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Caesarean delivery and risk of developing atopic diseases in children

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Abstract

Background Caesarean delivery has been suggested to alter neonatal immune responses and increase the risk of atopic diseases. However, previous studies have reported inconsistent findings.

Objective To investigate a possible association between caesarean delivery and the development of atopic diseases in children.

Methods This case-control study involved 100 children aged 3 months-12 years, in Sanglah Hospital, Denpasar, Indonesia. Fifty infants and children with a confirmed diagnosis of atopic diseases and 50 sex-paired controls (non-atopic infants and children) were enrolled. Demographic data was obtained, including mode of delivery and relevant history connected to atopic diseases. Skin prick test to four common aeroallergens was performed in all subjects. Possible confounding factors were considered in a multivariable logistic regression model.

Results Caesarean section was not significant as a risk factor for atopic diseases in a multivariate analysis [OR 2.4 (95%CI 0.7 to 8.4; P=0.164)]. However, multiple logistic regression analysis showed that atopic diseases was significantly associated with a positive family history of atopy. Furthermore, caesarean section was associated with a higher risk of atopic diseases in a subgroup analysis for family history of atopy [OR= 4 (95%CI 1 to 16.2; P= 0.04)].

Conclusion Children delivered by caesarean section and have a family history of atopy have a 4-fold higher risk of atopic diseases. **[Paediatr Indones. 2014;54:94-100.]**

Keywords*: atopic diseases, cesarean delivery, children.*

The prevalence of atopic diseases in childhood has increased in many countries.[1-5] Atopic diseases is typically chronic and may restrict physical, emotional, and social well-being.[6] The proportion of caesarean sections has increased up to 30% of all deliveries, compared to the 1970s, when this proportion was generally below 15%.[7] Children delivered by caesarean section have been shown to have delayed and altered establishment of gut flora and cytokine production.[8-10] Decreased exposure to microorganisms early in life leads to insufficient stimulation of Th1 lymphocytes and, therefore, a predominance of the Th2 allergic responses.[8-15] Some investigators have reported increased risk for developing asthma and atopic diseases among children delivered by caesarean section compared to those delivered vaginally,[8,16] while others have found no such relationship.[7,17,18]

Although the relationship between mode of delivery and the prevalence of allergic diseases has been investigated in many countries, there have

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been few such reports in Indonesia. The purpose of this study was to assess for a relationship between a history of caesarean delivery and atopic diseases in infants and children.

Methods

A case-control study was performed in the outpatient clinic at the Department of Child Health, Sanglah Hospital, Denpasar from December 2011 until July 2012. Inclusion criteria for the case group were children aged 3 months-12 years with a definite diagnosis of atopic diseases. An atopic disease was defined as the presence of or a history of at least one of the following: asthma, allergic rhinitis, atopic dermatitis, or food allergy. These diseasess were diagnosed by pediatricians/physicians (pediatric residents) of Sanglah Hospital. The diagnosis was confirmed by fulfillment of the Sanglah Hospital Guidelines Criteria, with or without the support of a positive skin prick test. We excluded children suffering from severe form of atopic diseases, undergoing treatment with antihistamines and/or corticosteroids, who had incomplete data or whose parents refused to participate in the study.

Inclusion criteria for the control group were children aged 3 months-12 years without a history of any atopic diseases. These children were seen in the hospital for other unrelated problems. For the control group, we also excluded children suffering from diseasess requiring steroid and/or long-term antihistamine treatment, and who had incomplete data. The minimum required sample size was calculated with type I error (α= 5%), power (1-β) 80%, OR = 2 (clinical judgment), and P2 = 0.3,[19] to be a total of 90 children.

Demographic data regarding birth weight, age, number of siblings, exposure to environmental cigarette smoke (exposure to any smoker at home), exposure to kitchen smoke (bedroom and kitchen under the same roof), cotton-filled mattress usage, carpet usage, pets, duration of breast feeding, the age at which semi-solid food was first introduced, the age at which formula milk was first introduced, and a family history of atopic diseases were obtained from a questionnaire completed by the parents.

Subjects underwent skin prick tests to common aeroallergens: house dust mite (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), cockroach (*Blattela germanica)*, and *Aspergillus sp* (Stallergens, France) on the volar aspect of the forearm or the back. Histamine was used as the positive control and saline as the negative control. A skin prick test was considered positive for a wheal-and-flare sized > 2 mm after 15 minutes, to at least one of the common aeroallergens.

Descriptive analyses of the characteristics of the control and case group were performed. Univariate analyses comparing variable differences between the control and case groups were done using Chi-square and Fisher's exact tests, where appropriate. A P-value of <0.05 was considered to be statistically significant. Odds ratios (ORs) and 95% CIs were estimated with the use of multivariate logistic regression analyses that allowed for potential confounders. A secondary analysis was performed to examine an association between caesarean delivery and atopic diseases, in the subgroup of those with a history of family atopy.

Ethical approval for this study was obtained from Udayana University Medical School Ethics Committee and informed consent was obtained from parents before enrollment into this study.

Results

One hundred two children were recruited into this study, but only 100 subjects were analyzed. Two subjects were excluded due to the presence of severe atopic dermatitis that the skin prick test could not be performed (1 subject) and due to treatment with corticosteroids (1 subject). The mean age of subjects was 5.8 (SD 3.2) years (range 5 months-12 years). Sixty-two subjects (62%) were delivered vaginally and 38 (38%) were delivered by caesarean section. Subjects' demographic characteristics are shown in **Table 1.** Most of our study subjects in the case group suffered from allergic rhinitis (36%), followed by asthma (30%), atopic dermatitis (21%), and food allergy (12%).

The relationships between each risk factor and the occurrence of atopic diseases were analyzed**.** We found a significant association between caesarean section and atopic diseases in a bivariate analysis, but not in multivariate analyses. Multiple logistic

Table 1. Characteristics of study subjects

Characteristics	Case (atopic) n = 50	Control (non-atopic) n = 50
Male gender, n (%)	25 (50)	25 (50)
Median age (SD), years	6.0 (3.2)	5.7 (3.2)
Median body weight (SD), kg	21.6 (9.4)	18.9 (7.2)
Median body height (SD), cm	111.8 (22.4)	105.1 (25.6)
Siblings, n (%)		
0	14 (28)	10 (20)
≥1	36 (72)	40 (80)
Birth weight, n (%)		
<2,500 g	0 (0)	2 (4)
≥2,500 g	50 (100)	48 (96)
Exclusively breastfed for the first 6 months, n (%)	17 (34)	17 (34)
Formula milk < 6 months, n (%)	33 (66)	33 (66)
Age when semi-solid food was introduced, n (%)		
<6 months	9 (18)	16 (32)
≥6 months	41 (82)	34 (68)
Family history of atopic diseases, n (%)		
Yes	46 (92)	14 (28)
No	4 (8)	36 (72)
Father has history of atopic diseases, n(%)		
Yes	31 (62)	9 (18)
No	19 (28)	41 (82)
Mother has history of atopic diseases, n(%)		
Yes	27 (54)	7 (14)
No	23 (46)	43 (86)
Siblings have history of atopic diseases, n(%)		
Yes	18 (36)	2 (4)
No	32 (64)	48 (96)
Kitchen smoke exposure, n (%)	31 (62)	20 (40)
Cigarette smoke exposure, n (%)	24 (48)	30 (60)
Cotton-filled mattress usage, n (%)	3 (6)	9 (18)
Carpet usage, n (%)	13 (26)	14 (28)
Mosquito coil smoke exposure, n (%)	6 (12)	11 (22)
Pets exposure, n (%)	25 (50)	15 (30)
Positive skin prick test, n (%)	48 (96)	18 (36)

regression analysis including significant confounders revealed that the significant risk factors associated with atopic diseases were a positive parental history of atopy, kitchen smoke exposure, and pets exposure **(Table 2).**

We also assessed for a possible association between caesarean delivery and atopic diseases in a subgroup of subjects who had a family history with atopic diseases; 60/100 subjects had a family history of atopic diseases **(Table 1).** Of these 60 subjects, 24 subjects from the case group and 3 subjects from the control group were delivered by caesarean section. Caesarean section was significantly associated with a higher risk of atopic diseases in this subgroup of family history of atopy [OR=4 (95%CI 1 to 16.2; P=0.04)].

Discussion

The relatively high rate of caesarean sections in Denpasar[20, 21] warrants an investigation for an association between mode of delivery and the prevalence of atopic diseases. We found that caesarean delivery was significant as a risk factor for atopic diseases by bivariate analysis, but not by multivariate analyses. In a subgroup analysis of subjects with a family history of atopic diseases, we found that there was an association between caesarean section and atopic diseases.

Caesarean section is associated with delayed intestinal colonization, which could deprive newborns of immunostimulatory impulses at a critical period in life when the immune system and the gut barrier

Table 2. Relationships between each risk factor and atopic diseases

Risk factors	Atopic diseases n		OR (95%CI)	P value	OR (95%CI)	P value
	Yes	No	Unadjusted		Adjusted*	
Family history of atopic diseases						
- Mother	27	7	7.2 (2.7 to 19.1)	< 0.0001	14.8 (4.0 to 54.7)	< 0.0001
- Father	31	9	7.4 (2.9 to 18.6)	< 0.0001	14.5 (4.0 to 51.8)	< 0.0001
- Siblings	18	2	13.5 (2.9 to 62.2)	< 0.0001	3.5 (0.6 to 19.6)	0.155
Male gender	25	25	1.0 (0.5 to 2.2)	1.000		
Siblings < 1	14	10	1.6 (0.6 to 3.9)	0.349		
Caesarean delivery	25	13	2.8 (1.2 to 6.6)	0.013	2.4 (0.7 to 8.4)	0.164
Birth weight < 2,500 g	0	2	0.5♦ (0.4 to 0.6)	0.495		
Exclusively breastfed	17	17	1.0 (0.4 to 2.3)	1.000		
Formula milk < 6 months	28	28	1.2 (0.5 to 2.6)	0.712		
Semi-solid food introduction at < 6 months of age	9	16	2.1 (0.8 to 5.5)	0.106	4.9 (0.9 to 25.1)	0.054
Kitchen smoke exposure	31	20	2.4 (1.1 to 5.5)	0.028	4.2 (1.3 to 13.9)	0.019
Cigarette smoke exposure	24	30	0.6 (0.3 to 1.4)	0.229	0.6 (0.16 to 1.9)	0.362
Cotton-filled mattress usage	3	9	0.3 (0.1 to 1.1)	0.065		
Carpet usage	13	14	0.9 (0.4 to 2.2)	0.822		
Mosquito coil smoke exposure	6	11	0.5 (0.2 to 1.4)	0.183	0.3 (0.06 to 1.8)	0.203
Pets exposure	25	15	2.3 (1.0 to 5.3)	0.041	6.1 (1.7 to 21.9)	0.005

♦ Fischer's exact test (2 cells (50,0%) have expected count less than 5. The minimum expected count is 1,00.)

* Adjusted by multivariate analysis (family history of atopic diseases, semi-solid food introduction at < 6 months of age, kitchen smoke exposure, cigarette smoke exposure, mosquito coil smoke exposure, and pets)

mature. Children delivered by caesarean section have been shown to have a delayed and altered development in the establishment of gut flora, as well as altered cytokines production. Decreased exposure to microorganisms early in life leads to insufficient stimulation of Th1 lymphocytes and, therefore, a predominance of the Th2 allergic responses.[8-15] When combining subjects with and without an atopic family history, we found that caesarean delivery was not associated with the risk of atopic diseases. This finding may have been due to major differences between the populations and the variables observed. We did not examine gut flora colonization or cytokines production in our study.

Previous studies on caesarean delivery and the development of allergic diseases has produced conflicting results.[16-19] Our study, consistent with data from an English birth cohort of 24,690 children,[16] found no convincing evidence that infants delivered by caesarean section had an increased risk of developing allergic diseases (asthma, hay fever, and eczema). Delivery by caesarean section was also not associated with the subsequent development of asthma, wheezing, or atopy in later childhood in a longitudinal birth cohort of children born in Bristol.[17] Outcome variables examined in the Bristol study were parental reports of asthma during the period 69-91 months of age (6-7 years old), similar to most children in ours as they were aged over 2 years. These last two studies used subjects with atopic and non-atopic family history, similar to that of our study.

The *Finnish Health Register* reported that the cumulative incidence of asthma at the age of 7 years was significantly higher in children delivered by caesarean section than in those delivered vaginally, but no associations were observed between caesarean section and other allergic diseasess (hay fever and atopic eczema). In a following study on this birth cohort of 219 children, they found a trend toward more positive skin prick reactions at that age.[18] A Finnish prospective birth cohort that involved 1,953 adults revealed a strong effect of caesarean section on physician-diagnosed asthma in adulthood, but showed no associations with atopy, allergic rhino conjunctivitis and atopic dermatitis.[19] Meta-analyses in 2008 concluded that caesarean delivery was associated with a moderately increased risk of allergic rhinitis, asthma, hospitalization for asthma, and perhaps food allergy/food atopy, but not with inhalant atopy and eczema/atopic dermatitis.[7] Factors such

as the duration of follow-up, investigated variables, and the definition of allergic diseases also may have produced conflicting results. Our study differed from previous studies in terms of outcomes, as we used the term 'atopic diseases,' a collection of various atopic diseasess, instead of single atopic diseases entity.

Therefore, although caesarean section is considered to be a risk factor for allergic diseasess, a definite association has not yet been determined. The lack of association in our subjects might due to the fact that most children in our study were already over 2 years of age. Since caesarean delivery exposure occurs only once at the beginning of life, while other risk factors such as parental history of atopy, and exposure to household pets and kitchen smoke, affect subjects for longer durations in life, the role of caesarean delivery as a risk factor may be less influential. A previous Hong Kong study reported a significant, dose-response association between household gas cooking and the prevalence of respiratory illnesses (allergic rhinitis, asthma, bronchitis, sinusitis, and pneumonia) in preschool children in a residential estate with low outdoor air pollution, after controlling for potential confounding factors. This study provides additional evidence that household gas cooking increases the risk of respiratory illnesses among preschool children.[22] An earlier US report indicated that exposure or allergic reactions to pets were the predominant risk factor for asthma among children and adolescents.[23] A significant, dose-response association between exposure to cats and the prevalence of asthma in children was also reported in Denpasar.[24]

Caesarean section was associated with allergic rhinitis and atopy in children with a parental history of asthma or allergies.[25] Also, caesarean delivery was associated with a 3-fold increase in the odds of parental reporting of food allergies (to egg, fish, or nuts) in 2,803 Norwegian children followed to the age of 2 years (95%CI for OR 1.4 to 7.3). The observed association between caesarean delivery and food allergy among Norwegian infants was stronger after the analysis was stratified by maternal history of allergy. Norwegian children who were delivered by caesarean section and had a maternal history of allergy had a 9-fold higher odds of food allergy than those who were delivered vaginally and had no maternal history of allergy (95% CI for OR 3.1 to 28).[26] We also examined whether the association between caesarean delivery and atopic diseases differed by family history of atopic diseasess. We found that subjects with a family history of atopy and delivered by caesarean section had a higher risk of atopic diseases.

Early life exposure to allergens may vary by mode of delivery, and absence or avoidance of these factors may reduce the risk for atopic diseases.[27] We were unable to collect data on other variables, including maternal smoking, gestational age, intrauterine infection, NICU admission, antibiotic administration after birth, or peripartum complications. Information on the type of milk formula given to our subjects (cow's milk formula, hydrolyzed cow's milk formula, or soy milk formula) was also not collected in this study. Nor was data regarding the use of probiotics collected in our study, so the factors mentioned above were not controlled for. Although we did not have information about dust mites, we did collect data on the presence of carpet and cotton-filled mattresses at home.

A limitation of our study was the wide age range of subjects, as the effect of caesarean delivery may have been different among older subjects, in terms of the interval between caesarean delivery and the event of atopic diseases. This is a case-control study in which the control was hospital-based, hence, the control group may not represent the general population of normal children. Recall bias may have also affected the questionnaire data collected. A limited statistical power on the subgroup analysis differed by family history of atopic diseasess in our study, probably due to a limited sample.

In conclusion, children who have a family history of atopy and are delivered by caesarean section have a 4-fold higher risk of atopic diseases. Caesarean section as a delivery option should be carefully considered in families with a history of atopy.

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Conflict of interest

None declared

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