HHS Public Access

Author manuscript

Pediatr Obes. Author manuscript; available in PMC 2018 April 01.

Published in final edited form as:

Pediatr Obes. 2017 April ; 12(2): 129–136. doi:10.1111/ijpo.12119.

Association of Prenatal Antibiotics with Fetal Size and Cord Blood Leptin and Adiponectin

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Abstract

Background—Early postnatal antibiotic use has been shown to promote excess weight gain, but it is unclear whether intrauterine exposure to antibiotics is associated with fetal growth and adiposity. The objective of this study was to examine associations of antibiotic prescription in each trimester of pregnancy with fetal size and adipokine levels at birth.

Methods—In 2128 pregnant women from the pre-birth Project Viva cohort, from electronic medical records, we estimated antibiotic prescribing by timing during pregnancy. Outcomes were sex-specific birth weight-for-gestational-age z-score (BW/GA-z) and levels of umbilical cord leptin and adiponectin. We used linear regression models adjusted for maternal age, pre-pregnancy

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Conflict of Interest Statement
No conflict of interest was declared.

Supporting Information
Table S1. Oral antibiotics prescribed to mothers in Project Viva according to antibiotic class and generic name.
Table S2. Number of oral antibiotic prescriptions during pregnancy.
Table S3. Associations of number of oral antibiotic prescriptions with fetal outcomes.
Table S4. Associations of prenatal oral antibiotic prescriptions, using alternative expressions of the exposure, with birth weight-for-gestational age z-scores
Table S5. Associations of prenatal oral antibiotic prescriptions, using alternative expressions of the exposure, with cord blood leptin and adiponectin.

BMI, parity, race/ethnicity, education, smoking during pregnancy, household income and child sex; and additionally adjusted cord blood leptin and adiponectin models for gestation length.

Results—Of the 2128 women in our sample, 643 (30.2%) were prescribed oral antibiotics during pregnancy. Mean (SD) BW/GA-z was 0.17 (0.97), cord blood leptin was 9.0 ng/mL (6.6), and cord blood adiponectin was 28.8 ng/mL (6.8). Overall, antibiotic prescription in pregnancy was associated with lower BW/GA-z (multivariable adjusted β −0.11; 95% CI −0.20, −0.01). In trimester-specific analyses, only 2nd trimester antibiotic prescription was associated with lower BW/GA-z (β −0.23; 95% CI −0.37,

−0.08). Overall, antibiotic prescription in pregnancy was not associated with cord blood leptin or adiponectin levels. However, in trimester-specific analyses, 3rd trimester antibiotic prescription was associated with higher cord blood leptin (β 2.28 ng/ml; 95% CI 0.38, 4.17).

Conclusions—Antibiotics in mid-pregnancy were associated with lower birth weight-for-gestational age, whereas 3rd trimester antibiotics were associated with higher cord blood leptin.

Keywords

Antibiotics; fetal growth; leptin; adiponectin

INTRODUCTION

Antibiotics are the most commonly prescribed pharmacologic agents during pregnancy[1], despite insufficient evidence to support their use in preventing adverse effects on pregnancy outcomes[2]. In addition to perturbing the maternal microbiome[3], a potentially unintended consequence of using antibiotics in pregnancy is the trans-placental effect of antibiotics on the fetus.[4]

While the intrauterine environment had been considered sterile[5], the recently discovered presence of bacterial DNA in the placenta[6], umbilical cord blood[7], and fetal membranes[8] from healthy pregnancies suggests maternal-fetal transfer of microbiota before birth. A mother-to-fetus transfer of bacteria may facilitate development of not only the naïve fetal immune system[5], but also metabolic systems and growth[9]. Antibiotics taken by pregnant women, which enter fetal circulation *via* the placenta[4], may disrupt a mother-to-fetus bacterial transfer and, in doing so, alter fetal growth and body composition, much like antibiotics are believed to do when taken during infancy[10] and childhood[11].

Yet whether prenatal antibiotic use is associated with fetal growth and adiposity is unclear. While observational studies suggest that the use of antibiotics in the 3rd trimester in pregnancy is associated with higher birth weight[12, 13], a more recent report indicated that use of antibiotics earlier in pregnancy was associated with lower birth weight[14]. Clinical trials have also been mixed, with many showing that antibiotic treatment increases birth weight[15–20], but others reporting a null effect[21–23]. The discrepancy in findings may be due to inconsistency in the outcomes used (birth weight vs. birth weight-for-gestational age), and timing, duration, dose and nature (chemical class) of the antibiotic exposure. Furthermore, no studies have examined prenatal antibiotics in relation to adipokines levels as reflection of fetal adiposity. Leptin and adiponectin are adipokines that regulate energy homeostasis and

metabolism[24], and higher levels of leptin and adiponectin in cord blood correlate with greater neonatal body fat stores[25]. Moreover, cord blood leptin levels have been associated with body weight status at age 3[26], suggesting the perinatal leptin has a programming role in weight regulation in early childhood.

In the present analysis of a large cohort of women and their offspring, our aim was to examine overall and trimester-specific antibiotic use in relation to birth weight-for-gestational age and cord blood leptin and adiponectin levels.

METHODS

Subjects

Project Viva is a pre-birth cohort study of pre and perinatal exposures, pregnancy outcomes, and offspring health. We recruited 2341 women in their 1st prenatal visit at Atrius Harvard Vanguard Medical Associates, a multi-specialty group practice in eastern Massachusetts. Details of participant recruitment and study protocol have been reported[27]. For the current study, we included 2128 (91% of total) Project Viva participants with a live singleton birth and data available concerning prenatal antibiotics. Among these participants, 2127 had data for birth weight and 839 also had data available for cord blood leptin and 880 for adiponectin. Mothers provided written informed consent at enrollment and for their infants after birth, and the Institutional Review Boards of the participating sites approved the study.

Measures

Exposures – Assessment of prenatal antibiotics—We extracted prescription data from the electronic medical records of the group practice to derive overall and trimester-specific oral antibiotic use (full list of oral antibiotics available in Table S1). We defined 1st trimester antibiotics as those prescribed between the last menstrual period and 91 days of gestation, 2nd trimester antibiotics as those prescribed 92–182 days of pregnancy, and 3rd trimester antibiotics as those prescribed >182 days of pregnancy to delivery date.

Outcomes – Assessment of fetal growth and umbilical cord leptin and adiponectin—We obtained infant birth weight in grams (g) and date of delivery from the hospital medical record. We calculated sex-specific birth weight-for-gestational age z-score from a US national reference as previously described[28]. We collected cord blood samples from the umbilical vein immediately after delivery of the infant, refrigerated whole blood for < 24 hours, then spun and aliquoted samples for storage in liquid nitrogen (−80°C). We measured concentrations of leptin and adiponectin in cord blood with a radioimmunoassay (Linco Research Inc, St Charles MO).

Covariates – Assessment of participant characteristics—Through interviews and questionnaires, we collected information on mothers' age, race/ethnicity, education, household income, smoking habits, and date of last menstrual period (LMP). For the 237 of 2128 (11%) mother-infant pairs where gestational age according to the 2nd trimester ultrasound differed from that according to the LMP by >10 days, we used the ultrasound result to determine gestational duration. We calculated mothers' pre-pregnancy body mass

index (BMI; kg/m^2) from self-reported weight (kg) and height (m). We calculated total gestational weight gain as the difference between self-reported pre-pregnancy weight and the last clinical weight recorded before delivery.

Data analysis

We used linear regression to evaluate associations of overall and trimester-specific prenatal antibiotic prescription with birth weight-for-gestational age z-score as our primary outcome, and with cord blood leptin and adiponectin levels as our secondary outcomes. All outcomes were normally distributed. For our trimester-specific analysis, we excluded individuals who were prescribed antibiotics in a trimester previous to the index trimester to avoid confounding. In sensitivity analyses, we examined the trimester exposures as prescribed antibiotics vs. *not prescribed antibiotics in each trimester without exclusions*. As additional sensitivity analysis, we examined prescribed antibiotics in each trimester vs. *not prescribed antibiotics at any point in pregnancy*.

To assess confounding, we began with an unadjusted model and then created a multivariable model that included: maternal age (continuous), pre-pregnancy BMI (continuous), parity (nulliparous v. multiparous), race/ethnicity (white, black, Asian, Hispanic, other), education (≥ college graduate v. less), smoking habits (smoked during pregnancy, formerly smoked, never smoked) and household income (> $70,000/year v. less) and child sex. We additionally adjusted cord blood leptin and adiponectin models for gestation length. We considered but did not include in the final model gestational weight gain, pre-pregnancy physical activity and diet during pregnancy, since the estimate for each primary exposure changed by <10%, which did not meet a standard confounder definition[29].

We evaluated effect modification on the multiplicative scale by including cross-product terms for trimester-specific antibiotic use and sex in multivariable models, considering $p < 0.05$ as evidence of interaction. Analyses were performed using SAS 9.3 (SAS institute, Cary, NC).

RESULTS

Antibiotic prescriptions overall and by trimester can be found in Table S1. In total, there were 1,150 total oral antibiotic prescriptions during pregnancy in this cohort. The majority of the prescriptions were for penicillins (39.0%), but nitrofurantoin, metronidazole, and macrolides each accounted for more than 14%. Penicillins were more likely to be prescribed in the 3rd trimester whereas metronidazole was more likely to be prescribed in the 2nd trimester.

Of the 2128 women included in the final analytic set, 643 (or 30.2%) women were prescribed antibiotics at some point during pregnancy. More than half (n=358; 56%) of women prescribed antibiotics received a single prescription, but 285 (44%) received ≥2 prescriptions (Table S2). Baseline characteristics for mother-infant dyads are shown in Table 1. Compared to women not prescribed antibiotics in pregnancy, women prescribed antibiotics were younger (31.0 y vs. 32.2 y), had higher pre-pregnancy BMI (25.5 kg/m^2 vs. 24.6 kg/m^2), were less likely to be college educated (53.7% vs. 69.4%), and were more

likely to be Black or Hispanic and to smoke in pregnancy (16.8% vs. 10.8%). In the overall cohort, mean (SD) birth weight-for-gestational age z score was 0.17 (0.97), cord blood leptin was 9.0 (6.6), and cord blood adiponectin was 28.8 (6.8).

Table 2 shows unadjusted and multivariable adjusted associations of prenatal antibiotics with birth weight-for-gestational age z scores. Any prescription of prenatal antibiotics was associated with smaller birth weight-for-gestational age z-scores before (β −0.09; 95% CI: −0.18, 0.00) and after (β −0.11; 95% CI: −0.20, −0.01) multivariable adjustment. The association appeared to differ qualitatively according to the trimester in which antibiotics were prescribed. In trimester-specific analyses, 2nd trimester antibiotic prescription was associated with lower birth weight-for-gestational age z score (β −0.23; 95% CI −0.37, −0.08). 1st trimester prescription also tended toward an inverse association (−0.09; 95% CI −0.21, 0.04) but with apparent smaller effect size than 2nd trimester exposure. In contrast, 3rd trimester antibiotic prescription tended to be associated with greater birth weight-for-gestational age z score, but this did not reach statistical significance (β 0.07; 95% CI −0.11, 0.25). There was not evidence of a dose-response between number of antibiotic prescriptions and birth weight-for-gestational age z scores, in overall or trimester-specific analyses (Table S3).

In Table 3 we present associations of antibiotics with cord blood leptin and adiponectin levels. Overall prescription of antibiotics in pregnancy was not associated with levels of leptin or adiponectin in cord blood. However, associations varied by the trimester in which antibiotics were prescribed. We observed that 3rd trimester antibiotic prescription was associated with higher cord leptin (adjusted β 2.28; 95% CI: 0.38, 4.17) in line with the direction of effect expected from birth weight-for-gestational age z-score analyses. Moreover, there was evidence that number of antibiotic prescriptions in 3rd trimester was positively associated with leptin levels in a dose-dependent fashion (compared with 0 prescriptions, adjusted β 1.67; 95% CI: −0.37, 3.71 for 1 prescription and adjusted β 5.72; 95% CI: 1.05, 10.39 for ≥2 prescriptions; Table S3). Results for adiponectin trended in the same direction but did not reach statistical significance (Tables 3 and Table S3).

Our overall findings did not vary appreciably when we used '*not prescribed antibiotics in each trimester without exclusions*' or '*not prescribed antibiotics at any point in pregnancy*' as reference groups for our trimester-specific antibiotic analyses (Table S4 and Table S5). We also did not find evidence for multiplicative effect modification by sex on the associations for overall or trimester-specific antibiotics with birth weight-for-gestational age z scores (p values > 0.20).

DISCUSSION

In this pre-birth cohort study we found that prescription of oral antibiotics in pregnancy was associated with fetal growth and cord blood leptin. Overall, prenatal antibiotic prescriptions were associated with lower birth weight-for-gestational age z scores. Antibiotics prescribed early in pregnancy, during the 1st but mostly the 2nd trimester, drove this inverse association. However, in babies of women who were prescribed antibiotics during the 3rd trimester, there was a tendency toward higher birth weight-for-gestational age z scores, and 3rd trimester

antibiotics were associated with higher levels of cord blood leptin, a marker of fetal adiposity[25].

Previous observational studies and clinical trials have been inconsistent about the direction of the association between antibiotic use in pregnancy and fetal growth. That inconsistency may be due, at least in part, to the differential timing of antibiotic use during gestation. Our finding that antibiotics prescribed earlier in pregnancy (in the 2nd trimester and to a lesser extent 1st trimester) are associated with lower birth weight-for-gestational age z scores is consistent with an observational study of 397 women in the Southeastern United States, which found that self-reported antibiotic usage between 8 weeks preconception and 20 weeks gestation was associated with 138 g lower birth weight, after adjusting for confounding factors including gestational age[14]. Yet, randomized controlled clinical trials of erythromycin vs. placebo (n = 324)[22] and metronidazole plus cephalexin vs. placebo (n=240)[21], initiated in the 2nd trimester of pregnancy with the aim of improving birth outcomes, showed antibiotic treatment had no effect birth weight or gestational length. Other clinical trials in the US studying metronidazole between 16–24 weeks gestation (n=953)[30] and metronidazole plus erythromycin between 21–25 weeks gestation (n=703)[31] for the prevention of preterm birth reported that antibiotic treatment did not prevent low (< 2500 g) birth weight, but these findings are not directly comparable with ours as the authors did not examine the relation to birth weight for gestational age as a continuous variable. The inverse association between early pregnancy antibiotics and fetal growth observed in observational studies, but not clinical trials, raises the hypothesis that underlying infections for which the antibiotics were prescribed may be driving the observed association.

On the other hand, most observational studies[12, 13] and clinical trials[15–20], but not all[21–23], converge on the finding that antibiotics used later in pregnancy have a positive association with fetal growth. McCormack et al. randomized 1071 US women between 22–32 weeks gestation to receive erythromycin, clindamycin, or placebo to determine whether antibiotic treatment prevents low birth weight. They found that while treatment with clindamycin and erythromycin initiated during the 2nd trimester of pregnancy had no effect on birth weight, treatment with erythromycin during the 3rd trimester of pregnancy increased mean birth weight by 144 g[17]. This trial did not report on whether antibiotic treatment affected gestational age. Moreover, two randomized, double blind, placebo-controlled trials in Kenya, conducted to explore the potential benefits of routine antimicrobial therapy, found that compared to women who received a placebo, those who received a single dose of either intramuscular ceftriaxone (n=400)[15] or oral cefetamet-pivoxil (n=320)[16] between 28–32 weeks gestation delivered babies with 153 g and 155 g greater birth weight, respectively, despite the antibiotic treatments not having an effect on gestational length. Of note, none of the aforementioned trials examined birth-weight for gestational age as an outcome and all of the clinical trials cited above were conducted in pregnancies at high-risk for preterm birth or low birth weight, whereas our observational study was conducted in a generally healthy population.

Our finding that antibiotics prescribed in the 3rd trimester had a positive association with cord blood leptin levels, despite not having an association with birth weight for gestational age, suggests that antibiotics in the 3rd trimester might affect fetal adiposity, since cord

blood leptin levels have been positively correlated with neonatal percent body fat at birth[25, 32]. Our observations may also be the effect of antibiotics on placenta, since placental tissues express and release leptin on both maternal and fetal sides[33] We also observed a parallel but non-significant association between 3rd trimester antibiotics and cord blood adiponectin levels. Adiponectin also positively correlates with fetal fat stores[25]. That 3rd trimester antibiotic prescriptions were associated with levels of leptin and adiponectin in a dose-response fashion (Table S2) is consistent with these associations having true biologic underpinnings. Future research is warranted to replicate these adipokine findings, and to determine whether they have long-term metabolic implications for the newborn.

Several limitations to our study are worth noting. First, in our study it was not possible to separate infection from antibiotic treatment as the two are linked, and we had no data on untreated prenatal infections. We do not know whether the infection for which the antibiotic was prescribed influenced fetal growth and adiposity. Yet one would expect while infections during pregnancy have been associated with preterm birth in other studies[34], we did not find any association between antibiotic prescriptions and gestational age in our study. Another limitation is possible exposure misclassification by use of prescription data from medical records, as treatment adherence was not studied. Finally, as this is an observational study, we cannot rule out unmeasured or residual confounding.

Strengths of our study include the comprehensive set of covariates to control for many potential confounders, and the information on specific type antibiotics and their date of prescription. Moreover, unlike previous studies on this topic, our study largely eliminated confounding by gestational age through use of gestational-age specific birth weights.

In conclusion, prenatal antibiotic prescription was associated with altered fetal growth measures, but the direction of the associations depended on the trimester in which the antibiotics were prescribed. Prescriptions in mid-pregnancy were associated with lower birth weight-for-gestational age, yet prescriptions in the 3rd trimester were associated with higher cord blood leptin. One possibility is that two separate phenomena are at play: early prescriptions may reflect the deleterious consequences of early infections, for which the antibiotics were intended to treat, whereas antibiotics prescribed late in pregnancy may affect the interplay of the maternal microbiome with fetal development. These hypotheses will require further testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Noel Theodore Mueller initiated and developed the research question, led the analytic plan, drafted the paper and approved the final paper as submitted. Sheryl L. Rifas-Shiman conducted data analysis, and contributed to result interpretation, revision of the paper and approved the final paper as submitted. Martin J. Blaser contributed to result interpretation, revision of the paper and approved the final version of the paper as submitted. Matthew W. Gillman and Marie-France Hivert contributed to the development of the research question and analytic plan, interpreted results, made major contributions to revising the paper and approved the final paper as submitted.

Funding R37 HD034568

References cited

1. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976–2008. American journal of obstetrics and gynecology. 2011; 205:51, e1–e8. [PubMed: 21514558]
2. Thinkhamrop J, Hofmeyr GJ, Adetoro O, Lumbiganon P, Ota E. Antibiotic prophylaxis during the second and third trimester to reduce adverse pregnancy outcomes and morbidity. The Cochrane database of systematic reviews. 2015; 6:CD002250. [PubMed: 26092137]
3. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends in molecular medicine. 2015; 21:109–117. [PubMed: 25578246]
4. Pacifici GM. Placental transfer of antibiotics administered to the mother: a review. International journal of clinical pharmacology and therapeutics. 2006; 44:57–63. [PubMed: 16502764]
5. Funkhouser LJ, Bordenstein SR. Mom knows best: the universality of maternal microbial transmission. PLoS biology. 2013; 11:e1001631. [PubMed: 23976878]
6. Aagaard K, Ma J, Antony KM, Ganu R, Petrosino J, Versalovic J. The placenta harbors a unique microbiome. Science translational medicine. 2014; 6:237ra65.
7. Jimenez E, Fernandez L, Marin ML, Martin R, Odriozola JM, Nueno-Palop C, et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. Current microbiology. 2005; 51:270–274. [PubMed: 16187156]
8. Steel JH, Malatos S, Kennea N, Edwards AD, Miles L, Duggan P, et al. Bacteria and inflammatory cells in fetal membranes do not always cause preterm labor. Pediatr Res. 2005; 57:404–411. [PubMed: 15659699]
9. Dai Z, Wu Z, Hang S, Zhu W, Wu G. Amino acid metabolism in intestinal bacteria and its potential implications for mammalian reproduction. Molecular human reproduction. 2015; 21:389–409. [PubMed: 25609213]
10. Saari A, Virta LJ, Sankilampi U, Dunkel L, Saxen H. Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life. Pediatrics. 2015; 135:617–626. [PubMed: 25825533]
11. Schwartz BS, Pollak J, Bailey-Davis L, Hirsch AG, Cosgrove SE, Nau C, et al. Antibiotic use and childhood body mass index trajectory. Int J Obes (Lond). 2015
12. Jepsen P, Skriver MV, Floyd A, Lipworth L, Schonheyder HC, Sorensen HT. A population-based study of maternal use of amoxicillin and pregnancy outcome in Denmark. British journal of clinical pharmacology. 2003; 55:216–221. [PubMed: 12580995]
13. Czeizel AE, Rockenbauer M, Olsen J. Use of antibiotics during pregnancy. European journal of obstetrics, gynecology, and reproductive biology. 1998; 81:1–8.
14. Vidal AC, Murphy SK, Murtha AP, Schildkraut JM, Soubry A, Huang Z, et al. Associations between antibiotic exposure during pregnancy, birth weight and aberrant methylation at imprinted genes among offspring. Int J Obes (Lond). 2013; 37:907–913. [PubMed: 23609933]
15. Temmerman M, Njagi E, Nagelkerke N, Ndinya-Achola J, Plummer FA, Meheus A. Mass antimicrobial treatment in pregnancy. A randomized, placebo-controlled trial in a population with high rates of sexually transmitted diseases. The Journal of reproductive medicine. 1995; 40:176–180. [PubMed: 7776299]
16. Gichangi PB, Ndinya-Achola JO, Ombete J, Nagelkerke NJ, Temmerman M. Antimicrobial prophylaxis in pregnancy: a randomized, placebo-controlled trial with cefetamet-pivoxil in pregnant women with a poor obstetric history. American journal of obstetrics and gynecology. 1997; 177:680–684. [PubMed: 9322642]
17. McCormack WM, Rosner B, Lee YH, Munoz A, Charles D, Kass EH. Effect on birth weight of erythromycin treatment of pregnant women. Obstetrics and gynecology. 1987; 69:202–207. [PubMed: 3543767]
18. Kass EH, McCormack WM, Lin JS, Rosner B, Munoz A. Genital mycoplasmas as a cause of excess premature delivery. Transactions of the Association of American Physicians. 1981; 94:261–266. [PubMed: 7344224]

19. Elder HA, Santamarina BA, Smith S, Kass EH. The natural history of asymptomatic bacteriuria during pregnancy: the effect of tetracycline on the clinical course and the outcome of pregnancy. American journal of obstetrics and gynecology. 1971; 111:441–462. [PubMed: 4937729]
20. McGregor JA, French JI, Reller LB, Todd JK, Makowski EL. Adjunctive erythromycin treatment for idiopathic preterm labor: results of a randomized, double-blinded, placebo-controlled trial. American journal of obstetrics and gynecology. 1986; 154:98–103. [PubMed: 3511709]
21. Sen A, Mahalanabis D, Mukhopadhyay S, Chakrabarty K, Singh AK, Bisai S, et al. Routine use of antimicrobials by pregnant Indian women does not improve birth outcome: a randomized controlled trial. Journal of health, population, and nutrition. 2005; 23:236–244.
22. Paul VK, Singh M, Buckshee K. Erythromycin treatment of pregnant women to reduce the incidence of low birth weight and preterm deliveries. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 1998; 62:87–88.
23. Eschenbach DA, Nugent RP, Rao AV, Cotch MF, Gibbs RS, Lipscomb KA, et al. A randomized placebo-controlled trial of erythromycin for the treatment of Ureaplasma urealyticum to prevent premature delivery. The Vaginal Infections and Prematurity Study Group. American journal of obstetrics and gynecology. 1991; 164:734–742. [PubMed: 2003533]
24. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature. 1998; 395:763–770. [PubMed: 9796811]
25. Tsai PJ, Yu CH, Hsu SP, Lee YH, Chiou CH, Hsu YW, et al. Cord plasma concentrations of adiponectin and leptin in healthy term neonates: positive correlation with birthweight and neonatal adiposity. Clinical endocrinology. 2004; 61:88–93. [PubMed: 15212649]
26. Boeke CE, Mantzoros CS, Hughes MD, S LR-S, Villamor E, Zera CA, et al. Differential associations of leptin with adiposity across early childhood. Obesity. 2013; 21:1430–1437. [PubMed: 23408391]
27. Oken E, Baccarelli AA, Gold DR, Kleinman KP, Litonjua AA, De Meo D, et al. Cohort profile: project viva. International journal of epidemiology. 2015; 44:37–48. [PubMed: 24639442]
28. Oken E, Kleinman KP, Rich-Edwards J, Gillman MW. A nearly continuous measure of birth weight for gestational age using a United States national reference. BMC pediatrics. 2003; 3:6. [PubMed: 12848901]
29. Grayson DA. Confounding confounding. American journal of epidemiology. 1987; 126:546–553. [PubMed: 3618585]
30. Carey JC, Klebanoff MA, Hauth JC, Hillier SL, Thom EA, Ernest JM, et al. Metronidazole to prevent preterm delivery in pregnant women with asymptomatic bacterial vaginosis. National Institute of Child Health and Human Development Network of Maternal-Fetal Medicine Units. The New England journal of medicine. 2000; 342:534–540. [PubMed: 10684911]
31. Andrews WW, Sibai BM, Thom EA, Dudley D, Ernest JM, McNellis D, et al. Randomized clinical trial of metronidazole plus erythromycin to prevent spontaneous preterm delivery in fetal fibronectin-positive women. Obstetrics and gynecology. 2003; 101:847–855. [PubMed: 12738139]
32. Josefson JL, Zeiss DM, Rademaker AW, Metzger BE. Maternal leptin predicts adiposity of the neonate. Hormone research in paediatrics. 2014; 81:13–19. [PubMed: 24334975]
33. Masuzaki H, Ogawa Y, Sagawa N, Hosoda K, Matsumoto T, Mise H, et al. Nonadipose tissue production of leptin: leptin as a novel placenta-derived hormone in humans. Nature medicine. 1997; 3:1029–1033.
34. Andrews WW, Hauth JC, Goldenberg RL. Infection and preterm birth. American journal of perinatology. 2000; 17:357–365. [PubMed: 12141522]

Table 1

Participant characteristics, overall and by pregnancy oral antibiotic prescription, among 2128 mother-infant pairs in Project Viva

		Any antibiotic in pregnancy	
	Total (*n* = 2128)	**Yes (*n* = 643)**	**No (*n* = 1485)**
	Mean (SD) or N (%)		
Maternal characteristics			
Pre-pregnancy BMI, kg/m^2	24.9 (5.6)	25.5 (5.9)	24.6 (5.4)
Age, years	31.8 (5.2)	31.0 (6.0)	32.2 (4.8)
Nulliparous, %			
No	1111 (52.2%)	381 (59.3%)	730 (49.2%)
Yes	1017 (47.8)	262 (40.7)	755 (50.8)
Race/ethnicity, %			
Black	348 (16.5)	144 (22.7)	204 (13.9)
Hispanic	154 (7.3)	69 (10.9)	85 (5.8)
Asian	120 (5.7)	29 (4.6)	91 (6.2)
White	1399 (66.5)	365 (57.5)	1034 (70.4)
Other	83 (3.9)	28 (4.4)	55 (3.7)
Married or cohabitating, %			
No	180 (8.6)	81 (12.8)	99 (6.7)
Yes	1923 (91.4)	554 (87.2)	1369 (93.3)
College graduate, %			
No	744 (35.4)	294 (46.3)	450 (30.6)
Yes	1360 (64.6)	341 (53.7)	1019 (69.4)
Household income >$70K/year, %			
No	728 (38.8)	264 (48.7)	464 (34.8)
Yes	1146 (61.2)	278 (51.3)	868 (65.2)
Smoking status, %			
Never	1443 (68.5)	418 (65.6)	1025 (69.7)
Former	398 (18.9)	112 (17.6)	286 (19.5)
During pregnancy	266 (12.6)	107 (16.8)	159 (10.8)
Pregnancy weight gain, kg	15.5 (5.7)	15.3 (5.9)	15.6 (5.6)
Mode of delivery, %			
Vaginal	1600 (76.3)	496 (77.3)	1104 (75.8)
Cesarean section	498 (23.7)	146 (22.7)	352 (24.2)
Infant characteristics			
Sex, %			
Male	1096 (51.5)	350 (54.4)	746 (50.2)
Female	1032 (48.5)	293 (45.6)	739 (49.8)
Gestational age, wk	39.4 (2.0)	39.3 (1.9)	39.5 (2.0)
Birth weight, g	3461 (592)	3429 (589)	3475 (593)
BW/GA z-score	0.17 (0.97)	0.11 (0.98)	0.20 (0.96)

		Any antibiotic in pregnancy	
	Total (*n* = 2128)	**Yes (*n* = 643)**	**No (*n* = 1485)**
Cord blood leptin, ng/ml	9.0 (6.6)	9.1 (6.8)	9.0 (6.5)
Cord blood adiponectin, mg/ml	28.8 (6.8)	28.5 (6.8)	28.9 (6.8)

BMI, body mass index; BW-GA-*z*, birth weight for gestational age *z*-score; SD, standard deviation

Table 2

Associations of prenatal oral antibiotic prescriptions, by trimester, with birth weight-for-gestational age z-scores, among 2128 mother-infant pairs in Project Viva

	N (%)	Unadjusted β (95% CI)	Adjusted β (95% CI)
Any during pregnancy (yes vs. no)	643 (30.2)	−0.09 (−0.18, 0.00)	−0.10 (−0.19, 0.00)
1st trimester *	304 (14.3)	−0.15 (−0.27,−0.03)	−0.08 (−0.20, 0.04)
2nd trimester **	212 (11.6)	−0.17 (−0.31,−0.04)	−0.20 (−0.35, −0.06)
3rd trimester ***	127 (7.9)	0.18 (0.00, 0.35)	0.08 (−0.10, 0.25)

Adjusted for maternal age, pre-pregnancy BMI, parity, race/ethnicity, education, smoking habits, and household income, and child sex and gestation length.

* Among 2128 women

** Among 1824 women who were not prescribed antibiotics in the 1st trimester

*** Among 1612 women who were not prescribed antibiotics in the 1st or 2nd trimester

CI, confidence interval; BMI, body mass index

Table 3

Associations of prenatal oral antibiotic prescriptions with levels of leptin and adiponectin from venous umbilical cord blood at delivery.

		Unadjusted β (95% CI)	Adjusted β (95% CI)
Cord blood leptin, ng/ml	N (%)		
Any during pregnancy (yes vs. no)	236 (28.1)	0.06 (−0.94, 1.05)	0.14 (−0.89, 1.17)
1st trimester *	109 (13.0)	−0.62 (−1.96, 0.71)	−0.29 (−1.66, 1.07)
2nd trimester **	77 (10.5)	−0.57 (−2.15, 1.00)	−1.13 (−2.76, 0.50)
3rd trimester ***	**50 (7.7)**	**2.05 (0.13, 3.97)**	**2.28 (0.38, 4.17)**
Cord blood adiponectin, mg/ml	N (%)		
Any during pregnancy (yes vs. no)	250 (28.4)	−0.41 (−1.40, 0.59)	−0.02 (−1.10, 1.06)
1st trimester *	117 (13.3)	−0.72 (−2.04, 0.60)	−0.65 (−2.08, 0.77)
2nd trimester **	81 (10.6)	−1.20 (−2.75, 0.35)	−0.59 (−2.30, 1.12)
3rd trimester ***	52 (7.6)	1.40 (−0.49, 3.29)	1.65 (−0.35, 3.64)

Adjusted for maternal age, pre-pregnancy BMI, parity, race/ethnicity, education, smoking habits, household income, and child sex and gestation length.

* Among 839 women for leptin analyses and 880 women for adiponectin analyses

** Among 730 women (for leptin analyses) and 763 women (for adiponectin analyses) who were not prescribed antibiotics in the 1st trimester

*** Among 653 women (for leptin analyses) and 682 women (for adiponectin analyses) who were not prescribed antibiotics in the 1st or 2nd trimester