objective. To study the association between bronchial asthma during pregnancy and gestational age/birth weight, and also preterm birth and low birth weight.

Method. In the population-based large data set of the Hungarian Case-Control Surveillance System of Congenital Abnormalities, 1980–1996, controls without congenital abnormalities were analysed.

Results. Of 38,151 newborn infants, 757 (2.0%) had mothers with bronchial asthma during pregnancy, 88% were medically recorded prospectively. Mothers with bronchial asthma in pregnancy had 0.6 week shorter gestational age and a higher proportion of preterm births (14.1% vs. 9.1%). These findings were reflected with a lower mean birth weight (3,102 vs. 3,279 gram) and higher proportion of low birth weight newborns (9.0% vs. 5.6%).

Conclusion. The old fashioned anti-asthmatic drugs were not able to prevent the bronchial asthma-related preterm birth, thus there is an urgent need to use modern inhaled therapies.

Keywords: *Bronchial asthma, gestational age, preterm birth, birth weight.*

Introduction

Bronchial asthma (BA) is among the most frequent chronic diseases during pregnancy affecting about 1–2% of pregnant women [1–3]. The main symptoms of BA are dyspnoea, coughing, retrosternal chest pain and whistling due to reversible obstructive ventilatory disorder, chronic inflammation, mucosal oedema and bronchial hyper-responsiveness. Uncontrolled asthma may lead to arterial hypoxemia, and even to the life-threatening state of severe acute asthma.

Most studies evaluating the course of BA during pregnancy confirmed that only one third of all patients particularly with severe BA show worsening of the disease during pregnancy, while previously mild BA usually improves [4]. BA requires adequate pharmacology therapy during pregnancy as well, thus anti-asthmatic drugs are one of the most common reasons for medical treatment in pregnant women [5]. At the evaluation of fetal development in pregnant women with BA, it is necessary to differentiate the effect of BA,

the related drug treatments and the triggering factors of BA such as allergens, cold air, respiratory viral and bacterial infections, irritants, air pollution, stress, etc. which might induce the acute exacerbation of BA.

Previous studies showed an association between chronically poor control of BA and intrauterine growth restriction, low birth weight and preterm delivery [6,7]. The latter was not associated with the severity of symptoms of BA, but was associated with the use of controller medications [8]. Recently women with well-controlled asthma during pregnancy, however, have had outcomes as good as those in their non-asthmatic counterparts [7].

The large population-based data set of the Hungarian Case-Control Surveillance of Congenital Abnormalities (HCCSCA) [9] seemed to be appropriate for the study of birth weight and gestational age, in addition to the proportion of low birth weight and preterm birth as indicators of fetal development in the control newborn infants without any defect born to mothers with or without BA.

Methods

Cases with congenital abnormality were identified from the Hungarian Congenital Abnormality Registry [10] for the HCCSCA. In general, two controls without defect were selected for every case from the National Birth Registry of the Central Statistical Office, matching individually according to sex, week of birth and district of parents' residence of cases. If selected controls were twins, only one of them was randomly included in the data set of the HCCSCA. The exposure data of medicines (drugs and pregnancy supplements), maternal diseases including BA, and pregnancy complications, were obtained from three sources of information: (i) Prospective data through antenatal care logbooks and other medical records, particularly discharge summaries before the birth of babies. Antenatal care obstetricians are obliged to record all maternal diseases existing during pregnancy and related drug treatments in the logbook. (ii) Retrospective data by a structured questionnaire completed by mothers after the birth of newborn infants. In addition, 200 non-respondent families were visited and questioned at home as part of a validation study [11]. Information was available on 83.1% of control mothers (82.6% from reply, 0.5% from visit) without families with wrong or unknown new addresses. Antenatal care logbook was available in 93.8% of these mothers. The time between the end of pregnancy and return of questionnaire was 5.2 ± 2.9 months. The diagnosis of BA was based partly on the recorded BA. However, bronchitis asthmatica or unspecified bronchitis treated with anti-asthmatic drugs in medical records and/or questionnaires were also considered as BA in the study. Our previous validation study showed that maternal self-reported information regarding their diseases during pregnancy is reliable [11]. Only the 17 years' data set of the HCCSCA (1980–1996) are evaluated because the method of data collection was changed after 1996.

The details of the HCCSCA's methods have been described previously [9]. Birth weight and gestational age were evaluated in *controls* because congenital abnormalities may have a more drastic effect for these variables than BA. Both birth weight and gestational age were medically recorded. We calculated gestational age from the first day of the last menstrual period. The definition of preterm birth was less than 37 completed weeks (less than 259 days), while post-term birth was 42 completed weeks or more (i.e., 294 days or more). Thus term births occurred from 37 to less than 42 completed weeks (259–293 days).

Statistical analysis of data

Statistical analyses were carried-out with the software SAS version 8.02 (SAS Institute Ins., Cary, North Carolina, USA). We calculated prevalence odds ratios (POR) and their 95% confidence intervals (CI) for categorical data, while Student *t*-test was used for quantitative variables. Employment status was exceptional because chi-square test was used for the evaluation of subgroups. At the calculation of adjusted *t* and POR, maternal age, birth order, employment status as indicator of socio-economic status, anti-asthmatic drugs and pregnancy supplements were used as confounders.

Results

The number of births was 2,146,574 in Hungary during the study period. We sampled 38,151 of these births as controls without any congenital abnormalities, representing 1.8% of Hungarian births during the study period. Of the 38,151 controls, 757 (2.0%) had mothers with BA. Sex ratio, i.e., the proportion of boys, was higher in mothers with BA (530; 70.0%) compared to the group of mothers without BA (24,496; 65.5%) ($\chi^2_1 = 37.4$; $p < 0.0001$). In our data set 88% of pregnant women with BA were recorded prospectively in the antenatal logbooks and/or other medical records. The rest was based on the maternal information.

Table I gives distributions of potential confounders in mothers with or without BA. While mean maternal age was somewhat higher, mean birth order was lower in mothers with BA, than in mothers without BA. There was no obvious difference in the distribution of maternal employment status, though the proportion of professionals, managerial and skilled workers was a bit larger, while the proportion of semi- and unskilled workers and housewives was somewhat smaller in mothers with BA. (In Hungary most housewives belong to the low socio-economic status.)

Among acute maternal disorders during pregnancy (Table II), only diseases of the respiratory system showed a higher prevalence in mothers with BA. Among chronic maternal disorders, rhinitis (in general allergic hay fever) occurred more frequently in pregnant women with BA. It is worth mentioning that diabetes mellitus and epilepsy were not reported in the group of 757 mothers with BA.

Among pregnancy complications (Table III), the proportion of threatened abortions, preeclampsia-eclampsia and particularly threatened preterm births was higher in mothers with BA than in the mothers without BA.

Table I. Characteristic variables (potential confounders) in the control groups with or without bronchial asthma (BA).

	Controls					
Variables	Without BA (<i>N</i> = 37,394)		With BA (<i>N</i> = 757)		Difference between the two groups	
<i>Quantitative</i>	Mean	SD	Mean	SD	test	<i>p</i> -value
Maternal age (years)						
≤ 24	17,656	47.2	338	44.7	$\chi^2_2 = 2.0$	<i>p</i> = 0.37
25–29	12,616	33.7	269	35.5		
30 +	7,122	19.1	150	19.8		
Mean ± SD	25.4 ± 4.9		25.8 ± 4.9		<i>t</i> = 1.8	<i>p</i> = 0.08
Birth order						
1	22,283	59.6	467	61.7	$\chi^2_1 = 1.4$	<i>p</i> = 0.24
2 or more	15,111	40.4	290	38.3		
Mean ± SD	1.6 ± 0.9		1.5 ± 0.7		<i>t</i> = 2.1	<i>p</i> = 0.04
<i>Categorical</i>	<i>n</i>	%	<i>n</i>	%	POR	95% CI
Unmarried	1,195	3.2	22	2.9	0.9	0.6–1.4
Employment status						
Professional	4,257	11.4	96	12.7	$\chi^2_6 = 9.6$	<i>p</i> = 0.14
Managerial	9,919	26.5	215	28.4		
Skilled worker	11,451	30.6	239	31.6		
Semi-skilled worker	5,670	15.2	113	14.9		
Unskilled worker	1,830	4.9	29	3.8		
Housewife	2,010	5.4	28	3.7		
Other	2,257	6.0	37	4.9		

Table II. The prevalence of acute and chronic maternal diseases in the control group with or without bronchial asthma (BA).

Diseases	Controls				Comparison	
	Without BA (<i>n</i> = 37,394)		With BA (<i>n</i> = 757)			
	<i>n</i>	%	<i>n</i>	%	POR	95% CI
<i>Acute infectious diseases</i>						
Influenza/common cold	6,933	18.5	129	17.0	0.9	0.7–1.1
Respiratory system	3,364	9.0	92	12.0	1.4	1.1–1.7
Digestive system	910	2.4	23	3.0	1.3	0.8–1.9
Urinary tract	2,258	6.0	43	5.7	0.9	0.7–1.3
Genital organs	2,822	7.6	63	8.3	1.1	0.9–1.4
Others	499	1.3	13	1.7	1.3	0.7–2.3
<i>Chronic maternal diseases</i>						
Diabetes mellitus	52	0.1	0	0.0	-	-
Epilepsy	69	0.2	0	0.0	-	-
Rhinitis, allergic	312	0.8	22	2.9	3.6	2.3–5.5
Obstipation	139	0.4	5	0.7	1.8	0.7–4.4
Others (without BA)	6,065	16.2	138	18.2	1.2	0.9–1.4

Medicinal products were evaluated in three categories (Table IV). Among the most frequently used drugs, allylestrenol, diazepam, drotaverine, magnesiums and senna showed a higher prevalence in mothers with BA. Allylestrenol, diazepam, drotaverine and magnesiums are used for the treatment and/or prevention of threatened abortion in Hungary. The higher use of senna can be explained by the somewhat higher prevalence of obstipation in pregnant women with BA. Of course, all anti-asthmatic drugs were used by women with BA. Aminophylline,

bromhexine and terbutaline were used for other indications as well, e.g., terbutaline is frequently used for the inhibition of uterine contractions in threatened preterm delivery. There was a lower use of calciums, vitamin D and multivitamins, while a higher use of tocopherol (vitamin E) among pregnancy supplements in the mothers with BA.

The distribution of gestational age and birth weight groups is shown in Table V. Mean gestational age was 0.6 week shorter in the mothers with BA compared with mothers without BA. The shorter

Table III. The prevalence of pregnancy complications in control mothers with or without bronchial asthma (BA).

Pregnancy complications	Controls				Comparison	
	Without BA (<i>n</i> = 37,394)		With BA (<i>n</i> = 757)			
	<i>n</i>	%	<i>n</i>	%	POR	95% CI
Threatened abortion	6,273	16.8	239	31.6	2.3	2.0–2.7
Nausea-vomiting (excessive)	3,793	10.1	76	10.0	1.0	0.8–1.3
Preeclampsia-eclampsia	1,128	3.0	33	4.4	1.5	1.0–2.1
Hypertension	1,066	2.9	19	2.5	0.9	0.6–1.4
Oedema	898	2.4	14	1.9	0.8	0.5–1.3
Proteinuria	338	0.9	11	1.5	1.6	0.9–3.0
Placental disorders*	573	1.5	19	2.5	1.7	0.9–2.6
Threatened preterm delivery**	5,098	13.6	348	46.0	5.4	4.7–6.2
Anaemia	6,211	16.6	145	19.2	1.2	0.9–1.4
Poly/oligohydramnios	201	0.5	4	0.5	1.0	0.4–2.7
Gestational diabetes	266	0.7	4	0.5	0.7	0.3–2.0
Prolonged pregnancy	497	1.3	11	1.5	1.1	0.6–2.0

*Placenta praevia, premature separation of placenta, antepartum haemorrhage. **Including cervical incompetence.

Table IV. Medications used during pregnancy.

Medications	Controls				Comparison	
	Without BA (<i>n</i> = 37,394)		With BA (<i>n</i> = 757)			
	<i>N</i>	%	<i>N</i>	%	POR	95% CI
<i>Most frequently used</i>						
Allylestrenol	5,138	13.7	219	28.9	2.6	2.2–3.0
Ampicillin	2,560	6.9	64	8.5	1.3	0.9–1.6
Clotrimazole	3,005	8.0	72	9.5	1.2	0.9–1.5
Diazepam	3,894	10.4	236	31.2	3.9	3.3–4.6
Drotaverine	3,386	9.1	95	12.6	1.4	1.2–1.8
Magnesiums	1,895	5.1	55	7.3	1.5	1.1–1.9
Noraminophenazone	2,076	5.6	45	5.9	1.1	0.8–1.5
Penamocillin	2,200	5.9	46	6.1	1.0	0.8–1.4
Senna	898	2.4	39	5.2	2.2	1.6–3.1
<i>Used for the treatment of BA</i>						
Aminophylline	2,141	5.7	143	18.9	3.8	3.2–4.6
Beclometasone	0	0.0	13	1.7	-	-
Bromhexine	776	2.1	24	3.2	1.5	1.0–2.3
Budenoside	0	0.0	11	1.5	-	-
Clenbuterol	0	0.0	56	7.4	-	-
Dexamethasone	249	0.7	82	10.8	18.1	14.0–23.5
Ephedrine	0	0.0	131	17.3	-	-
Fenoterol	0	0.0	403	53.2	-	-
Intal	0	0.0	14	1.9	-	-
Ipratropium	0	0.0	2	0.3	-	-
Orciprenaline	0	0.0	6	0.8	-	-
Salbutamol	0	0.0	77	10.2	-	-
Terbutaline	3,753	10.0	241	31.8	4.2	3.6–4.9
Theophylline	0	0.0	9	1.2	-	-
<i>Pregnancy supplements</i>						
Iron	26,254	70.2	520	68.7	0.9	0.8–1.1
Calcium	3,572	9.6	54	7.1	0.7	0.6–0.9
Folic acid	0,350	54.4	425	56.1	1.1	0.9–1.2
Vitamin B6	3,991	10.7	95	12.6	1.2	0.9–1.5
Vitamin D	9,801	26.2	162	21.4	0.8	0.6–0.9
Vitamin C	1,076	2.9	23	3.0	1.1	0.7–1.6
Tocopherol	2,200	5.9	87	11.5	2.1	1.7–2.6
Multivitamins	2,491	6.7	35	4.6	0.7	0.5–0.9

Table V. The distribution of mean gestational age and birth weight groups in newborn infants born to mothers with (BA) or without bronchial asthma (NO BA).

Gestational age (wk)	−36		37–41		42 +		TOTAL				Gestational age				
							BA		NO BA		BA		NO BA		
Birth weight (g)	BA	NO BA	BA	NO BA	BA	NO BA	No.	%	No.	%	Mean	S.D.	Mean	S.D.	
< = 2,499	40	1,244	28	805	0	51	68	9.0	2,100	5.6	35.2	3.1	35.6	3.3	
2,500–3,499	66	2,118	402	18,783	23	1,447	491	64.9	22,348	59.8	38.6	1.8	39.1	1.8	
3,500 > =	1	28	166	10,608	31	2,310	198	26.2	12,946	34.6	40.2	1.3	40.5	1.1	
Total	No.	107	3,390	596	30,196	54	3,808	757	100	37,394	100	38.8	2.2	39.4	2.1
	%	14.1	9.1	78.7	80.8	7.1	10.2	100	–	100	–	–	–	–	–
Birth weight*	Mean	2484	2483	3220	3326	3541	3617	3102	–	3279	–	–	–	–	–
	SD	487	437	434	430	411	487	520	–	511	–	–	–	–	–

*Unadjusted *t*-test for birth weight: $t=7.5$, $p < 0.0001$, adjusted for employment status: $t=7.8$, $p < 0.0001$; **Unadjusted *t*-test for gestational age: $t=7.6$, $p < 0.0001$, adjusted for employment status: $t=8.5$, $p < 0.0001$; Chi-square test for preterm birth: $\chi^2_1 = 22.9$, $p < 0.0001$; Chi-square test for low birth weight: $\chi^2_1 = 15.7$, $p < 0.000$.

gestational age was obvious in all birth weight groups. The difference was 177 g in the mean birth weight between liveborn babies born to mothers with BA and without BA. Of three gestational age groups, two had a lower mean birth weight, the exception was preterm group with similar birth weight. Both the proportion of preterm births (14.1% vs. 9.1%) and low birthweight (9.0% vs. 5.6%) was much higher in the group of mothers with BA. There was no difference in these variables between boys and girls born to mothers with BA.

Discussion

Our study showed a shorter gestational age in women with BA and it explains the significantly higher proportion of preterm births. The lower birth weight and higher proportion of low birth weight newborns are mainly the secondary consequences.

Some unexpected findings were also seen in the study. The higher proportion of boys in general is explained by the matching criterion, because cases with congenital abnormalities have a boy excess due to mainly the frequent defects of male genital organs (hypospadias and undescended testis) and controls were matched to cases according to sex as well. However, the proportion of boys was significantly higher in the newborn infants of mothers with BA compared to mothers without BA. The proportion of threatened abortions was 1.9 times higher in the mothers with BA, but a higher rate of fetal death in general associated with a boy excess thus it may result in a higher proportion of girls among liveborn babies of mothers with BA. Thus the expected and observed sex ratio is different, and possible association between the sex of offspring and maternal BA needs further studies. A somewhat higher rate of constipation and related drug treatment was also found in pregnant women with BA. The prevalence

of threatened preterm births was also 3.4 times higher in mothers with BA than in mothers without BA, but the proportion of preterm births was only 1.5 times higher in the mothers with BA. On the other hand our study confirmed some well-known facts, namely the higher occurrence of acute infectious diseases of the respiratory system and allergic rhinitis in women with BA.

The strengths of HCCSCA can be explained by the large and population-based data set of an ethnically homogeneous European people in which most BA were recorded by medical professionals before the birth (i.e., prospectively), gestational age and birth weight were medically recorded and potential confounding factors were available for analysis. Of course, limitations of the data set need to be mentioned as well. Response rate was 83%. Only 200 non-respondent families were visited at home, because the ethics committee considered that this follow-up would be disturbing to the parents of all healthy children [9]. The prevalence of pregnancy complications including BA, however, did not show differences between respondent and non-respondent families [11]. The major weakness of our study is the lack of data regarding maternal smoking as confounder. Our previous validation study showed the low validity of retrospective maternal self-reported information regarding smoking in the mothers of cases with congenital abnormalities [12], therefore these data were collected only in a minor part of the data set of the HCCSCA based on the home visit. Of 200 controls, 38 (19%) smoked during pregnancy.

The major finding of the study is that the shorter gestational age in women with BA may indicate the hazard of BA for the intrauterine development of the fetus. Our results are in agreement with some previous reports [6,7,13,14], however, the findings of recent studies did not show an association between BA and preterm delivery [15,16]. The most

widely accepted hypothesis of BA effects on delivery is hypoxia caused by the exacerbation of the disease during pregnancy [17]. Bracken et al. [8] explained the higher proportion of preterm delivery by drugs used for the treatment of BA during pregnancy. Gestation was reduced by 2.22 weeks in women treated by oral steroids daily and by 1.11 weeks after theophylline. We were not able to differentiate the effect of asthma and anti-asthmatic drugs [18,19] because only ten pregnant women with BA were not treated by anti-asthmatic drugs. However, other factors, e.g., environmental contamination, stress, etc. cannot also be excluded in the origin of shorter gestational duration. On the other hand an increased risk (24%) for intrauterine growth restriction was found associated with each increased symptom step. Inhaled therapies are the cornerstone of modern treatment [20] because after their use a higher proportion of preterm birth and/or low birth weight was not found [21].

Unfortunately, our findings indicate that the Hungarian old-fashioned protocols of anti-asthmatic therapies were not appropriate for the protection of fetal development from the hazards of maternal BA, thus it is necessary to introduce urgently modern BA therapies during pregnancy as well.

In conclusion, our findings during the study period indicate that BA can shorten the gestational age, explained mainly by the less effective previous anti-asthmatic drugs.

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