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Higher Body Mass Index after Intrapartum Antibiotic Exposure in Children Persists over 10-years

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Abstract

Exposure to intrapartum antibiotic prophylaxis to reduce perinatal group B streptococcal disease was associated with increased childhood BMI persisting to age 10 years compared to no exposure (Δ BMI at 10yrs: vaginal delivery 0.14 kg/m^2, cesarean 0.40 kg/m^2).

Keywords

childhood obesity; body mass index; intrapartum antibiotic prophylaxis; delivery mode; group B streptococcal disease

INTRODUCTION

While intrapartum antibiotic prophylaxis (IAP) has been extremely successful in preventing the vertical transmission of group B *Streptococcus* (GBS), GBS IAP also contributes to a high proportion of newborns exposed to intrapartum antibiotics [1, 2]. The universal maternal GBS screening approach used in the United States, as well as approaches that target a narrower pool of GBS IAP candidates such as in the United Kingdom, identify

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a substantial proportion of pregnant women for GBS IAP. The relatively low population risk of newborn GBS infection in the absence of GBS IAP continues to fuel debate on the risk-to-benefit balance of intrapartum antibiotic exposure [3], including recommendations to discontinue GBS screening [4].

We previously reported in two independent studies of body mass index (BMI) trajectories from birth to 5 years of age that maternal IAP administration was associated with a higher BMI starting in infancy [5, 6]. For the current analysis, we extended the follow-up through the age of 10 years to investigate if the observed association persisted.

PATIENTS AND METHODS

Details of this retrospective cohort study of infants (n=173,895) born between 2007 and 2015 in Kaiser Permanente Southern California, an integrated healthcare system, are published elsewhere[5]. Briefly, we excluded infants whose mothers lacked ≥3 months of continuous health plan enrollment before delivery, and who were health plan members for <12 months after birth [5]. For the current analysis, we restricted the cohort to healthy, singleton, term-born children with up to 10-year follow-up BMI (Figure S1).

The KPSC Institutional Review Board (IRB) approved the study and granted a waiver for informed consent. This activity was reviewed by CDC and was conducted consistent with applicable federal law and CDC policy.

The intrapartum exposure to antibiotics was classified based on the time from first antibiotic administration to delivery as: 1) no antibiotics, 2) IAP for perinatal GBS disease (GBS IAP) defined as administration of penicillin G, ampicillin, cefazolin, clindamycin and/or vancomycin for ≥4 hours before delivery [7], or 3) any other type or duration of intrapartum antibiotics. The GBS IAP definition was consistent with GBS prevention guidelines published by the American College of Obstetricians and Gynecologists 2019. Women undergoing cesarean section delivery universally receive surgical site infection prophylaxis (typically cefazolin) within 60 minutes prior to delivery. Because of this universal exposure in the intrapartum period among women undergoing cesarean section the population was *a priori* stratified by delivery mode (vaginal or cesarean section). For infants delivered vaginally, the reference group consisted of those born to mothers without intrapartum antibiotic administration. For infants delivered by cesarean section, the reference was infants born exposed to other type or duration of antibiotics including surgical site infection prophylaxis [5]. BMI development over 10 years was compared between exposure categories using non-linear multivariate models with B-spline functions, stratified by delivery mode and adjusted for demographics, maternal factors, breastfeeding, and childhood antibiotic exposure (Table S1). E-values were calculated for each of the adjustment variables using the R package Evalue (Table S2) [8, 9]. We divided the follow-up into increments of 0.1 years for all models to align time-varying and other factors. Multiple imputation with N=5 imputations was used to fill in missing values for parity and pre-pregnancy weight gain using the MICE package version 3.13.0 in R. Quadratic B-spline functions with knots at 0.47, 2.1, and 4.7 years of age were fitted to allow for flexible modeling of BMI trajectories over time and for varying fit by exposure group [5]. These

models included a random effect of child to account for the repeated measures within each child. All statistical analyses were conducted using R version 4.0.4.

RESULTS

The cohort of children (n = 173,895) had 1,238,180 person-years, with a mean follow-up time of 7.12 years (SD 2.59) and a median of 17 (interquartile range 12 to 22) BMI measures per child during follow-up (Table S1). In this cohort, 95,244 (54.8%) were vaginal deliveries unexposed to antibiotics during the intrapartum period, 22,528 (13.0%) were vaginal deliveries exposed to GBS IAP, 8,774 (5.0%) were vaginal deliveries exposed to other intrapartum antibiotics, 5,279 (3.0%) were cesarean deliveries exposed to GBS IAP, and 42,070 (23.8%) were cesarean deliveries exposed to antibiotics of other type or duration. The majority (89.4%) of cesarean deliveries exposed to antibiotics of other types or duration were exposed to surgical site infection prophylaxis (typically cefazolin) within 60 minutes prior to delivery.

For vaginal deliveries, exposure to GBS IAP was associated with a higher BMI from birth to 10 years of age (adjusted Δ BMI at age 10 = 0.14 kg/m^2, 95% CI 0.08 kg/m^2 to 0.21 kg/m^2, $P<0.001$, Table 1, Figure S2–A) compared to no antibiotic exposure. Exposure to other antibiotics was associated with a lower BMI at 10 years of age (adjusted Δ BMI at age 10 = −0.12 kg/m^2, 95% CI −0.22 kg/m^2 to −0.03 kg/m^2, $P<0.001$) but a higher BMI at several time points over 10 years compared to no antibiotic exposure.

For cesarean deliveries, exposure to GBS IAP was associated with a higher BMI from birth to 10 years of age. At 10 years of age, the adjusted Δ BMI in children exposed to GBS IAP was 0.40 kg/m^2 (95% CI 0.28 to 0.53 kg/m^2, $P<0.001$, Table 1, Figure S2–B adjusted analysis) higher compared to other antibiotic exposure.

DISCUSSION

In this cohort of 173,895 healthy term-born children, the higher BMI over time associated with maternal intrapartum antibiotic administration observed at the age of 5 years [5] persisted up to the age of 10 years in both children delivered vaginally and those delivered via cesarean section. The difference in BMI associated with GBS IAP increased between the ages of 5 and 10 years from 0.09 to 0.14 kg/m^2 in children from vaginal deliveries and from 0.13 to 0.40 kg/m^2 in cesarean deliveries. IAP reduces a newborn's risk of GBS infection but is also associated with a small but enduring increase in body mass starting at a very early age [5, 6]. The population implications of an association between IAP and a child's body weight may be substantial given the exposure prevalence among pregnant women.

Recent studies indicate that early life weight trajectories are important predictors for the risk of obesity during adolescence and adulthood [10]. The absolute magnitude of our findings is not large, but small changes in BMI at the individual level can have significant effects at the population level. In comparison, the difference in BMI of 0.4 kg/m^2 as observed in this study in children who were delivered via cesarean section is higher than the change in BMI of 0.1 kg/m^2 in youth ages 8–11 observed since 1999 in National Health and Nutrition Examination Survey (NHANES) data from 1999–2006 and 2011–2018 [11]. Our findings

suggest that the widespread administration of GBS IAP can contribute to a significant upshift in body weight early in life.

In the United States, an estimated 40% of pregnant women receive antibiotics while giving birth, due to the combined indications of GBS IAP, concern for evolving intraamniotic infection, and surgical skin prophylaxis with cesarean delivery [12]. In the present cohort, only 16% of women were counted as exposed to GBS IAP. The proportion of exposed women was lower than the expected proportion of GBS-colonized parturients, as we restricted women exposed to GBS IAP to those treated according to the GBS guidelines with a full 4 hour duration prior to delivery [7]. In absence of GBS IAP, approximately 50% of women colonized with GBS will transmit their bacteria to their infants and 1% of these infants will develop invasive GBS disease [12]. Because GBS IAP is also active against other bacteria, some keystone species in the microbiome such as vaginal *Lactobacillus* spp. and gastrointestinal *Bacteriodes* and *Bifidobacteria* are reduced while other opportunistic bacteria become early colonizers [12]. The downstream consequences of GBS IAP may be intensified when combined with other factors associated with early microbiome disruption such as cesarean delivery and lack of breastfeeding.

The study benefitted from the long follow-up over 10 years with frequent BMI measures throughout childhood and careful adjustment for factors related to pregnancy, birth, infancy, and childhood, especially the exposure to antibiotics after the intrapartum period. This adjustment reduced the chance of possible bias inherent in case-control and hospital-based studies. Study limitations include the possibility of residual confounding inherent to the observational design, the possibility of differential distribution of unmeasured or incompletely measured confounders, and the lack of data on exclusive breastfeeding. Results from the current study may only apply to healthy, term-born infants.

Conclusions

Exposure of infants to GBS IAP antibiotics was associated with an increase in BMI that persisted over the first 10 years of age. The small but significant excess weight gain appears relevant on a population level due to the proportion of U.S. deliveries exposed to intrapartum antibiotics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

BMI	Body mass index
CDC	Centers for Disease Control and Prevention
GBS	Group B streptococcal infection
IAP	Intrapartum antibiotic prophylaxis
IQR	Interquartile range
KPSC	Kaiser Permanente Southern California
SD	Standard deviation

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Table 1:

Body mass index difference between children unexposed to intrapartum antibiotics (None), children exposed to intrapartum antibiotic prophylaxis as recommended for the prevention of perinatal group B streptococcal disease (GBS IAP), and any other type or duration of intrapartum antibiotic administration (Other IAP) stratified by delivery mode.

	Vaginal delivery			Cesarean delivery	
Children's age (years)	**None (BMI, kg/m^2)**	**GBS IAP (Δ BMI, kg/m^2)**	**Other IAP (Δ BMI, kg/m^2)**	**Other IAP (BMI, kg/m^2)**	**GBS IAP (Δ BMI, kg/m^2)**
Total cohort, N	95244	22528	8774	42070	5279
Crude model	Reference			Reference	
0.0	13.35 (0.04)	−0.07 (−0.09, −0.04)	−0.07 (−0.11, −002)	13.41 (0.05)	−0.09 (−0.15, −0.03)
1.0	17.15 (0.04)	0.02 (0.00, 0.05)	0.02 (−0.02, 0.05)	17.30 (0.05)	0.04 (−0.01, 0.09)
2.0	16.58 (0.04)	0.03 (0.01, 0.06)	0.03 (−0.01, 0.06)	16.73 (0.05)	0.10 (0.05, 0.14)
3.0	16.18 (0.04)	0.05 (0.03, 0.08)	0.04 (0.00, 0.07)	16.35 (0.05)	0.12 (0.08, 0.17)
4.0	15.99 (0.04)	0.09 (0.07, 0.11)	0.04 (0.00, 0.07)	16.20 (0.05)	0.15 (0.11, 0.02)
5.0	16.03 (0.04)	0.13 (0.11, 0.15)	0.04 (0.00, 0.08)	16.29 (0.05)	0.18 (0.13, 0.23)
6.0	16.29 (0.04)	0.16 (0.14, 0.19)	0.05 (0.01, 0.08)	13.61 (0.05)	0.21 (0.16, 0.26)
7.0	16.77 (0.04)	0.19 (0.16, 0.21)	0.04 (0.00, 0.08)	17.15 (0.05)	0.24 (0.18, 0.29)
8.0	17.47 (0.04)	0.21 (0.18, 0.24)	0.03 (0.02, 0.07)	17.90 (0.05)	0.29 (0.23, 0.35)
9.0	18.39 (0.04)	0.22 (0.19, 0.25)	−0.01 (−0.06, 0.03)	18.84 (0.05)	0.36 (0.03, 0.43)
10.0	19.52 (0.04)	0.22 (0.17, 0.28)	−0.09 (−0.18, 0.00)	19.97 (0.05)	0.47 (0.36, 0.59)
Full Model (adjusting for covariates from birth through childhood) [#]					
0.0	13.01 (0.04)	−0.09 (−0.12, −0.06)	−0.04 (−0.09, 0.00)	12.94 (0.05)	−0.13 (−0.02, −0.07)
1.0	16.79 (0.04)	0.00 (−0.03, 0.02)	0.02 (0.01, 0.06)	16.81 (0.05)	−0.01 (−0.06, 0.05)
2.0	16.18 (0.04)	0.00 (−0.02, 0.02)	0.03 (0.01, 0.07)	16.20 (0.05)	0.04 (−0.01, 0.10)
3.0	15.74 (0.04)	0.02 (−0.01, 0.04)	0.04 (0.01, 0.08)	15.77 (0.05)	0.08 (0.02, 0.13)
4.0	15.54 (0.04)	0.05 (0.03, 0.11)	0.05 (0.01, 0.08)	15.59 (0.05)	0.11 (0.05, 0.16)
5.0	15.55 (0.04)	0.09 (0.06, 0.11)	0.06 (0.02, 0.10)	15.64 (0.05)	0.13 (0.08, 0.19)
6.0	15.78 (0.04)	0.12 (0.09, 0.11)	0.07 (0.03, 0.11)	15.92 (0.05)	0.15 (0.10, 0.21)
7.0	16.23 (0.04)	0.14 (0.11, 0.17)	0.07 (0.03, 0.11)	16.42 (0.05)	0.17 (0.11, 0.23)
8.0	16.91 (0.04)	0.15 (0.12, 0.18)	0.04 (0.00, 0.09)	17.14 (0.05)	0.22 (0.15, 0.28)
9.0	17.81 (0.04)	0.15 (0.12, 0.19)	−0.02 (−0.22, −0.03)	18.06 (0.05)	0.29 (0.22, 0.36)

	Vaginal delivery			Cesarean delivery	
Children's age (years)	**None (BMI, kg/m^2)**	**GBS IAP (Δ BMI, kg/m^2)**	**Other IAP (Δ BMI, kg/m^2)**	**Other IAP (BMI, kg/m^2)**	**GBS IAP (Δ BMI, kg/m^2)**
10.0	18.96 (0.04)	0.14 (0.008, 0.21)	−0.12 (−0.22, −0.03)	19.18 (0.05)	0.40 (0.28, 0.53)

[#]Full Model includes adjustment for demographics, maternal and birth-related factors including infant sex, gestational age at birth, birth weight, infant's race/ethnicity (White, Black, Hispanic, Asian or Pacific Islander, other or unknown), year of birth, medical center of birth, maternal education, parity, maternal diabetes, maternal pre-pregnancy BMI, maternal gestational weight gain, maternal smoking during pregnancy, antepartum antibiotic exposure, neonatal antibiotic exposure, breastfeeding, indirect antibiotic exposure during breastfeeding, and childhood antibiotic exposure.

Values are Δ (95% CI) or mean (SE).