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Does antimicrobial use during pregnancy impact excess weight in early childhood? Findings from the 2015 Pelotas (Brazil) Birth Cohort Study

O uso de antimicrobianos durante a gravidez impacta o excesso de peso na primeira infância? Resultados do Estudo de Coorte de Nascimentos de Pelotas (Brasil) de 2015

¿El uso de antimicrobianos durante el embarazo impacta en el exceso de peso en la primera infancia? Resultados del estudio de Cohorte de Nacimientos de Pelotas (Brasil) de 2015

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Abstract *This study aimed to investigate the association between the use of antimicrobials during pregnancy and excess weight in children at ages three, 12, 24 and 48 months. Data of participants from the 2015 Pelotas (Brazil) Birth Cohort study were analyzed. The use of antimicrobials during pregnancy was assessed using standardized questionnaires and excess weight was defined as BMI for age in z-score ≥ 1. Over 43% of women used at least one antimicrobial during pregnancy. Overall, most associations investigated between the use of antimicrobials during pregnancy and excess weight in children were null. On average, children whose mothers used antimicrobials in one trimester of pregnancy had a BMI-for-age z-score at 12mo 0.11 z-score higher than those from mothers who did not use antimicrobials. An increased risk in excess weight at 48 months was observed among children whose mothers' used antimicrobials in the first trimester of pregnancy. Given that most of the associations investigated had either null results or a small magnitude of association, this study does not support previous findings that the use of antimicrobial during pregnancy impacts excess weight in early childhood.*
Key words *Pregnancy, Childhood, Prenatal, Antimicrobial, Overweight, Obesity, Cohort study*

Resumo *O estudo teve como objetivo investigar a associação entre o uso de antimicrobianos durante a gestação e o excesso de peso em crianças de 3, 12, 24 e 48 meses de idade. Foram analisados dados de participantes da Coorte de Nascimentos de Pelotas, Rio Grande do Sul, Brasil, em 2015. O uso de antimicrobianos durante a gestação foi avaliado por meio de questionários padronizados e o excesso de peso foi definido como IMC para idade no escore-z ≥ 1. Mais de 43% das mulheres utilizaram pelo menos um antimicrobiano durante a gestação. De modo geral, a maioria das associações investigadas entre o uso de antimicrobianos durante a gestação e o excesso de peso em crianças foi nula. Em média, as crianças cujas mães usaram antimicrobianos em um trimestre de gestação apresentaram um escore-z de IMC/idade de 12 a 0,11 maior do que aquelas de mães que não usaram antimicrobianos. Observou-se aumento do risco de excesso de peso aos 48 meses entre as crianças cujas mães utilizaram antimicrobianos no primeiro trimestre de gestação. Dado que a maioria das associações investigadas teve resultados nulos ou de pequena magnitude de associação, este estudo não corrobora achados anteriores de que o uso de antimicrobianos durante a gestação impacta o excesso de peso na primeira infância.*
Palavras-chave *Gravidez, Infância, Pré-natal, Antimicrobianos, Sobrepeso, Obesidade, Estudo de coorte*

Resumen *Este estudio tuvo como objetivo investigar la asociación entre el uso de antimicrobianos durante el embarazo y el exceso de peso en niños de 3, 12, 24 y 48 meses de edad. Se analizaron los datos de los participantes del estudio de cohorte de Nacimientos de Pelotas (Brasil) de 2015. El uso de antimicrobianos durante el embarazo se evaluó mediante cuestionarios estandarizados y el exceso de peso se definió como el IMC para la edad en puntuación z ≥ 1. Más del 43% de las mujeres utilizaron al menos un antimicrobiano durante el embarazo. En general, la mayoría de las asociaciones investigadas entre el uso de antimicrobianos durante el embarazo y el exceso de peso en los niños fueron nulas. En promedio, los niños cuyas madres usaron antimicrobianos en un trimestre del embarazo tuvieron una puntuación z de IMC para la edad a los 12 meses de 0,11 más alta que aquellos de madres que no usaron antimicrobianos. Se observó un mayor riesgo de exceso de peso a los 48 meses entre los niños cuyas madres utilizaron antimicrobianos en el primer trimestre del embarazo. Dado que la mayoría de las asociaciones investigadas tuvieron resultados nulos o una pequeña magnitud de asociación, este estudio no respalda hallazgos previos de que el uso de antimicrobianos durante el embarazo impacta sobre el exceso de peso en la primera infancia.*
Palabras clave *Embarazo, Infancia, Atención Prenatal, Antimicrobianos, Sobrepeso, Obesidad, Estudios de cohortes*

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Introduction

Adverse factors acting in the embryonic, fetal and early life period can result in adaptations in human development[1,2]. These adaptations occur due to a biological programming process that produces structural, physiological and metabolic changes, which influence the occurrence of diseases across the lifespan[1,2].

Studies have suggested that prenatal exposure to antimicrobials might be associated with the development of overweight and obesity during childhood[3-5], although it is still unclear whether the association of maternal antimicrobial use during pregnancy with overweight and obesity during childhood is causal. Pathophysiological mechanisms may explain this relationship. For example, the interference in the mother's microbiome caused by the use of antimicrobials during pregnancy, which plays an important role in the fetal placental circulation[6,7], may alters colonization and maturation of the infant intestinal microbiome by increasing susceptibility to obesity[8].

Observational studies about the association between the use of antimicrobials during pregnancy and overweight and obesity in children have shown conflicting findings. In the US, participants of a cohort with 436 children who were exposed to antimicrobials during the second or third trimester of pregnancy had 84% higher risk of obesity than those unexposed[8]. Furthermore, a study conducted in China identified that the use of antibiotics during pregnancy was positively associated with the risk of obesity at five years of age. Conversely, in a cohort of 43,435 Danish children, prenatal exposure to small-spectrum antimicrobials was not associated with overweight at ages 7 and 11[4]. Also, in a cohort of 53,320 children, the use of antibiotics during pregnancy was not associated with BMI-z in childhood at five years of age[9].

Although prospective observational studies provide important insights, the relationships between the use of antimicrobials during pregnancy and the development of excess weight in early childhood are still poorly understood. In addition, the relationships observed in population-based studies are susceptible to bias due to residual or unmeasured contextual confounding factors[10]. Moreover, to date, most studies that investigated the association between the use of antimicrobials during pregnancy and early childhood excess weight lack information about the time of use, type of spectrum, the class of the antimicrobial, and critical confounding variables as maternal obesity and gestational diabetes[11].

Therefore, the aim of this study was to investigate the association between the use of antimicrobials during pregnancy and excess weight in Brazilian children at 3, 12, 24 and 48 months of age.

Methods

Population and sample

This study used data from the 2015 Pelotas (Brazil) Birth Cohort study. This population-based cohort enrolled 99% of children born in all maternity hospitals in Pelotas, a city located in southern Brazil with approximately 350,000 inhabitants, whose mothers lived in the urban area of the municipality or in Jardim América in 2015 (n = 4,219 mothers, 4,275 children). An antenatal study was conducted with 73.8% of women whose children were enrolled in the cohort (n = 3,155). For this, all 123 health units and private clinics that provided antenatal care in the city were visited or contacted weekly between May 2014 and December 2015 to identify pregnant women who were expected to deliver their babies between January 1 and December 31, 2015.

Mothers and children were invited to further data collections when infants were three (97.2%), 12 (95.4%), 24 (95.4%) and 48 months old (95.4%). Domiciliary interviews were conducted at ages 3 and 12 months. In contrast, at 24 and 48 months, the follow-up assessments were conducted in a research clinic in the Center for Epidemiological Research of the Federal University of Pelotas. Of the 4,275 children born in 2015 and whose mothers provided information about the use of medicines during pregnancy, 4,056, 3,948, 3,718 and 3,757 had anthropometric data when they were aged three, 12, 24 and 48 months, respectively. Data collection and measurements were standardized and collected by trained research assistants through RedCap[12]. Further details about the study design and protocols have been published previously[13].

Use of antimicrobials during pregnancy

Information about the use of antimicrobials during pregnancy was collected using standardized questionnaires during the antenatal and perinatal assessments using the following questions: "Did you use any medication during

pregnancy?"; "What are the names of the medicines that you used during pregnancy?"[14]. Subsequently, the International Anatomical Therapeutical Chemical (ATC) classification of the World Health Organization[15] was used to classify the drugs by therapeutic groups up to the fifth level. For this study, the use of medicines in the 'group J', which are anti-infectious for systemic use, were considered.

Additionally, antimicrobials were classified according to their spectrum into narrow-spectrum or broad-spectrum. Narrow-spectrum antimicrobials are considered those that act on a few types of bacteria, for example only gram+, or only gram-, and broad-spectrum those capable of inhibiting several types of bacteria. In this paper, the following antimicrobials were considered to be narrow-spectrum: J01MB02 nalidixic acid; J01CA04 amoxicillin; J01CA01 ampicillin; J01CE01 benzylpenicillin; J01DB first-generation cephalosporins; J01XX05 methenamine; J01XE01 nitrofurantoin; J01MA06 norfloxacin; J04AB02 rifampicin; J01CE02 phenoxymethylpenicillin; J01CF04 oxacillin; J01XA01 vancomycin, and the following were considered to be broad-spectrum: J01MB02 nalidixic acid; J01CA04 amoxicillin; J01CA01 ampicillin; J01CE01 benzylpenicillin; J01DB first-generation cephalosporins; J01XX05 methenamine; J01XE01 nitrofurantoin; J01MA06 norfloxacin; J04AB02 rifampicin; J01CE02 phenoxymethylpenicillin; J01CF04 oxacillin; J01XA01 vancomycin[16].

The following binary (yes/no) variables regarding the use of antimicrobials during pregnancy were investigated: a) Use of at least one antimicrobial during pregnancy; b) use of antimicrobial during the first trimester of pregnancy; c) use of antimicrobial during the second trimester of pregnancy; d) use of antimicrobial during the third trimester of pregnancy. Additionally, the number of trimesters of pregnancy in which antimicrobials were used (none; one; two or three), use of at least one low-spectrum antimicrobial during pregnancy (yes/no), and the use of at least one broad-spectrum antimicrobial (yes/no) were analyzed.

Anthropometric assessment

At ages 3, 12, 24 and 48 months, children had their weight (g) and length/height (cm) measured by trained research assistants using standardized protocols. Weight was measured using a portable electronic scale (capacity of up to 50 kg and accuracy of 10g) at three months. For measurement of weight at 12 and 24 months, children were weighted on their mothers' laps using SECA 803 scales (SECA, Germany) with 100 g precision; child's weight was obtained as the difference between total weight (mother and children) and the weight of the mother. In all assessments, children were naked, and mothers were wearing light clothes when they were weighted. At age 48 months, a portable digital scale of the Tanita® with a maximum capacity of 150 Kg and accuracy of 100g was used. Child length at three and 12 months was measured using a portable anthropometer of the SANNY model ES2000 with an amplitude of 20 to 105 cm and precision of 0.5 cm. At 24 months, a fixed Harpenden with a range of 30 to 110 cm and precision of 0.1 cm was used, whereas a fixed Harpenden with maximum height of 2.06 m and accuracy of 1 mm was used when children were aged 48 months. At 24 and 48 months, 90% of measurements were performed in a research clinic in the Center for Epidemiological Research. In the remaining 10% of participants, when measurements had to be performed at home, validated portable anthropometers and stadiometers were used[16].

In each follow-up assessment, body mass index-for-age in z-scores was calculated according to the World Health Organization (WHO) Child Growth Standards[17]. WHO *ANTHRO* macros for STATA were used according to the methodology recommended by the WHO[18]. For this study, excess weight was defined as BMI-for-age z-score ≥ 1 standard deviation[17].

Covariates

The following confounding variables were measured using standardized questionnaires and included in the analyses: number of pregnancies (one/ two/three or more); number of prenatal consultations (< 6/7 or more); maternal smoking during pregnancy (no/yes); maternal consumption of alcohol during pregnancy (no/yes), hypertension (no/yes) and self-reported diabetes mellitus (no/yes) during pregnancy, maternal skin color (white/black/brown); maternal age (13-19 / 20-24 / 25-29 / 30-34 / 35 or more); maternal education (0-4 / 5-8 / 9-11 / 12 years or more); maternal marital status (with partner / no partner) and pre-gestational maternal BMI (≤ 24.9 / 25 to < 30.0 / ≥ 30.0 kg/m^2).

Statistical analysis

Descriptive statistics were used to describe and compare sociodemographic characteristics of the original cohort with the analytical sample of each follow-up assessment. Absolute and relative frequencies were used to describe the use of antimicrobials during pregnancy. Mean and standard deviation of BMI-for-age in z-score, and prevalence of excess weight in each age were described according to the use of antimicrobials during pregnancy (as previously described).

The associations of each variable used to describe the use of antimicrobials during pregnancy with BMI-for-age z-score and excess weight at each age were examined using, respectively, linear regression and Poisson regression models with adjustment for robust variance. Crude and adjusted analyses were conducted. The potential confounders were considered, but only those associated with the dependent variable (p-value of < 0.20) were included in the final model. Given the number of comparisons and the potential for type 1 error, interpretation of findings was based on the magnitude of associations (regression coefficients) and overlap of 95% confidence intervals (CI). All analyses were performed in the Stata 15.0.

Ethical aspects

This study was approved by the School of Physical Education Ethics Committee at the Federal University of Pelotas (CAAE registration number: 26746414.5.0000.5313). In all interviews written informed consent was obtained from children's parents or legal guardians.

Results

Sociodemographic and health characteristics of the participants in the original cohort and each follow-up are presented in Table 1. There were no marked differences between the original cohort and those who participated in the follow-up assessments. At the time of delivery, most women were aged 20-34 years, had white skin color, had a partner, had 9-11 years of formal education, and nearly 20% of women were obese before pregnancy. Most women reported seven or more prenatal consultations (76.1%), 44.5% had only one child, 16.5% reported smoking during pregnancy, and 7.4% consumed alcohol. One in four women reported hypertension during pregnancy, and 8.6% had gestational diabetes (Table 1).

The prevalence of total antimicrobial use during pregnancy was 43.4% (95%CI 41.9; 44.9). The proportion of women who used antimicrobials in each trimester was approximately 20% (18%, 21%, and 21% in the first, second and third trimester, respectively); 30.4% of women reported use in only one trimester, and 13.0% reported use of antimicrobials in two or three trimesters of pregnancy. One-third of the women used antimicrobials classified as a small spectrum, and only 2.9% used antimicrobials classified as broad-spectrum (Table 2). The most used antimicrobials were cephalexin (23.6%), amoxicillin (15.8%), nitrofurantoin (15.6%) and ampicillin (5.9%) (Table 3).

The mean BMI-for-age z-score was 0.06 (SD = 0.02), 0.68 (SD = 0.02), 0.56 kg/m^2 (SD = 0.02) and 1.08 (SD = 0.04), at three, 12, 24 and 48 months, respectively. The prevalence of excess weight was 17.6% (95%CI 16.5; 18.8) at three months, 39.4% (95%CI 37.9; 40.9) at 12, 32.4% (95%CI 30.9; 33.9) at 24 and 43.8% (95%CI 42.2; 45.4) at 48 months. Overall, not marked variations in the distribution of BMI-for-age and excess weigh at each age according to use of antimicrobials during pregnancy was observed (Table 2).

Crude and adjusted associations of use of antimicrobials during pregnancy with BMI-for-age and excess weight at 3, 12, 24 and 48 months are presented in Tables 4 and 5, respectively. Overall, the use of antimicrobials during pregnancy was not associated with either BMI-for-age or excess weight, regardless of the age. Of the 56 associations investigated, statistically significant findings (based on 95%CI) were only observed on three occasions, although with a small magnitude of associations. Children from mothers who used antimicrobials during the second trimester had on average 0.12 lower z-score of BMI-for-age at age 3 months than children whose mother did not use antimicrobials in the second trimester. At age 12 months, the z-score of BMI-for-age was slightly higher (β: 0.11; 95%CI: 0.01; 0.20) in children whose mothers used one antimicrobial during pregnancy than in those children of mothers who did not use antimicrobials. Children aged 48 months, whose mothers used antimicrobials in the first trimester of pregnancy, had a higher risk of excess weight than those of mothers who did not use antimicrobials in the first trimester [RR = 1.13 (95%CI 1.04; 1.23)] (Table 5).

Table 1. Sample characteristics of the 2015 Pelotas (Brazil) Birth Cohort Study.

	Original cohort (n = 4,275) n (%)	3 months (n = 4,056)* n (%)	12 months (n = 3,948)* n (%)	24 months (n = 3,718)* n (%)	48 months (n = 3,757)* n (%)
Maternal age (in years)					
13-19	623 (14.6)	594 (14.7)	577 (14.6)	546 (14.7)	546 (14.5)
20-24	1,008 (23.6)	959 (23.6)	932 (23.6)	866 (23.3)	903 (24.0)
25-29	1,006 (23.5)	961 (23.7)	930 (23.6)	873 (23.5)	879 (23.4)
30-34	1,004 (23.5)	953 (23.5)	931 (23.6)	888 (23.9)	879 (23.4)
35+	633 (14.8)	588 (14.5)	578 (14.6)	545 (14.6)	550 (14.7)
Maternal skin color					
White	3,071 (71.9)	2,912 (71.9)	2,827 (71.7)	2,653 (71.4)	2,680 (71.4)
Brown	561 (13.1)	608 (15.0)	603 (15.3)	574 (15.5)	579 (15.4)
Black	639 (15.0)	532 (13.1)	514 (13.0)	487 (13.1)	494 (13.2)
Maternal marital status					
Single mother	607 (14.2)	576 (14.2)	548 (13.9)	512 (13.8)	528 (14.1)
With partner	3,667 (85.8)	3,479 (85.8)	3,399 (86.1)	3,205 (86.2)	3,228 (85.9)
Maternal education (years)					
0-4	391 (9.2)	366 (9.0)	348 (8.8)	336 (9.0)	327 (8.7)
5-8	1,095 (25.6)	1,043 (25.7)	1,013 (25.7)	970 (26.1)	981 (26.1)
9-11	1,458 (34.1)	1,397 (34.5)	1,376 (34.9)	1,288 (34.7)	1,312 (35.0)
12+	1,330 (31.1)	1.249 (30.8)	1,210 (30.6)	1,123 (30.2)	1,136 (30.2)
Pre-pregnancy BMI (kg/m^2)					
≤ 24.9	2,193 (53.0)	2,076 (52.8)	2,021 (52.8)	1,919 (53.1)	1,910 (52.4)
25.0 until < 30.0	1,169 (28.2)	1,108 (28.2)	1,077 (28.1)	995 (27.6)	1,037 (28.4)
≥ 30.0	779 (18.8)	750 (19.0)	733 (19.1)	696 (19.3)	699 (19.2)
Number of prenatal consultations					
< 6	1,001 (23.9)	929 (23.3)	891 (23.0)	829 (22.7)	841 (22.8)
7 or more	3,185 (76.1)	3,052 (76.7)	2,988 (77.0)	2,828 (77.3)	2,852 (77.2)
Parity (number of previous children)					
1	1,900 (44.5)	1,805 (44.5)	1,765 (44.7)	1,655 (44.5)	1,665 (44.3)
2	1,285 (30.0)	1,228 (30.3)	1,200 (30.4)	1,108 (29.8)	1,146 (30.5)
3 or more	1,089 (25.5)	1,022 (25.2)	982 (24.9)	954 (25.7)	945 (25.2)
Pregnancy smoking					
No	3,567 (83.5)	3,393 (83.7)	3,314 (84.0)	3,112 (83.8)	3,142 (83.7)
Yes	705 (16.5)	661 (16.3)	631 (16.0)	603 (16.2)	612 (16.3)
Pregnancy alcohol					
No	3,957 (92.6)	3,760 (92.8)	3,657 (92.7)	3,438 (92.5)	3,472 (92.5)
Yes	315 (7.4)	294 (7.2)	288 (7.3)	277 (7.5)	282 (7.5)
Gestational arterial hypertension					
No	3,183 (74.5)	3,018 (74.5)	2,934 (74.4)	2,780 (74.8)	2,804 (74.7)
Yes	1,089 (25.5)	1,035 (25.5)	1,012 (25.6)	935 (25.2)	950 (25.3)
Gestational diabetes					
No	3,906 (91.4)	3,706 (91.4)	3,600 (91.2)	3,389 (91.2)	3,425 (91.2)
Yes	366 (8.6)	347 (8.6)	346 (8.8)	326 (8.8)	329 (8.8)

*Analytical sample.

Source: Authors.

Discussion

It is well known that the exposure of the fetus to certain substances can affect many aspects of child development[19,20]. In this unique representative population-based cohort study conducted in a large middle-income country, we used a range of different exposure variables, a comprehensive list of potential confounders and two indicators of children nutritional status in four time points to explore the extent to which maternal use of antimicrobials during pregnan-

Table 2. Use of antimicrobials and nutritional indicators at 3, 12, 24 and 48 months. 2015 Pelotas (Brazil) Birth Cohort Study.

	Use of antimicrobials	Nutritional status (z-score)				Excess of weight*			
	N (%)	Mean (SD) 3m	Mean (SD) 12 m	Mean (SD) 24 m	Mean (SD) 48 m	% 3 m	% 12 m	% 24 m	% 48 m
Total use									
No	2,383 (56.6)	0.06 (0.03)	0.65 (0.03)	0.56 (0.03)	1.11 (0.05)	17.8	38.5	32.4	43.7
Yes	1,827 (43.4)	0.05 (0.03)	0.72 (0.03)	0.56 (0.03)	1.06 (0.05)	17.5	40.6	32.8	44.3
1st trimester									
No	3,451 (82.0)	0.06 (0.02)	0.67 (0.02)	0.55 (0.02)	1.08 (0.04)	17.6	38.7	32.1	42.8
Yes	759 (18.0)	0.06 (0.04)	0.73 (0.05)	0.59 (0.04)	1.13 (0.08)	18.2	42.6	34.6	49.1
2nd trimester									
No	3,306 (78.5)	0.08 (0.02)	0.69 (0.02)	0.57 (0.02)	1.09 (0.04)	18.1	39.8	32.4	44.0
Yes	904 (21.5)	-0.02 (0.04)	0.64 (0.04)	0.53 (0.04)	1.09 (0.09)	16.2	38.1	32.9	43.8
3rd trimester									
No	3,311 (78.7)	0.05 (0.02)	0.67 (0.02)	0.55 (0.02)	1.11 (0.04)	17.5	39.4	32.5	44.2
Yes	899 (21.3)	0.09 (0.04)	0.73 (0.05)	0.59 (0.04)	1.04 (0.06)	18.4	39.7	32.5	43.4
Pregnancy									
No	2,383 (56.6)	0.07 (0.03)	0.64 (0.03)	0.56 (0.03)	1.11 (0.05)	17.8	38.5	32.4	43.7
1	2,383 (30.4)	0.05 (0.03)	0.76 (0.04)	0.57 (0.03)	1.08 (0.06)	17.5	41.9	33.0	44.0
2+	545 (13.0)	0.05 (0.05)	0.63 (0.05)	0.54 (0.05)	1.01 (0.07)	17.5	37.8	32.1	45.2
Small spectrum									
No	2,932 (68.8)	0.06 (0.02)	0.67 (0.03)	0.57 (0.02)	1.12 (0.05)	17.5	39.1	32.8	44.1
Yes	1,327 (31.2)	0.06 (0.03)	0.69 (0.04)	0.53 (0.03)	1.03 (0.06)	18.2	40.3	32.0	43.7
Broad-spectrum									
No	4,137 (97.1)	0.06 (0.02)	0.68 (0.02)	0.56 (0.02)	1.09 (0.04)	17.6	39.4	32.3	43.7
Yes	122 (2.9)	0.10 (0.09)	0.72 (0.11)	0.71 (0.13)	1.10 (0.16)	18.6	41.7	40.2	51.8

Excess of weight: z-score ≥ 1 standard deviation (SDs) up to ≥ 2 SDs.

Source: Authors.

cy may impact children BMI-for-age and excess weight during the first 48 months postpartum. Overall, the findings of this study suggest that antimicrobial use during pregnancy does not influence the nutritional status of children up to age 48 months.

The proportion of women who used at least one antimicrobial during pregnancy in our study (43%) was higher than the prevalence of antimicrobial use by pregnant women in large population-based studies conducted in New Zealand (35.7%)[21] and the United States (25.2%)[22]. Probably, this may be due to the higher prevalence of urinary infection (UTI) in the pregnant women in our study, which was 45% (data not shown in results), since UTI is the most prevalent infection in pregnant women[23]. Another likely explanation may be due to the population, as they come from a population with lower income than in the United States and New Zealand, a lower level of education, which leads to more urinary and genital infections. In a study carried out in the city of Rio de Janeiro, Brazil, with a final sample of 1091 pregnant women, 45.9% had UTI[23], data very similar to ours.

Moreover, as previously reported[24], the prevalence of antimicrobial use tends to be the lowest in the first trimester. This can be caused by the high prevalence of urinary and genital infections in the second and third trimester of pregnancy[25]. Furthermore, early in the pregnancy, women may be more afraid to use medications due to the risk of causing adverse effects on the fetus.

Findings from previous studies that investigated the association between the use of antimicrobials during pregnancy and childhood nutrition status have shown conflicting results. Cassidy-Bushrow *et al.* (2018)[26] evaluated 24 months old infants and found no evidence of association between the use of antimicrobials during the prenatal period and the excess

Table 3. Distribution of antimicrobials used by pregnant women according to Anatomical Therapeutic Chemical Classification* (ATC; levels 1, 2 and 5). 2015 Pelotas (Brazil) Birth Cohort Study.

drugs	n	%
J – Antiinfectives for systemic use	**2565**	**12,21****
J01 - Antibacterials for systemic use	**1797**	**70,08*****
J01DB01 - cefalexin	605	23,58
J01CA04 - amoxicillin	405	15,78
J01XE01 - nitrofurantoin	399	15,56
J01CA01 - ampicillin	151	5,89
J01FA10 - azithromycin	49	1,91
J01CR02 - amoxicillin and beta-lactamase inhibitor	45	1,75
J01CE08 - benzathine benzylpenicillin	41	1,60
J01MA06 - norfloxacin	31	1,21
J01FA02 - spiramycin	16	0,62
J01EE01 - sulfamethoxazole and trimethoprim	11	0,43
J01DD04 - ceftriaxone	7	0,27
J01MA12 - levofloxacin	6	0,23
J01EC02 - sulfadiazine	4	0,16
J01AA07 - tetracycline	4	0,16
J01MB02 - nalidixic acid	2	0,08
J01DC02 - cefuroxime	3	0,12
J01DC04 - cefaclor	1	0,04
J01DB05 - cefadroxil	1	0,04
J01DB04 - cefazolin	1	0,04
J01DD01 - cefotaxime	1	0,04
J01FF02 - lincomycin	1	0,04
J01GB03 - gentamicin	1	0,04
other	12	0,47
J02 - Antimycotics for systemic use	**25**	**0,97**
J02AC01 - Fluconazole	15	0,58
other	10	0,39
J04 - Antimycobacterials	**5**	**0,19**
J04AB02 - rifampicin	1	0,04
J04AM02 - rifampicin and isoniazid	1	0,04
J04AM05 - rifampicin, pyrazinamide and isoniazid	1	0,04
other	2	0,08
J05 - Antivirals for systemic use	**45**	**1,75**
J05AR10 - lopinavir and ritonavir	14	0,55
J05AR01 - zidovudine and lamivudine	5	0,19
J05AR12 - lamivudine and tenofovir disoproxil	2	0,08
J05AF01 - zidovudine	2	0,08
J05AF05 - lamivudine	2	0,08
J05AF07 - tenofovir disoproxil	2	0,08
J05AG03 - efavirenz	1	0,04
other	17	0,66
Not classified	**693**	**27,01**

it continues

* World Health Organization. Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2014. Available at: whocc.no/atc_ddd_index/. ** Percentage in relation to the total number of medicines used (N=21015). *** Percentage in relation to the total antimicrobials used (ATC 1= J) N=2565

Note: drugs identified as "other" belong to levels J01, J02, J04 and J05 where they are. However, they were not classified up to level 5 of the ATC classification as the others. Medications indicated as "Not classified" belong to level 1 = J of the ATC classification but do not have classification at the following levels.

Source: Authors.

weight. Similar to our findings, they also found isolated positive association when they analyzed the use of antimicrobials per trimester of pregnancy, yet with a small magnitude of associations observed[26]. Conversely, Lin *et al.* (2020)[27] have found that among 4,909 children aged one to four years, exposure to antimicrobials during pregnancy was associated with a higher risk of excess weight only in female children aged 12 months. In our study, sensitivity analyses were conducted and showed that associations observed did not vary by sex (data not shown).

Regarding the type of antimicrobial used, Cassidy-Bushrow *et al.* (2018)[26] found a significant association between the use of macrolides during pregnancy with BMI-for-age (BMI z-score 0.37; SD:0.18; p = 0.039). They found no association with other types of antimicrobials[26]. Macrolides are broad-spectrum antibacterial. In the present study, most pregnant women used small-spectrum antimicrobials, and no association with overweight was found according to the type of antimicrobials used.

A recent systematic review of 23 studies which analyzed data from over 1.2 million participants found that prenatal antimicrobial exposure is not associated with an excess of weight or childhood obesity. However, subgroup analyses were performed in this review indicating an increased risk of excess weight when use was in the second trimester of pregnancy (RR = 1.13; 95%CI: 1.06; 1.22; p = 0.001)[28]. Thus, the results

Table 4. Association between use of antimicrobials during pregnancy and child nutritional status at 3, 12, 24 and 48 months. 2015 Pelotas (Brazil) Birth Cohort Study.

	3 months		12 months		24 months		48 months	
	β crude (95%CI)	β adjusted (95%CI)	β crude (95%CI)	β adjusted (95%CI)	β crude (95%CI)	β adjusted (95%CI)	β crude (95%CI)	β adjusted (95%CI)
Total use								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-0.02	-0.03	0.08	0.06	-0.006	-0.02	-0.05	-0.06
	(-0.08; 0.05)	(-0.10; 0.03)	(-0.008; 0.16)	(-0.02; 0.15)	(-0.08; 0.07)	(-0.10; 0.05)	(-0.19; 0.09)	(-0.20; 0.09)
1st trimester								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-0.002	-0.005	0.06	0.04	0.04	0.02	0.05	0.03
	(-0.09; 0.08)	(-0.09; 0.08)	(-0.04; 0.17)	(-0.07; 0.15)	(-0.06; 0.13)	(-0.07; 0.12)	(-0.13; 0.23)	(-0.15; 0.21)
2nd trimester								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-0.10	-0.12	-0.05	-0.06	-0.04	-0.05	0.002	0.02
	(-0.18; -0.02)	(-0.20; -0.04)	(-0.15; 0.05)	(-0.17; 0.04)	(-0.13; 0.47)	(-0.14; 0.04)	(-0.17; 0.17)	(-0.15; 0.19)
3rd trimester								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.03	0.02	0.06	0.05	0.03	0.02	-0.07	-0.07
	(-0.05; 0.11)	(-0.06; 0.10)	(-0.04; 0.16)	(-0.05; 0.15)	(-0.06; 0.12)	(-0.07; 0.12)	(-0.24; 0.10)	(-0.24; 0.09)
Pregnancy								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	-0.01	-0.03	0.12	0.11	0.004	-0.01	-0.03	0.02
	(-0.09; 0.06)	(-0.11; 0.04)	(0.02; 0.21)	(0.01; 0.20)	(-0.08; 0.09)	(-0.10; 0.07)	(-0.19; 0.13)	(-0.18; 0.14)
2+	-0.02	-0.04	-0.02	-0.04	-0.03	-0.05	-0.10	-0.13
	(-0.12; 0.08)	(-0.14; 0.06)	(-0.15; 0.11)	(-0.17; 0.09)	(-0.14; 0.08)	(-0.16; 0.06)	(-0.32; 0.11)	(-0.35; 0.08)
Small spectrum								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	-0.001	-0.03	0.01	-0.01	-0.04	-0.07	-0.09	-0.11
	(-0.07; 0.07)	(-0.10; 0.05)	(-0.08; 0.10)	(-0.10; 0.08)	(-0.12; 0.04)	(-0.15; 0.01)	(-0.24; 0.06)	(-0.26; 0.05)
Broad spectrum								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.04	0.08	0.04	0.06	0.16	0.12	0.008	-0.15
	(-0.15; 0.24)	(-0.12; 0.28)	(-0.20; 0.29)	(-0.19; 0.31)	(-0.06; 0.37)	(-0.10; 0.34)	(-0.41; 0.42)	(-0.56; 0.27)

β: regression coefficient; 95%CI: 95% confidence interval. Adjusted for maternal age, maternal skin colour, maternal marital status, maternal education, family income, maternal prepregnancy BMI, number of prenatal consultations, parity, pregnancy smoking, pregnancy alcohol, gestational hypertension and gestational diabetes.

Source: Authors.

of this review are in accordance with the isolated findings found in our and previous studies[26].

A study with 10,000 school-age children in Denmark found an association between the use of antimicrobials with excess weight in school children whose birth weight was more than 3500g and whose mothers used antimicrobials during pregnancy (PR=1.30, 95%CI 1.05; 1.61)[3]. In that study, antimicrobial exposure in the second trimester (PR: 1.39, 95% CI: 1.11; 1.73) and in the third trimester of pregnancy (PR: 1.43, 95% CI: 1.17; 1.76) were associated with increased excess weight in school-age children. Furthermore, the prevalence of excess weight increased according to the number of antimicrobials prescribed to the mother (p = 0.001) but not with the type of antimicrobial[3]. Sensitivity analyzes in our study were conducted and did not show differential associations according to birth weight status of children (data not shown).

Among members of Kaiser Permanente Northern California cohort study[29], with data collected from 2007 to 2015, there was no increased risk of obesity in children whose mothers had controlled infection, either by type of antimicrobials or in terms of dose-response ratio. However, untreated maternal infection (i.e., those mothers who required an antimicrobial

Table 5. Association between use of antimicrobials during pregnancy and excess weight* at 3, 12, 24 and 48 months. 2015 Pelotas (Brazil) Birth Cohort Study.

	3 months		12 months		24 months		48 months	
	RR_{crude} (95%CI)	$RR_{adjusted}$ (95%CI)	RR_{crude} (95%CI)	$RR_{adjusted}$ (95%CI)	RR_{crude} (95%CI)	$RR_{adjusted}$ (95%CI)	RR_{crude} (95%CI)	$RR_{adjusted}$ (95%CI)
Total use								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.98	0.97	1.05	1.04	1.01	0.98	1.01	1.01
	(0.86; 1.12)	(0.85; 1.11)	(0.98; 1.14)	(0.96; 1.13)	(0.92; 1.11)	(0.89; 1.07)	(0.94; 1.09)	(0.94; 1.08)
1st trimester								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.03	1.04	1.10	1.08	1.08	1.05	1.15	1.13
	(0.86; 1.25)	(0.87; 1.23)	(1.00; 1.21)	(0.98; 1.19)	(0.96; 1.21)	(0.93; 1.18)	(1.05; 1.25)	(1.04; 1.23)
2nd trimester								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	0.90	0.90	0.96	0.96	1.01	0.99	0.99	1.00
	(0.74; 1.08)	(0.76; 1.06)	(0.87; 1.05)	(0.87; 1.05)	(0.91; 1.13)	(0.88; 1.11)	(0.91; 1.09)	(0.92; 1.10)
3rd trimester								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.06	1.06	1.01	1.00	1.00	0.98	0.98	0.98
	(0.89; 1.26)	(0.90; 1.25)	(0.92; 1.11)	(0.91; 1.10)	(0.89; 1.12)	(0.87; 1.10)	(0.90; 1.07)	(0.90; 1.07)
Pregnancy								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
1	0.98	0.97	1.09	1.07	1.02	0.99	1.01	1.01
	(0.83 - 1.16)	(0.84; 1.13)	(1.00; 1.18)	(0.98; 1.17)	(0.92; 1.13)	(0.89; 1.10)	(0.93; 1.09)	(0.93; 1.09)
2+	0.98	0.97	0.98	0.97	0.99	0.96	1.03	1.03
	(0.78 - 1.23)	(0.79; 1.20)	(0.87; 1.11)	(0.85; 1.09)	(0.86; 1.15)	(0.83; 1.11)	(0.93; 1.15)	(0.92; 1.14)
Small spectrum								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.04	1.02	1.03	1.01	0.98	0.94	0.99	0.98
	(0.90; 1.20)	(0.88; 1.18)	(0.95; 1.12)	(0.93; 1.10)	(0.88; 1.08)	(0.85; 1.05)	(0.92; 1.07)	(0.91; 1.06)
Broad-spectrum								
No	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
Yes	1.06	1.11	1.06	1.06	1.24	1.20	1.18	1.14
	(0.72; 1.55)	(0.76; 1.62)	(0.85; 1.31)	(0.85; 1.32)	(0.99; 1.57)	(0.94; 1.53)	(0.99; 1.42)	(0.94; 1.37)

RR: Relative risk; 95%CI: 95% confidence interval. Adjusted for maternal age, maternal skin colour, maternal marital status, maternal education, family income, maternal prepregnancy BMI, number of prenatal consultations, parity, pregnancy smoking, pregnancy alcohol, gestational hypertension and gestational diabetes. Excess of weight: z-score ≥ 1 standard deviation (SDs) up to ≥ 2 SDs.

Source: Authors.

but did not use it) was associated with a higher risk of obesity (OR = 1.09 CI: 1.03; 1.16). These results were confirmed utilizing a sensitivity analysis among discordant siblings, i.e., pairing with children of the same mother with pregnancy without infection or using antimicrobials, which allowed additional control of unmeasured confounding factors, including genetic, intrauterine maternal and family factors.

Limitations of our study should be acknowledged. Maternal diet during pregnancy was not assessed, which can directly interact with the children's weight. However, our analyses accounted for maternal pre-pregnancy BMI as a potential confounder. Self-reported antimicrobial use may lead to misclassification of antimicrobials, as mothers may confuse the names of medications or not remember if they used antimicrobials. However, this may be more important to symptomatic or less impactful treatments in the context of pregnancy, which is not the case for the treatment of infections. The time and duration of antimicrobial use were not assessed in our study, only the frequency of use per trimester of pregnancy. However, our analyses of the number of trimesters that antimicrobials were used showed similar results to those from trimester-specific use.

Conclusion

Despite the controversies regarding the association between the use of antimicrobials during pregnancy and excess weight in children, the findings of our study suggest that the use of antimicrobials during pregnancy may not impact children excess weight up to 48 months postpartum.

Collaborations

AD Bertoldi, TR Flores, MPT Silveira, MF Silveira, and GI Mielke conducted fieldwork and data collection for the 2015 cohort. AD Bertoldi and TR Flores contributed to the study conception and design. TR Flores and GI Mielke conducted the statistical analyses, and all authors contributed to the interpretation of the findings. MPT Silveira, I Emmerick, and AC Boing conducted the literature review, and TR Flores wrote the initial draft of the paper. All authors contributed to subsequent versions, critically reviewed the paper, and approved the final version.

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Data availability statement

The data sources adopted in the research are indicated in the article's body.

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