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

Birth by caesarean delivery interrupts transmission of maternal microbiome and compromises intestinal microbiome programming in an infant. This disruption influences immunologic development and increases the risk of development of allergic diseases.[1] However, because 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 (ClinicalTrials.gov Identifier: NCT01174875).

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 and the Domain Specific Review Board of Singapore National Healthcare Group. 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 the question, "Has your child ever been diagnosed with eczema?" Wheezing was assessed by asking the questions, "Has your child ever wheezed?" and "Has your child been prescribed with nebulizer/inhaler treatment?" Rhinitis was assessed by asking the 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 before 18 months required a single episode that lasted for at least 4 weeks or 2 or more episodes each lasting at least 2 weeks. New cases of rhinitis after 18 months were defined by 1 or more episodes that lasted at least 2 weeks. This study had regular follow-up visits, and the main reason for noncompletion 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 individuals who have missing data for more than 30% 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 performed at 18, 36, and 60 months. At 60 months, skin prick testing was also performed to shrimp and crab allergens. All allergens for SPT were obtained from the Greer Laboratories (Lenoir, North Carolina), except for *B tropicalis*, which was obtained from our laboratory. The choice of these allergens stems from the high rates of sensitization to these allergens in Singaporean children.[3]

Statistical analysis was performed using SPSS statistical software, version 20.0 (IBM Inc, Armonk, New York). Logistic regression analysis was adjusted for maternal age, ethnicity, educational level, parity, maternal history of allergy, gestational diabetes mellitus status, early pregnancy body mass index ($\leq$14 weeks' gestation), offspring sex, and gestational age at delivery.

Of 1,237 enrolled women with singleton pregnancies, 1,170 retained in the study until delivery stage, and 1,077 pregnant women had no premature rupture of amniotic membranes and formed the study population. Of these 1,077 women, 330 (30.6%) had caesarean delivery, whereas 747 (67.4%) had vaginal delivery. Women who delivered by caesarean were more likely to be primiparous (50.3% vs 43.0%), had a higher early pregnancy body mass index (calculated as weight in kilograms divided by square of height in meters) (mean [SD], 24.6 [4.9] vs 23.4 [4.7]), and had earlier gestational age at delivery (mean [SD], 38.1 [1.6] vs 38.5 [1.3] weeks) compared with those who delivered vaginally. There were no significant differences in maternal age, ethnicity, educational level, history of allergy, gestational diabetes mellitus status, and offspring sex between women who delivered by caesarean and vaginally ($P \geq .05$).

At 18 months, 107 offspring (13.6%) had a positive SPT results, 171 (20.9%) had eczema, 64 (9.8%) had wheezed and used a nebulizer or inhaler, and 132 (19.1%) had rhinitis. At 36 months, 185 offspring (23.5%) had a positive SPT result, 199 (24.4%) had eczema, 169 (19.2%) had wheezed and used a nebulizer or inhaler, and 244 (35.4%) had rhinitis. At 60 months, 254 offspring (35.2%) had a positive SPT result, 213 (26.4%) had eczema, 159 (22.2%) had wheezed and used a nebulizer or inhaler, and 269 (39.7%) had rhinitis. The prevalence of allergic outcomes at 18, 36, and 60 months did not differ significantly between caesarean delivery and vaginal delivery groups. There were no significant associations of caesarean delivery with allergic outcomes in the first 5 years of life (Table 1).

Our findings are in line with the Avon Longitudinal Study of Parents and Children (n = 13,867), indicating that caesarean delivery was not associated with development of asthma, wheezing, or atopy in later childhood.[4] Similarly, caesarean delivery was not associated with hospitalizations for asthma in a Hong Kong study (n = 8,327).[5] In contrast, the Norwegian Mother and Child Cohort Study (n = 37,171) found that children delivered by caesarean had an increased risk of asthma at 36 months.[6] Another cohort study from Norway (n = 1,756,700) found that children delivered by caesarean had a 52% increased risk of asthma compared with those born through vaginal delivery.[7]

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Table 1
Associations Between Mode of Delivery and Allergic Outcomes in the First 5 Years of Life

Outcome	Caesarean delivery, no. (%)	Vaginal delivery, no. (%)	Multivariable analysis Adjusted OR (95% CI)[a]
Outcomes by 18 months			
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 nebulizer or 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 nebulizer or 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 nebulizer or inhaler	53 (23.8)	106 (21.5)	1.0 (0.6–1.7)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Adjusted for maternal age, ethnicity, educational level, parity, maternal history of allergy, gestational diabetes mellitus status, early pregnancy body mass index (≤14 weeks' gestation), offspring sex, and gestational age at delivery with vaginal delivery group as the reference group.

It has been proposed that the association noted between caesarean delivery and allergic disorders is influenced by the underlying indication for caesarean delivery.[8] A Swedish cohort sibling study found an increased risk of asthma medication use until the age of 13 years in participants born via emergency caesarean delivery compared with elective caesarean delivery, alluding to the fact that vaginal microflora might not be the protective factor but rather the indication of caesarean delivery plays a bigger role in the risk of allergic diseases.[9] Other possible reasons for the differences in observations may be attributable to the difference in maternal diet, population size, variations in methods, 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 time points. 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.

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Cost and health care utilization in patients with asthma and high oral corticosteroid use

For patients with asthma, oral corticosteroids (OCSs) have long been a component of disease management,[1] although known adverse events[2–5] have led to a greater reliance on inhaled corticosteroids.[6] OCSs also are a well-established treatment for patients with chronic obstructive pulmonary disease (COPD). Even with treatment, OCS-dependent patients have frequent, severe exacerbations and higher costs.[7,8] We compared the clinical and economic outcomes between high-OCS and low-OCS users to identify evidence of the risks and benefits of OCS treatment in patients with asthma and in the subgroup with concomitant COPD.

This retrospective cohort study used a Health Insurance Portability and Accountability Act-compliant database containing de-identified data from electronic medical records and administrative claims. The study was exempt from review by a human subjects protection committee.

We identified patients who had moderate to severe persistent asthma in 2013 based on definitions in the National Heart, Lung, and Blood Institute Expert Panel Report 3 (EPR-3) and determined their OCS use.[9] Using a validated method, we identified patients at least 18 years of age who received therapy steps 4 to 6.[10] High-OCS users were defined, based on prior research, as those with at least 1 OCS fill with at least 30 days of supply or at least 6 bursts of OCS.[5] Low-OCS users were those who had no OCS fills with at least 30 days of supply and no more than 1 burst of OCS. A subgroup of patients with asthma and COPD was defined by the presence of a claim for COPD (*International Classification of Diseases, Ninth Revision,* Clinical Modification codes 491.x, 496.x, 492.x).

The main outcomes of interest were overall and asthma-related health care use and costs. Additional variables included demographics, smoking and COPD status, use of asthma medications, and evidence of poor asthma control (asthma-related hospitalization or emergency department visit, ≥2 OCS bursts, or ≥6 short-acting β_2-agonist fills in 1 year).[9,10]

To compare outcomes between high- and low-OCS users, analysis of covariance and logistic regression were used for continuous and dichotomous variables, respectively. Adjustors were patient demographics and characteristics, such as age group, sex, race, region, usual physician specialty, Charlson comorbidity index, pneumonia or influenza hospitalization, and EPR-3 step therapy. Adjusted means and odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). All tests were 2-sided with a significance level of .05.

We identified 17,225 patients with moderate to severe persistent asthma. Of these, 3,117 were younger than 18 years; 8,852 did not receive EPR-3 therapy steps 4 to 6; 871 were not continuously enrolled for the 12-month study period; and 1,030 did not meet the definition of high- or low-OCS use. The primary study cohort included 3,355 patients of whom 30.8% (n = 1,035) had concomitant COPD.

Mean age was 58.8 years (SD 15.9), 66.6% were women, and 8.9% (n = 300) were current smokers and 29.2% (n = 979) were former smokers. There were 517 patients (15.4%) classified as high-OCS users. Patients with asthma alone had a mean age of 56.8 years among high-OCS users and a mean age of 54.6 years among low-OCS users. In patients with asthma and COPD, mean ages were 67.1 and 67.9 years, respectively. High-OCS users had more all-cause office visits than low-OCS users overall (22.4 vs 14.9; $P < .001$) and in the asthma-only and asthma plus COPD subgroups. High-OCS users also had more hospitalizations and emergency department visits compared with low-OCS users (with the same pattern in subgroups). Mean total annual health care costs were $63,939 in high-OCS users and $27,494 ($P < .001$) in low-OCS users. In patients with asthma alone, high-OCS users had a mean total annual health care cost of $40,933 compared with $19,365 for low-OCS users ($P < .001$). In patients with asthma and COPD, high-OCS users had a mean total annual health care cost of $80,580 compared with $50,752 ($P < .001$) for low-OCS users.

In adjusted analyses, of patients with asthma alone, high-OCS users had higher odds of hospitalization than low-OCS users (all-cause OR 1.81, 95% CI 1.25–2.62; asthma-related OR 4.95, 95% CI 1.98–12.40; Fig 1). They had an excess of $17,122 (SE $2,395; $P < .001$) in total annual health care costs compared with low-OCS users. High-OCS users also had an excess of 7.2 (SE 0.9; $P < .001$) annual office visits and 2.0 (SE 0.2; $P < .001$) annual asthma-related office visits. In patients with asthma and COPD, the OR for all-cause hospitalization in high- vs low-OCS users was 2.03 (95% CI 1.52–2.71) and the OR for

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