Delivery by Caesarean Section and Infant Cardiometabolic Status at One Year of Age

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Abstract

Objective: Disruption of the gut microbiome has been associated with overweight/obesity, insulin resistance, and type 2 diabetes. Recently, it has been reported that Caesarean section disrupts the normal gut microbiome of neonates. As such, these data have raised the intriguing possibility that CS could lead to an adverse cardiometabolic risk profile early in life. Thus, we sought to compare the cardiometabolic status of infants delivered by CS to that of infants delivered vaginally.

Methods: In this prospective observational cohort study, 104 women underwent cardiometabolic evaluation in pregnancy followed by similar assessment of their infants at one year of age, thereby enabling comparison of infants delivered vaginally (n = 74) to those delivered by CS (n = 30). Infant assessment included anthropometric evaluation and measurement of variables associated with cardiometabolic risk.

Results: At one year of age, there were no differences between infants delivered vaginally and those delivered by CS with respect to mean BMI, sum of skinfolds, fasting glucose, insulin resistance, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, C-reactive protein, leptin, and adiponectin, both before and after covariate adjustment. Of note, maternal and infant levels of adiponectin (r = 0.31, P = 0.007) and of total cholesterol, LDL-cholesterol, and HDL-cholesterol (all $r \geq 0.23$, $P < 0.05$) were associated in the vaginal delivery group only, whereas the analogous association for leptin was observed only in the CS group (r = 0.44, P = 0.02).

Conclusion: Caesarean section was not found to be associated with an adverse infant cardiometabolic risk profile at one year of age, although it potentially may affect the impact of maternal determinants of this profile.

Key Words: Cardiovascular risk, infant, Caesarean, mode of delivery, gut microbiome

Competing Interests: None declared.

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Résumé

Objectif : La perturbation du microbiome intestinal a été associée à la surcharge pondérale / à l'obésité, à l'insulinorésistance et au diabète de type 2. On a récemment signalé que la césarienne perturbe le microbiome intestinal normal du nouveau-né. Ainsi, ces données ont soulevé l'intrigante hypothèse selon laquelle la césarienne pourrait mener à un profil de risque cardiométabolique indésirable tôt aux débuts de la vie. Nous avons donc cherché à comparer l'état cardiométabolique de nouveau-nés issus d'une césarienne à celui de nouveau-nés issus d'un accouchement vaginal.

Méthodes : Dans le cadre de cette étude de cohorte observationnelle prospective, 104 femmes se sont soumises à une évaluation cardiométabolique pendant la grossesse, le tout ayant été suivi d'une évaluation semblable de leurs nouveau-nés à l'âge d'un an, ce qui a permis la comparaison des nouveau-nés issus d'un accouchement vaginal (n = 74) et des nouveau-nés issus d'une césarienne (n = 30). L'évaluation des nouveau-nés comprenait un examen anthropométrique et la mesure des variables associées au risque cardiométabolique.

Résultats : À l'âge d'un an, aucune différence n'a été constatée entre les nouveau-nés issus d'un accouchement vaginal et les nouveau-nés issus d'une césarienne en ce qui concerne l'IMC moyen, la somme des plis cutanés, la glycémie à jeun, l'insulinorésistance, le cholestérol total, le cholestérol LDL, le cholestérol HDL, les triglycérides, la protéine C-réactive, la leptine et l'adiponectine, tant avant qu'après la neutralisation des effets des covariables. Fait à souligner, les taux maternels et infantiles d'adiponectine (r = 0,31, P = 0,007) et de cholestérol total, de cholestérol LDL et de cholestérol HDL (tous $r \geq 0,23$, $P < 0,05$) n'ont été associés

qu'au sein du groupe « accouchement vaginal », tandis qu'une association analogue pour ce qui est de la leptine n'a été constatée qu'au sein du groupe « césarienne » (r = 0,44, P = 0,02).

Conclusion : Nous n'avons pas constaté que la césarienne était associée à un profil de risque cardiométabolique indésirable chez l'enfant à l'âge d'un an; toutefois, il est possible qu'elle puisse affecter les effets des déterminants maternels de ce profil.

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INTRODUCTION

The normal microflora of the digestive tract (gut microbiome) plays an essential role in human metabolism by contributing to the processing of nutrients and harvesting of energy.[1–3] Disruption of this gut microbiome has been associated with low-grade endotoxemia and consequent cardiometabolic risk factors and disorders, including overweight/obesity, insulin resistance, and type 2 diabetes.[4–7] Interestingly, in humans the mode of delivery is a key determinant of the nascent gut microbiome of neonates.[8–10] Indeed, infants delivered vaginally have bacterial communities that resemble the maternal vaginal and gut flora, whereas infants delivered by Caesarean section are colonized by bacteria from the maternal skin.[8–10] In light of the observation that delivery by CS has been associated with increased body mass index in childhood and adolescence,[11] it has been hypothesized that the apparent disruption of the normal neonatal gut microbiome by CS may lead to altered metabolic function and consequently an adverse cardiometabolic risk profile early in life.[11] Thus, our objective was to compare the cardiometabolic status of infants delivered by CS with those delivered vaginally.

METHODS

This analysis was conducted as a substudy of a prospective observational cohort, the protocol of which has previously been described in detail.[12–14] All mothers provided written informed consent for infant participation. In this study, pregnant women were recruited in the late second trimester or early third trimester at the time of clinical screening for gestational diabetes mellitus. Women with and without an abnormal screening 50 g glucose challenge test were recruited, and all underwent a three hour 100 g oral glucose tolerance test. Gestational diabetes mellitus was diagnosed according to National Diabetes Data Group criteria.[15] The recruitment of women after an abnormal glucose challenge test served to enrich the study population for gestational diabetes mellitus, as previously described.[13] Variables correlating with maternal cardiometabolic risk were measured in a fasting serum specimen taken at the time of the oral glucose tolerance test. Data on obstetrical outcomes were obtained from an institutional database tracking labour and delivery. At one year of age, after an overnight fast (or a fast of at least 4 to 5 hours, if feeding was required) infants attended the clinical investigation unit where they underwent anthropometric assessment (including weight and skinfold thickness), and mothers completed interviewer-administered questionnaires.[12–14] Infant venous blood samples were drawn for measurement of the following variables correlating with cardiometabolic risk: total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, insulin, C-reactive protein, leptin, and adiponectin. Total cholesterol, HDL-cholesterol, and triglycerides were measured by Roche Cobas 6000 c 501 analyzer (Roche Diagnostics, Laval QC). LDL-cholesterol was calculated by the Friedwald formula. Specific insulin was measured by Roche Elecsys 1010 immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval QC). High-sensitivity C-reactive protein was measured by endpoint nephelometry using the Dade-Behring BN Prospec and N high-sensitivity C-reactive protein reagent (Dade-Behring Canada Inc., Mississauga ON). Leptin was measured by enzyme-linked immunosorbent assay #EZHL-80SK (Millipore Linco, St. Charles, MO). Total adiponectin was measured by enzyme-linked immunosorbent assay (Millipore Linco, St. Charles, MO). Specific insulin was measured by electrochemiluminescence immunoassay kit and Elecsys 1010 immunoassay-analyzer (Roche Diagnostics, Laval QC). Insulin resistance was evaluated by homeostasis model assessment of insulin resistance, as previously described.[16]

Statistical analyses were performed with Statistical Analysis System 9.2 (SAS Institute Inc., Cary, NC). Continuous variables were tested for normality of distribution, with natural log transformations of skewed variables used for subsequent analyses. Comparisons between the vaginal delivery and CS groups were performed using Wilcoxon two-sample test for continuous variables and chi-square test for categorical variables (Table 1). Mean adjusted levels of variables associated with cardiometabolic risk were compared between the groups by analysis of covariance, after adjustment for infant age, sex, ethnicity, and duration of exclusive breastfeeding (Table 2). To address the possibility that the sample size might have limited the capacity for detecting a difference, this analysis was repeated using the bootstrap method (data not shown). Finally, to determine whether the relationships between maternal and infant levels of the cardiometabolic risk variables differed according to mode of delivery, univariate associations between maternal levels and the analogous levels in the infants were assessed by Spearman correlation analyses in each group (Table 3A). As pre-pregnancy BMI differed between the