**Associations between caesarean delivery and allergic outcomes: Results from the GUSTO study**

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Birth by caesarean section (C-section) interrupts transmission of maternal microbiome and compromises intestinal microbiome programming in an infant. This influences immunological development and has been shown to increase the risk of development of allergic diseases (1). However as most studies are conducted in European populations with limited studies in Asia, we evaluated associations between caesarean delivery and allergic outcomes in infants using data from the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study.

Details of the GUSTO cohort study has been previously described (2). Briefly, we recruited 1237 healthy pregnant mothers who agreed to enroll their offspring for future follow-up. Ethical approval was obtained from the Centralized Institutional Review Board of SingHealth (reference 2009/280/D) and Domain Specific Review Board of Singapore National Healthcare Group (reference D/09/021). Data on demographics and offspring health were collected through interview by clinical research staff. Questionnaires were administered at 3 weeks and 3, 6, 9, 12, 15, 18, 24, 36, 48 and 60 months. Eczema was assessed by asking question “Has your child ever been diagnosed with eczema?”. “Wheezing” was assessed by asking questions “Has your child ever wheezed?” and “Has your child been prescribed with nebulizer/inhaler treatment?” while “rhinitis” was assessed by asking question “Has your child ever had sneezing, running nose, blocked or congested nose, snoring or noisy breathing during sleep or when awake that has lasted for 2 or more weeks duration?” A case prior to 18 months required a single episode that lasted for at least 4 weeks or two or more episodes each lasting at least 2 weeks. New cases of rhinitis after 18 months were defined by one or more episodes lasting at least 2 weeks. There were very regular follow up visits in this study and the main reason for non-completion of the questionnaires was the mothers’ not having been contactable at some point in the study and hence not having a home visit. In this study we excluded subjects who have missing data for more than 30 percent of the visits with negative responses at other timepoints. Skin prick testing (SPT) to inhalant allergens (house dust mites *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae,* and *Blomia tropicalis*) and food allergens (egg, peanut and cow’s milk) was carried out at 18, 36 and 60 months. At 60 months, skin prick testing was also carried out to shrimp and crab allergens. All allergens for SPT were obtained from the Greer Laboratories (Lenoir, NC, USA), except for *B. tropicalis*, which was obtained from our laboratory. The choice of these allergens stems from the high rates of sensitisation to these allergens in Singaporean children (3).

Statistical analysis was carried out using SPSS version 20.0 (IBM SPSS Statistics, Armonk, NY). Logistic regression analysis was adjusted for maternal age, ethnicity, education, parity, maternal history of allergy, gestational diabetes mellitus (GDM) status, early pregnancy body mass index (BMI, ≤14 weeks’ gestation), offspring sex and gestational age at delivery.

Of 1237 enrolled women with singleton pregnancies, 1170 retained in the study until delivery stage and there were 1077 pregnant women with no premature rupture of amniotic membranes and formed the study population. Out of these 1077 women, 330 (30.6%) had C-section delivery while 747 (67.4%) had vaginal delivery. Women who delivered by C-section were more likely to be primiparous (50.3% vs. 43.0%), had higher early pregnancy BMI (24.6 ± 4.9 kg/m2 vs. 23.4± 4.7 kg/m2) and earlier gestational age at delivery (38.1 ± 1.6 weeks vs. 38.5 ± 1.3 weeks) compared to those who delivered vaginally. There were no significant differences in maternal age, ethnicity, education, history of allergy, GDM status and offspring sex between women who delivered by C-section and vaginally(p≥0.05).

At 18 months, 107 (13.6%) offspring had a positive SPT , 171 (20.9%) had eczema, 64 (9.8%) had wheezed and used nebulizer/inhaler, and 132 (19.1%) had rhinitis. At 36 months, 185 (23.5%) offspring had a positive SPT, 199 (24.4%) had eczema, 169 (19.2%) had wheezed and used nebulizer/inhaler, and 244 (35.4%) had rhinitis. At 60 months, 254 (35.2%) offspring had a positive SPT , 213 (26.4%) had eczema, 159 (22.2%) had wheezed and used nebulizer/inhaler, and 269 (39.7%) had rhinitis. The prevalence of allergic outcomes at 18, 36 and 60 months did not differ significantly between C-section and vaginal delivery groups. There were no significant associations of C-section with allergic outcomes in the first 5 years of life.

Our findings are in line with the Avon Longitudinal Study of Parents and Children (n=13,867), showing C-section was not associated with development of asthma, wheezing or atopy in later childhood (4). Similarly, C-section was not associated with hospitalisations for asthma in a Hong Kong study (n=8327) (5). In contrast, the Norwegian Mother and Child Cohort Study (n=37,171) found that children delivered by C-section had an increased risk of asthma at 36 months (6). Another cohort study from Norway (n=1,756,700) showed that children delivered by C-section had a 52% increased risk of asthma compared to those born through vaginal delivery (7).

It has been proposed that the association noted between C-section and allergic disorders is influenced by the underlying indication for C-section (8). A Swedish cohort sibling study found an increased risk of asthma medication usage until the age of 13 years in participants born with emergency C-section as compared to elective C-section, alluding to the fact that vaginal microflora might not be the protective factor but rather the indication of C-section plays a bigger role in the risk of allergic diseases (9). Other possible reasons for the differences in observations may be due to the difference in maternal diet, population size, variations in methodology and length of follow up (10).

The strengths of our study lie in the prospective collection of child health information and the objective assessment of allergen sensitization through skin prick testing at multiple timepoints. In conclusion, we found no evidence in this Asian prospective cohort that caesarean delivery was associated with allergic outcomes in the first 5 years of life. Longer follow up will be needed as asthma develops later in life.

**Table 1: Associations between mode of delivery and allergic outcomes in the first 5 years of life**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cesarean delivery**  | **Vaginal delivery**  | **Multivariable analysis**  |
| **Outcomes by 18 months** | **N(%)** | **N(%)**  | **Adjusted OR (95% CI)\*** |
| Allergen sensitization | 37 (15.7) | 70 (12.8) | 1.6 (0.9-2.8) |
| Eczema | 54 (21.4) | 117 (20.7) | 1.1 (0.7-1.9) |
| Rhinitis | 35 (16.2) | 97 (20.5) | 0.8 (0.4-1.4) |
| Wheeze and use of nebuliser/inhaler | 26 (12.9) | 38 (8.4) | 1.6 (0.8-3.5) |
|  |  |  |  |
| **Outcomes by 36 months** |  |  |  |
| Allergen sensitization | 50 (20.3) | 135 (24.9) | 1.1 (0.6-1.8) |
| Eczema | 60 (23.8) | 139 (24.6) | 1.2 (0.8-2.0) |
| Rhinitis | 66 (30.6) | 178 (37.6) | 0.8 (0.5-1.2) |
| Wheeze and use of nebuliser/inhaler  | 55 (20.2) | 114 (18.8) | 1.0 (0.6-1.6) |
|  |  |  |  |
| **Outcomes by 60 months** |  |  |  |
| Allergen sensitization | 68 (30.6) | 186 (37.2) | 1.1 (0.7-1.9) |
| Eczema | 65 (26.2) | 148 (26.5) | 1.4 (0.8-2.2) |
| Rhinitis | 75 (35.7) | 194 (41.5) | 0.9 (0.6-1.5) |
| Wheeze and use of nebuliser/inhaler | 53 (23.8) | 106 (21.5) | 1.0 (0.6-1.7) |

\*Adjusted for maternal age, ethnicity, education, parity, maternal history of allergy, gestational diabetes mellitus (GDM) status, early pregnancy body mass index (BMI, ≤14 weeks’ gestation), offspring sex and gestational age at delivery with vaginal delivery group as the reference group. Results were presented as odds ratio (OR) and 95% confidence intervals (CI).

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