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Comparable risk of childhood asthma after vaginal delivery and emergency caesarean section

Nis Brix¹, Lonny Stokholm², Fjola Jonsdottir³, Kim Kristensen⁴ & Niels Jørgen Secher^{5,6}

ABSTRACT

INTRODUCTION: Caesarean section is thought to be a risk factor for childhood asthma, but this association may be caused by confounding from, for instance, familial factors. To address this problem, we used twin pairs to assess the risk of childhood asthma after emergency caesarean section.

METHODS: The study was a register-based nation-wide matched cohort study using twin pairs to minimise residual confounding. Included were twin pairs in which the first twin was delivered vaginally and the second by emergency caesarean section during the study period from January 1997 through December 2012.

RESULTS: In total, 464 twin pairs (928 twins) were included. In 30 pairs, the first twin (vaginal delivery) was diagnosed with asthma, but the second twin (emergency caesarean section) was not. In 20 pairs, the second twin (emergency caesarean section) was diagnosed with asthma, but the first twin (vaginal delivery) was not. In 11 pairs, both twins developed asthma. In the unadjusted analysis, emergency caesarean section did not affect the risk of asthma (odds ratio = 0.67 (95% confidence interval: 0.38-1.17); $p = 0.16$). After adjusting for birth weight, gender, umbilical cord pH, Apgar score at 5 min. and neonatal respiratory morbidity, the risk of childhood asthma following emergency caesarean section remained unchanged.

CONCLUSION: Emergency caesarean section was not associated with childhood asthma.

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TRIAL REGISTRATION: not relevant.

The prevalence of childhood asthma [1] as well as the prevalence of caesarean section (CS) [2] have increased during the past decades, and two meta-analyses have indicated that delivery by CS is associated with an increased risk of asthma in the offspring [3, 4]. However, earlier studies may lack sufficient control for confounding from familial and genetic factors [5]. To address the problem of residual confounding, some studies have used sibling pairs to assess the risk of asthma after delivery by CS [6, 7]. This type of analysis greatly reduces confounding from familial factors, but there may still be residual confounding by factors that may have differed between the births of either sibling. Hence, factors such

as maternal smoking, socioeconomic status or pregnancy complications could differ when comparing two pregnancies in the same woman.

We aimed to assess the risk of childhood asthma following emergency CS using twin pairs to further address the problem with residual confounding.

METHODS

Study design

The study was a nation-wide matched cohort study using population-based register data on all twins born in Denmark during the study period from January 1997 through December 2012. The start of the study period coincides with the onset of the electronic version of the Danish National Birth Registry.

Data sources and variables

The study was based on the Danish National Birth Registry and the Danish National Patient Registry [8]. Cross-linkage between registers was performed using the personal identification number allocated to all individuals living in Denmark [9]. From the two registers we extracted the following prospectively collected data: Mode of birth, gestational age in weeks (< 28, 28-32, 33-36, 37-40, 40+), birth weight in grams (< 1,500, 1,500-2,499, 2,500-3,499, $\geq 3,500$), small for gestational age (yes, no) defined as birth weight below the tenth percentile according to the formula developed by Marsal et al in 1996 [10], gender, umbilical cord pH < 7.25, Apgar score at 5 min. ≤ 8 , admission to the neonatal intensive care unit (yes, no), treatment with continuous positive airway pressure and/or mechanical ventilation (yes, no), diagnosis of childhood asthma, age at first diagnosis of asthma in years (0-5, 6-15), age at follow-up in years (0-5, 6-15), diagnosis type (primary or secondary diagnosis) and whether the asthma diagnosis was given at an inpatient or outpatient visit.

Exposure and outcome

The exposure was emergency CS with vaginal delivery as the reference.

A child was regarded as having the outcome, asthma, if that child was registered with any of the diagnosis codes J45, J45.0-9, J46 or J46.9 in the International

ORIGINAL ARTICLE

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Classification of Diseases, Version 10 at any inpatient or outpatient visit, whether or not the diagnosis was primary or secondary. Follow-up time started at birth and ended by December 2012 or at the time of the asthma diagnosis, whichever came first.

Inclusion and exclusion criteria

Twin pairs were included if the first twin was delivered vaginally and the second twin by emergency CS. Twins

were excluded if one or both twins died before the end of the study period.

Statistical methods

To assess the risk of asthma after emergency CS, conditional logistic regression was used for unadjusted and multivariable analysis with twins delivered vaginally as the reference. The following parameters known to be associated with childhood asthma were entered into the multivariable analysis: birth weight (continuous), gender (male, female), umbilical cord pH (continuous), Apgar score after 5 min. (continuous) and neonatal respiratory morbidity (yes, no) as expressed by need for continuous positive airway pressure (CPAP) or mechanical ventilation [11-15]. Results are presented as odds ratios with 95% confidence intervals (CI). In case of missing values, a complete case analysis was performed. The statistical analyses were performed using STATA version 12 (Stata-Corp, College station, TX, USA).

Study approval

The Danish Data Protection Board approved the study (reference number: 2013-41-1804).

Trial registration: not relevant.

RESULTS

During the study period from January 1997 through December 2012, a total of 42,628 twin births occurred in Denmark. We identified 519 twin pairs in which the first twin was delivered vaginally and the second by emergency CS. In all, we excluded 55 twin pairs; 19 due to death of one or both twins during the study period, and 36 due to missing information on birth order. Among the excluded twins, none were discordant with respect to asthma. In total, 464 twin pairs were included in the analysis. Descriptive characteristics are presented in **Table 1**.

Among the included twins, 72 (7.8%) were diagnosed with asthma (**Table 2**). In 30 cases, the first twin (vaginal delivery) developed asthma and the second (emergency CS) did not. In 20 cases, the second twin (emergency CS) developed asthma and the first (vaginal delivery) did not. In 11 twin pairs, both twins developed asthma.

In the unadjusted analysis, the risk of asthma was unaffected by mode of delivery (odds ratio = 0.67 (95% CI: 0.38-1.17); $p = 0.16$). In the multivariable analysis, the risk of childhood asthma following emergency CS remained unchanged after adjustment for birth weight, gender, Apgar score after 5 min., umbilical cord pH and need for CPAP or mechanical ventilation (**Table 3**).

Due to a high proportion of missing values on covariate of umbilical cord pH, data were analysed in an-

TABLE 1

Descriptive characteristics of all 928 included twins born in Denmark, 1997-2012. The values are n (%)

Characteristics	Vaginal delivery, 1st twin (N = 464)	Emergency CS, 2nd twin (N = 464)
<i>Gestational age^a</i>		
< 28 wks	10 (2.6)	10 (2.6)
28-32 wks	15 (3.3)	15 (3.3)
33-36 wks	137 (29.7)	137 (29.7)
37-40 wks	290 (62.8)	290 (62.8)
> 40 wks	10 (2.2)	10 (2.2)
<i>Birth weight^a</i>		
< 1,500g	22 (4.7)	17 (3.7)
1,500-2,499 g	146 (31.5)	153 (33.0)
2,500-3,499 g	276 (59.5)	273 (58.8)
≥ 3,500 g	15 (3.2)	14 (3.0)
Small for gestational age ^a	161 (35.2)	191 (42.0)
Gender, male ^a	236 (50.9)	270 (58.2)
Umbilical cord pH ≤ 7.25 ^c	46 (9.9)	99 (21.3)
Apgar at 5 min. ≤ 8 ^a	17 (3.7)	42 (9.1)
Admission to NICU ^b	198 (42.7)	234 (50.4)
Need for CPAP ^b	0 (10.8)	84 (18.1)
Need for mechanical ventilation ^b	8 (1.7)	7 (1.5)
<i>Age at diagnosis of asthma^a</i>		
0-5 yrs	36 (87.8)	30 (96.8)
6-15 yrs	5 (12.2)	1 (3.2)
<i>Age at follow-up^a</i>		
0-5 yrs	224 (48.3)	220 (47.4)
6-15 yrs	240 (51.7)	244 (52.6)
<i>Asthma diagnosis type^a</i>		
Primary	37 (90.2)	26 (83.9)
Secondary	4 (9.8)	5 (16.1)
<i>In- or outpatient asthma diagnosis^a</i>		
Inpatient	21 (51.2)	18 (58.1)
Outpatient	20 (48.8)	13 (41.9)

CPAP = continuous positive airway pressure; CS = caesarean section; NICU = neonatal intensive care unit.

a) < 5% missing values; b) 27% missing values; c) 50% missing values.

TABLE 2

Risk of asthma after emergency caesarean section (CS) according to twin pairs.

1st twin, vaginal delivery	2nd twin, emergency CS	
	with asthma	without asthma
With asthma	11 pairs	30 pairs
Without asthma	20 pairs	403 pairs



Twins delivered by caesarean section.

other multivariable model excluding umbilical cord pH, but this did not change the results. We also repeated the analysis after exclusion of factors that could be regarded as intermediates such as Apgar score at 5 min., need for CPAP or mechanical ventilation and umbilical cord pH. However, the results remained unchanged even after excluding these factors.

DISCUSSION

To our knowledge, this is the first study to address the issue of an association between delivery by emergency CS and asthma in the offspring using a matched cohort design based on twin pairs. Our study could not confirm the findings from earlier studies linking delivery by CS with asthma [3, 4], and, consequently, earlier findings of an increased risk of childhood asthma following delivery by emergency CS may be explained by residual confounding.

An important strength of our study is that it was based on prospectively collected data from a nationwide population. Furthermore, the design in which the risk of asthma was compared within twin pairs almost ruled out confounding from factors known to be associated with asthma. Such factors include, but may not be limited to, maternal age [16], maternal diseases such as asthma [16], maternal body mass index during pregnancy [17], maternal smoking [16], socioeconomic status [18], exposure to animals [12], preterm birth [16], previous miscarriages [16] and previous maternal deliveries

TABLE 3

Results from conditional logistic regression – unadjusted and adjusted risk of asthma after emergency caesarean section.

	Patients, n	OR (95% CI) ^a	
		unadjusted	adjusted
<i>Unadjusted analysis</i>	100	0.67 (0.38-1.17)	–
Emergency CS			
<i>Multivariable analysis:</i> <i>risk of asthma when adjusting for</i>	96	–	0.74 (0.41-1.34)
Birth weight ^b			
Gender ^c	100	–	0.67 (0.38-1.19)
Umbilical cord pH ^b	28	–	0.47 (0.12-1.84)
Apgar at 5 min. ^b	92	–	0.60 (0.31-1.16)
CPAP or mechanical ventilation ^c	100	–	0.69 (0.39-1.22)
<i>Multivariable analysis:</i> <i>risk of asthma when adjusting for</i>	26	–	0.28 (0.05-1.69)
Model 1 ^d			
Model 2 ^e	90	–	0.71 (0.34-1.50)
Model 3 ^f	96	–	0.74 (0.41-1.36)

CI = confidence interval; CPAP = continuous positive airway pressure; CS = caesarean section; OR = odds ratio.

a) Conditional logistic regression; b) Continuous variables; c) Dichotomous variables; d) Adjusted for the combination of birth weight, gender, umbilical cord pH, Apgar at 5 min., and CPAP or mechanical ventilation; e) Adjusted for the combination of birth weight, gender, Apgar at 5 min., and CPAP or mechanical ventilation; f) Adjusted for the combination of birth weight and gender.

[16]. However, after delivery some potential confounding factors are not necessarily shared by the twins, and therefore, confounding might still be present. Such factors include Apgar score, need for CPAP or mechanical ventilation and umbilical cord pH, which, however, could all be regarded as intermediates. In this case, they should not be adjusted for, and therefore we repeated the analysis after removing them. This did not change our results (Table 3).

Our study is limited by a number of factors. We had a relatively small sample size due to the rarity of twin births in which the first twin was born vaginally and the second by CS, and we can therefore not rule out that a larger study would have revealed different results. However, it is worth mentioning that although the difference was not statistically significant, asthma was more often diagnosed in twins delivered vaginally than in those delivered by CS. Furthermore, twins differ from singletons in a number of ways, but we find it unlikely that the mechanisms by which emergency CS could lead to asthma differ between singletons and twins. Moreover, the diagnosis codes used for asthma are often used for wheezing episodes in children younger than three years of age, and these children may not grow up to have asthma later in life. Finally, asthma diagnoses made by the general practitioner are not registered in the Danish National Patient Registry, which could lead to underestimation of the number of asthma cases in the study population.

Given the study design, we could study only the effect of emergency CS and not elective CS, whereas previous studies have generally studied the effect of both elective and emergency CS in combination [3, 4, 19]. The distinction between elective CS and emergency CS may be crucial, since the child delivered by emergency CS is usually exposed to labour, whereas the child delivered by elective CS is not. Thus, absence of labour was suggested to be the reason why children delivered by elective CS but not emergency CS had an increased risk of hospitalisation for bronchiolitis, which is an early indicator of childhood asthma [20]. Furthermore, elective CS may be more likely than emergency CS to affect the risk of asthma in the child, since another hypothesis aimed at explaining a possible link between childhood asthma and delivery by CS suggests that the aberrant gut flora found in children delivered by CS could be responsible for asthma [19]. Thus, in emergency CS, the membranes are usually not intact, and therefore the child may be colonised with the mother's vaginal microflora in utero. According to this hypothesis, our results could be biased since the close contact between twins is likely to promote transferral of microorganisms from one twin to the other, which could dilute the effect of an aberrant microbial colonisation acquired perinatally.

CONCLUSION

This study, in which confounding was maximally controlled for, could not confirm earlier findings of an increased risk of asthma in children delivered by emergency CS. Our results suggest that emergency CS can be carried out without increasing the risk of asthma in the offspring.

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