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ORIGINAL ARTICLE

The effect of microbiome exposure at birth on pediatric outcomes using a twin cohort discordant for microbiome exposure at birth

Kelly B. Zafman[a], Eric P. Bergh[b], Natalie Cohen[c], Elizabeth Odom[c] and Nathan S. Fox[c,d]

[a]Department of Obstetrics, Gynecology, and Reproductive Sciences, Hospital of the University of Pennsylvania, Philadelphia, PA, USA; [b]Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Texas at Houston, Houston, TX, USA; [c]Department of Obstetrics, Gynecology, and Reproductive Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [d]Maternal Fetal Medicine Associates, PLLC, New York, NY, USA

ABSTRACT

Objective: Microbiome exposure at birth has been associated with long-term pediatric outcomes. However, it is difficult to determine if differences in outcomes are truly due to microbiome exposure at birth or other exposures after birth and in early infancy. Using a twin cohort, we sought to determine the association between length of exposure to the maternal vaginal-fecal microbiome and long-term pediatric health outcomes by comparing outcomes between presenting and nonpresenting twins born to women who labored.

Methods: We performed a mail-based survey study of women in a single maternal-fetal medicine practice who delivered twin pregnancies ≥24 weeks. The survey study was sent to women when twins were between 2 and 10 years old to assess the long-term health outcomes, including any medical diagnoses or problems with grown and development. For this study, we included all women who labored, and we compared health outcomes for the presenting versus nonpresenting twin with the primary outcome being the development of asthma/reactive airway disease and allergies. The length of exposure to the maternal vaginal-fecal microbiome was measured using the time from rupture of membranes (ROM) to delivery of each twin. Chi-square and Student's *t*-test were used.

Results: Two hundred fifty-seven sets of twins were eligible for analyses. The presenting twin had a longer time of ROM than the nonpresenting twin (617 ± 2408 min versus 2 ± 5 minutes, $p < .001$). There were no significant differences between health outcomes for the presenting versus nonpresenting twin in the overall cohort, including the development of asthma/reactive airway disease (9.3 versus 10.1%, $p = .77$) or allergies (12.5 versus 7.8%, $p = .08$). There were no differences in any outcomes when comparing the presenting versus nonpresenting twin for those twins delivered vaginally or by cesarean delivery.

Conclusion: In twins born to women who labored and either delivered vaginally or via cesarean section, delivery order was not associated with any significant increase in defined adverse pediatric outcomes, including the development of asthma or allergies. Using twins as a model for microbiome exposure may help to elucidate the role of the maternal vaginal-fecal microbiome on long-term pediatric health outcomes.

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Microbiome; pediatric outcomes; twins; pediatric allergies; pediatric asthma

Introduction

Research on the human microbiome has shed light on the potential importance of microorganisms in homeostasis and disease susceptibility. These multitudes of microbes may be related to the epidemic of chronic noncommunicable diseases prevalent in the industrialized world [1]. In particular, events that adversely influence the establishment of a robust microbiome at birth may have significant future health implications. Current research suggests that the composition of the intestinal microbiome of the neonate is derived predominantly from exposure to the maternal vaginal-fecal microbiome at birth and that neonates delivered via cesarean do not receive the benefits of this early colonization [2,3]. This lack of intestinal colonization may be a contributing source of chronic disease and many associations between cesarean delivery and adverse infant and pediatric outcomes have been reported. These include increased risk for childhood asthma [4,5], allergies [6], autoimmune diseases [7], obesity [2,8,9] and behavioral disorders such as attention deficit hyperactivity disorder (ADHD) and autism [10,11].

Despite the evidence suggesting an association between cesarean birth, lack of exposure to the

CONTACT Kelly B. Zafman kelly.zafman@gmail.com Icahn School of Medicine at Mount Sinai, 50 East 98th Street, New York, NY, USA
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vaginal-fecal microbiome, and adverse pediatric outcomes, these studies are limited by comparisons between neonates born from different parents and different pregnancies and different environments, all of which are potential confounding variables. Twin pregnancies provide a unique opportunity to study pediatric outcomes as influenced by both the method of delivery and the exposure to the vaginal microbiome in a single pregnancy. For twins who labor and are delivered by cesarean, the presenting twin would have exposure to the vaginal microbiome during labor, and the second twin would not. For twins delivered vaginally, the presenting twin would have a longer duration of exposure to vaginal flora. In our practice, we routinely employ active management of the second stage of labor in twins, including breech extraction of the second twin and internal version of the nonengaged second twin to breech [12]. For this reason, the second twin will have a significantly shorter exposure to the vaginal microbiome even when both twins are delivered vaginally.

The objective of this study was to compare pediatric outcomes between first and second twins born to women who labored. We hypothesized that among women who labored, prolonged duration of exposure to the vaginal-fecal microbiome in the presenting twin would be associated with improved pediatric outcomes.

Materials and methods

This was a mail-based survey study of all women with twin pregnancies who were delivered by a single Maternal-Fetal Medicine practice from June 2005 to March 2014. Our protocol for survey administration has been previously described [13]. Briefly, surveys were mailed to mothers of twins in April 2016, such that all twins would be 2–10 years old. If clarification of any answers was needed, responders were contacted via telephone or e-mail. Nonresponders were followed up via phone or e-mail as well, and women who declined to participate were not contacted again. The survey questions were intended to be answered by parents, and were designed to elicit the long-term health outcomes of both twins including diagnosis of any chronic medical conditions, problems with growth or development, allergies, and medication use.

For this analysis, we included all women who labored with live twin births and were delivered at $24^{\circ/7}$ weeks of gestation or greater. We excluded twin pregnancies with twin–twin transfusion syndrome (TTTS), monoamniotic–monochorionic twins, twins with an intrauterine fetal death (IUFD) of either twin and any twins with major fetal anomalies or genetic abnormalities discovered before or after birth. We also excluded all women who did not attempt labor, that is, women who underwent planned cesarean delivery. Women who had a planned cesarean delivery were excluded even if they presented prior to cesarean in early labor as most of them would only have a short duration of vaginal microbiome exposure. Finally, we excluded twins that were born by vaginal–cesarean delivery, meaning twin A was born by vaginal delivery and twin B was born by cesarean delivery.

Over the course of the study period, our practice guidelines did not change. Decisions concerning the mode of delivery, timing of delivery, and labor-management were made clinically according to contemporary guidelines and best practices. Our protocol for twin delivery has been previously described [12]. Women are considered candidates for VD if the first twin is in cephalic presentation with no other contraindications to vaginal birth. If the second twin is noncephalic, the estimated fetal weight for the second twin must be $\geq$1500 g and the estimated fetal weight discordancy must be $\leq$20% to be eligible for vaginal birth. There must be no other contraindications to labor. In our practice, we utilize active management of the second stage for twin deliveries, which includes breech extraction of the noncephalic second twin as well as internal podalic version and breech extraction of a cephalic but unengaged second twin.

We compared pediatric outcomes between the presenting and nonpresenting twins. The time from rupture of membranes to delivery for each twin was used as a measure of the duration of exposure to the maternal vaginal-fecal microbiome. For each patient, we reviewed the computerized medical record and delivery information. We recorded maternal baseline characteristics as well as the rates of antibiotic use and chorioamnionitis for the overall cohort. We also collected delivery information for each twin, including the length of time for ruptured membranes, birth weight, and Apgar score. We then compared outcomes between the presenting versus nonpresenting twins from the results of the mail survey. The primary outcome for our study was the development of asthma/reactive airway disease or allergies, as these would most likely be identified by age 2–10 years, as opposed to other long-term outcomes such as obesity, diabetes, or hypertension.

We first analyzed baseline characteristics of women included in our cohort (IBM SPSS for Windows 22.0, IBM Corp). We then compared the likelihood of the

primary outcome and secondary outcomes for the presenting versus nonpresenting twins using chi-square and Student's *t*-test as appropriate. A subgroup analysis was performed comparing outcomes for those twins delivered vaginally and a separate analysis for those twins delivered by cesarean section.

This project was approved by the Biomedical Research Alliance of New York Institutional Review Board.

Table 1. Baseline characteristics of population of twins who labored.

Characteristics	*n* (%) or mean ± SD
Number of patients	257
Maternal age (years)	33.5 ± 6.3
Chorionicity	
Dichorionic	226 (87.9)
Monochorionic	31 (12.1)
In-vitro fertilization	164 (63.8)
White race	230 (89.5)
Maternal prepregnancy body mass index (kg/m^2)	23.1 ± 4.3
Maternal prepregnancy obesity (BMI ≥ 30)	18 (7.0)
Gestational diabetes	23 (8.9)
Preeclampsia	21 (8.2)
Gestational age at delivery (weeks)	35.9 ± 2.4
Planned to labor	186 (72.4)
Premature rupture of membranes	45 (17.5)
Antibiotics in labor	93 (36.2)
Chorioamnionitis	7 (2.7)
Cesarean delivery	101 (39.3)

Results

We identified 667 women who delivered live twin pregnancies ≥24 weeks between 2005 and 2014. A total of 437 women responded to the mail survey for a response rate of 65.5%. Of the responders, 272 women labored. Three sets of twins were excluded for TTTS, four sets for monoamniotic-monochorionic status, four sets for the anomaly of either twin, one set for IUFD, and three sets for neonatal demise. After accounting for the exclusion criteria, 257 twin pairs were eligible for analyses.

The baseline characteristics of the twins are shown in Table 1. The group tended to be dichorionic, conceived by IVF, white, and have low rates of maternal obesity. There were 45 (17.5%) twin pairs that had premature rupture of membranes and 93 (36.2%) received antibiotics in labor. There was a high rate of vaginal delivery in this cohort with 101 (39.3%) of twins delivered by cesarean delivery. The mean age of the twins at the time of survey response was 6.0 ± 2.4 years.

Outcomes for all twins exposed to labor are shown in Table 2. In the total cohort, the presenting twin was exposed to the vaginal microbiome for a significantly

Table 2. Outcomes of all twins who labored.

	Presenting twin (*n* = 257)	Nonpresenting twin (*n* = 257)	*p*-Value
Time of ruptured membranes (min)	617 ± 2408	2 ± 5	<.001
Gender			.077
Male	143 (55.6%)	123 (47.9%)	
Female	114 (44.4%)	134 (52.1%)	
Birthweight (g)	2397 ± 503	2375 ± 524	.619
5-min Apgar <7	1 (0.4%)	4 (1.6%)	.373
Has either twin been diagnosed with or treated for:			
Colic	16 (6.2%)	23 (8.9%)	.318
Asthma/reactive airways	24 (9.3%)	26 (10.1%)	.766
Any other chronic lung disease	1 (0.4%)	5 (1.6%)	.373
Gastrointestinal reflux	40 (15.6%)	49 (19.1%)	.294
Kidney (renal) disease	2 (0.8%)	1 (0.4%)	.999
Heart (cardiac) disease	5 (1.6%)	2 (0.8%)	.686
Necrotizing enterocolitis (NEC)	0 (0.0%)	0 (0.0%)	NA
Cerebral palsy	0 (0.0%)	0 (0.0%)	NA
Any learning disability	21 (8.2%)	18 (7.0%)	.617
Difficulty with hearing	9 (3.5%)	11 (4.3%)	.648
Diabetes	0 (0.0%)	0 (0.0%)	NA
High blood pressure	0 (0.0%)	0 (0.0%)	NA
Has your child ever required:			
Speech Therapy	79 (30.7%)	72 (28.0%)	.498
Occupational Therapy (OT)	62 (24.1%)	64 (24.9%)	.838
Physical Therapy (PT)	67 (26.1%)	63 (24.5%)	.685
At or after the age of 2 years, has your pediatrician ever had any concerns regarding your child's:			
Height (too short)	8 (3.1%)	7 (2.7%)	.793
Weight (too light)	16 (6.2%)	18 (7.0%)	.723
Weight (too heavy)	3 (1.2%)	6 (2.3%)	.504
Vision	30 (11.7%)	26 (10.1%)	.571
Hearing	11 (4.3%)	7 (2.7%)	.337
Motor skills	16 (6.2%)	18 (7.0%)	.723
Has your child undergone any operations	47 (22.2%)	51 (19.8%)	.516
Does your child take any medications	16 (6.2%)	22 (8.6%)	.312
Is your child allergic to any foods	20 (7.8%)	32 (12.5%)	.079
Has your child ever been evaluated or treated by a psychologist or psychiatrist?	20 (7.8%)	28 (10.9%)	.225
Does your child wear glasses?	36 (14.0%)	29 (11.3%)	.353

Table 3. Outcomes of twins who labored and ultimately had a cesarean delivery.

	Presenting twin ($n = 101$)	Nonpresenting twin ($n = 101$)	p-Value
Time (min) of ruptured membranes	863 ± 3780	1 ± 1	<.001
Gender			.121
Male	54 (53.5%)	43 (42.6%)	
Female	47 (46.5%)	58 (57.4%)	
Birthweight (g)	2253 ± 612	2219 ± 698	.703
5-min Apgar <7	0 (0.0%)	0 (0.0%)	.999
Has either twin been diagnosed with or treated for:			
Colic	8 (7.9%)	9 (8.9%)	.800
Asthma/reactive airways	12 (11.9%)	9 (8.9%)	.489
Any other chronic lung disease	1 (1.0%)	4 (4.0%)	.369
Gastrointestinal reflux	17 (16.8%)	20 (19.8%)	.585
Kidney (renal) disease	1 (1.0%)	1 (1.0%)	.999
Heart (cardiac) disease	2 (2.0%)	2 (2.0%)	.999
Necrotizing enterocolitis (NEC)	0 (0.0%)	0 (0.0%)	NA
Cerebral palsy	0 (0.0%)	0 (0.0%)	NA
Any learning disability	6 (5.9%)	6 (5.9%)	.999
Difficulty with hearing	2 (2.0%)	5 (5.0%)	.445
Diabetes	0 (0.0%)	0 (0.0%)	NA
High blood pressure	0 (0.0%)	0 (0.0%)	NA
Has your child ever required:			
Speech Therapy	35 (34.7%)	31 (30.7%)	.548
Occupational Therapy (OT)	30 (29.7%)	28 (27.7%)	.756
Physical Therapy (PT)	31 (30.7%)	30 (29.7%)	.878
At or after the age of 2 years, has your pediatrician ever had any concerns regarding your child's:			
Height (too short)	1 (1.0%)	3 (3.0%)	.621
Weight (too light)	6 (5.9%)	6 (5.9%)	.999
Weight (too heavy)	0 (0.0%)	3 (3.0%)	.246
Vision	15 (14.9%)	11 (10.9%)	.401
Hearing	2 (2.0%)	3 (3.0%)	.999
Motor skills	6 (5.9%)	9 (8.9%)	.421
Has your child undergone any operations	25 (24.8%)	23 (22.8%)	.741
Does your child take any medications	7 (6.9%)	11 (10.9%)	.323
Is your child allergic to any foods	10 (9.9%)	16 (15.8%)	.207
Has your child ever been evaluated or treated by a psychologist or psychiatrist?	10 (9.9%)	14 (13.9%)	.384
Does your child wear glasses?	16 (15.8%)	10 (9.9%)	.207

longer duration, with a mean time of ruptured membranes greater than the nonpresenting twin (617 ± 2408 min versus 2 ± 5 min, $p < .001$). There were no differences in rates of 5-min Apgar score <7 for the presenting compared to the nonpresenting twin (0.4 versus 1.6%, $p = .37$). There were no significant differences in the parent-reported rates of asthma or reactive airway disease between the twins (9.3 versus 10.1%, $p = .77$). The nonpresenting twin was more likely to develop allergies than the presenting twin, however, this was not significantly different (12.5 versus 7.8%, $p = .08$). There were no significant differences for all other outcomes, including the rates of all other chronic medical conditions or problems with growth or development.

Pediatric outcomes for twins delivered by cesarean delivery are shown in Table 3. For twins delivered by cesarean delivery, the presenting twin was exposed to the vaginal microbiome for a significantly longer duration, with a mean time of ruptured membranes greater than the nonpresenting twin (863 ± 3780 min versus 1 ± 1 min, $p < .001$). There were no significant differences in the parent-reported rates of asthma or reactive airway disease between the twins delivered by cesarean delivery (11.9 versus 8.9%, $p = .49$). More parents of twins delivered by cesarean delivery reported concerns about allergies in the nonpresenting twin than the presenting twin, but this was not significantly different (10.3 versus 6.4%, $p = .22$). There were no significant differences for all other outcomes, including the rates of all other chronic medical conditions or problems with growth or development.

Pediatric outcomes for twins delivered vaginally are shown in Table 4. Among those twins delivered vaginally, the presenting twin was exposed to the vaginal microbiome for a significantly longer duration, with a mean time of ruptured membranes greater than the nonpresenting twin (453 ± 453 min versus 3 ± 6 min, $p < .001$). There were no significant differences in the parent-reported rates of asthma or reactive airway disease between the twins delivered vaginally (7.7 versus 10.9%, $p = .33$). More parents of twins delivered vaginally reported allergies in the nonpresenting twin than the presenting twin, but this was not significantly different (10.3 versus 6.4%, $p = .21$). There were no significant differences for all other outcomes, including the rates of all other chronic medical conditions or problems with growth or development.

We performed an exploratory analysis to examine the association between the length of exposure to the

Table 4. Outcomes of twins who labored and ultimately had a vaginal delivery.

	Presenting twin ($n = 156$)	Nonpresenting twin ($n = 156$)	p-Value
Time of ruptured membranes (min)	453 ± 453	3 ± 6	<.001
Gender			.306
Male	89 (57.1%)	80 (51.3%)	
Female	67 (42.9%)	76 (48.7%)	
Birthweight (g)	2491 ± 391	2475 ± 416	.734
5-min Apgar < 7	1 (0.6%)	3 (1.9%)	.623
Has either twin been diagnosed with or treated for:			
Colic	8 (5.1%)	14 (9.0%)	.185
Asthma/reactive airways	12 (7.7%)	17 (10.9%)	.330
Any other chronic lung disease	0 (0.0%)	0 (0.0%)	NA
Gastrointestinal reflux	23 (14.7%)	29 (18.6%)	.362
Kidney (renal) disease	1 (0.6%)	0 (0.0%)	.999
Heart (cardiac) disease	2 (1.3%)	0 (0.0%)	.498
Necrotizing enterocolitis (NEC)	0 (0.0%)	0 (0.0%)	NA
Cerebral palsy	0 (0.0%)	0 (0.0%)	NA
Any learning disability	15 (9.6%)	12 (7.7%)	.546
Difficulty with hearing	7 (4.5%)	6 (3.8%)	.777
Diabetes	0 (0.0%)	0 (0.0%)	NA
High blood pressure	0 (0.0%)	0 (0.0%)	NA
Has your child ever required:			
Speech Therapy	44 (28.2%)	41 (26.3%)	.703
Occupational Therapy (OT)	32 (20.5%)	36 (23.1%)	.583
Physical Therapy (PT)	36 (23.1%)	33 (21.2%)	.682
At or after the age of 2 years, has your pediatrician ever had any concerns regarding your child's:			
Height (too short)	7 (4.5%)	4 (2.6%)	.541
Weight (too light)	10 (6.4%)	12 (7.7%)	.658
Weight (too heavy)	3 (1.9%)	3 (1.9%)	.999
Vision	15 (9.6%)	15 (9.6%)	.999
Hearing	9 (5.8%)	4 (2.6%)	.157
Motor skills	10 (6.4%)	9 (5.8%)	.813
Has your child undergone any operations	32 (20.5%)	28 (17.9%)	.566
Does your child take any medications	9 (5.8%)	11 (7.1%)	.644
Is your child allergic to any foods	10 (6.4%)	16 (10.3%)	.219
Has your child ever been evaluated or treated by a psychologist or psychiatrist?	10 (6.4%)	14 (9.0%)	.395
Does your child wear glasses?	20 (12.8%)	19 (12.2%)	.864

maternal vaginal microbiome and the development of allergies and asthma in the presenting twin. There were no significant differences in the mean time of rupture of membranes in presenting twins who developed allergies versus presenting twins who did not develop allergies (720 ± 1359 min versus 608 ± 2483 min, $p = .85$) or in presenting twins who developed asthma versus presenting twins who did not develop asthma (618 ± 1222 min versus 616 ± 2500 min, $p = .99$). Finally, we performed an exploratory analysis to examine the association between the development of allergies and asthma in the presenting twin based on mode of delivery. There were no significant differences in the rates of allergies (6.4 versus 7.2%, $p = .76$) or asthma (7.7 versus 9.4%) in the presenting twin for vaginal versus cesarean delivery.

Discussion

In this study, we found that among twins born to women who labored and either delivered vaginally or via cesarean section, delivery order was not associated with any significant increase in defined adverse pediatric outcomes, including asthma/reactive airway disease and the development of allergies. This was also true among the cohort of twins born to women who labored and ultimately delivered via vaginal delivery or cesarean section. Also, among presenting twins, the mode of delivery and the time of exposure to vaginal flora were not associated with long-term pediatric outcomes. These results suggest that exposure to vaginal flora is not a major contributor toward long-term pediatric health.

Previous research has shown that mode of delivery impacts the composition of the neonatal microbiome at birth in singleton fetuses delivered vaginally versus in those born via an unlabored cesarean section [14,15]. Whereas vaginally delivered infants' microbiome resembles the bacteria in their mother's birth canal, cesarean section infants acquire bacterial communities that resemble skin flora. A recent pilot study by Dominguez-Bello et al. suggests that the contribution of the maternal vaginal microbiome to a fetus delivered via cesarean section may be partially restored by a one-time exposure to vaginal "seeding" swabs at birth [16]. While encouraging, the lack of complete restoration of the microbiome suggests a possible temporal effect of fetal exposure to the secretions in the maternal birth canal. Additionally, there is

still insufficient evidence to recommend seeding outside the scope of a clinical trial, and, therefore, routine vaginal seeding is not supported by the American College of Obstetricians and Gynecologists [17]. It is with this in mind that we chose to study twin pregnancies in women who labored given the likely reduced duration of exposure of the nonpresenting twin regardless of mode of delivery.

Although our results showed no differences among groups, there are many assumptions that must be tested in a prospective study before any conclusions may be drawn from this data. We acknowledge that there are limitations to this study beginning with the retrospective design and inherent responder bias involved with performing a survey. Additionally, we may be limited by our sample size; though we did have over 200 twin pairs, we may not have been powered to find significant differences for all of our outcomes. Furthermore, we assumed that the duration of exposure to labor and ruptured membranes is related to microbiome exposure when in fact it may simply be an "all or none" phenomenon. However, when we did a subanalysis of presenting twins born by cesarean and born by vaginal delivery, we did not see any difference in outcomes.

One of the difficulties in studying microbiome exposure on long-term outcomes is that groups of women who undergo cesarean delivery and groups of women who have vaginal deliveries frequently have different baseline characteristics such as obesity, age, and comorbidities. Therefore, any differences in pediatric outcomes need to properly control for all these differences, as they can all be related to pediatric outcomes. Additionally, several confounders are also likely unmeasured. Twin pregnancies are an interesting model for the study of the fetal microbiome given the similar uterine environment, antibiotic exposures, maternal risk factors, family history, and environments after birth. Ideally, one would study women with twin pregnancies with vaginal delivery of the first twin and a cesarean delivery of the second twin, but in our practice, that only applies to less than 1% of our twin pregnancies [12]. Therefore, for this study we hypothesized that duration of exposure to the vaginal microbiome may result in differential microbial transfer and colonization, however it is unclear how long this may persist. Certainly, there is evidence that in adult twins, individuals share the microbiome with people they live with [18], but it is uncertain if communal living with siblings alone may correct microbial dysbiosis. While not all studies agree on this point, Zhou et al., found that in very young twins ages 0–6 who live together, a similar gut microbiome can be found in both twins [18]. If the microbiome does change so quickly after birth, that would imply the mode of delivery is not important in producing a healthy microbiome, as was supported by our data.

Our study indicates that the relationship between exposure to vaginal flora and long-term pediatric outcomes is still unclear, and if they are related, vaginal flora exposure does not appear to have a large effect on pediatric outcomes prior to the age of 10. We suggest that twin pregnancies are an ideal population for further studies into this important and interesting research and clinical question.

Disclosure statement

The authors do not report any potential conflict of interest.

ORCID

Nathan S. Fox http://orcid.org/0000-0001-5071-8182

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