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Review Article

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Prenatal and Perinatal Antibiotic Exposure and Long-Term Outcome

Thomas Gestels [1] **and Yvan Vandenplas** [2]

[1]Department of Pediatrics, Antwerp University Hospital, Edegem, Belgium
[2]Department of KidZ Health Castle, Universitair Ziekenhuis Brussels, Brussels, Belgium

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Correspondence to
Thomas Gestels
Department of Pediatrics, Antwerp University Hospital, Drie Eikenstraat 655, Edegem 2650, Belgium.
Email: thomas.gestels@uza.be

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ORCID iDs
Thomas Gestels
https://orcid.org/0000-0001-9732-4711
Yvan Vandenplas
https://orcid.org/0000-0002-1862-8651

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ABSTRACT

Antibiotics are frequently administered during pregnancy. Although necessary to address acute infections, their use facilitates antibiotic resistance. Other associations have also been found with the use of antibiotics, such as perturbations of gut bacteria, delays in microbial maturation, and increased risks of allergic and inflammatory diseases. Little is known about how the prenatal and perinatal administration of antibiotics to mothers affects the clinical outcomes of their offspring. A literature search was conducted of the Cochrane, Embase, and PubMed engines. The retrieved articles were reviewed by two authors and verified for relevance. The primary outcome was the effect of pre- and perinatal maternal antibiotic use on clinical outcomes. Thirty-one relevant studies were included in the meta-analysis. Various aspects are discussed, including infections, allergies, obesity, and psychosocial factors. In animal studies, antibiotic intake during pregnancy has been suggested to cause long-term alterations in immune regulation. In humans, associations have been found between antibiotic intake during pregnancy and different types of infections and an increased risk of pediatric infection–related hospitalization. A dose-dependent positive association between pre- and perinatal antibiotic use and asthma severity has been reported in animal and human studies, while positive associations with atopic dermatitis and eczema were reported by human studies. Multiple associations were identified between antibiotic intake and psychological problems in animal studies; however, relevant data from human studies are limited. However, one study reported a positive association with autism spectrum disorders. Multiple animal and human studies reported a positive association between pre- and perinatal antibiotic use by mothers and diseases in their offspring. Our findings have potentially significant clinical relevance, particularly considering the implications for health during infancy and later in life as well as the related economic burden.

Keywords: Microbiome; Antibiotics; Pregnancy; Neonate; Fetus; Gastroenterology

INTRODUCTION

Antibiotics are frequently used during pregnancy [1,2]. During pregnancy, various physiological changes can result in increased susceptibility to infections [2,3]. Roughly one in four pregnant women receive an antibiotic prescription [1]. Some antibiotics, such as beta-lactams, fosfomycin, metronidazole, nitrofurantoin, clindamycin, and vancomycin, are

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generally considered safe and effective during pregnancy. Others, such as fluoroquinolones and tetracyclines, are teratogenic and should be avoided during pregnancy [1].

Antibiotic use is necessary to address acute infections, but their long-term, frequent use creates bacterial resistance [2]. Furthermore, associations between antibiotic use and other long-term effects have been increasingly reported. Antibiotic use during infancy has been associated with an increased risk of disorders such as obesity, inflammatory bowel disease (IBD), asthma, and other allergic/inflammatory conditions [4]. Early antibiotic exposure has been hypothesized to cause a 6–12-month delay in microbial maturation [4], which normally develops over the first 18–24 months of life (**Table 1**) [5]. An increasing number of studies suggest that perturbations of the neonatal gut bacterial composition are a possible consequence of maternal antibiotic use [1,4,5].

Moreover, associations between antibiotic use during pregnancy and clinical outcomes in the offspring have been reported. This narrative review focuses on the different clinical outcomes in animals and children associated with the pre- and perinatal use of antibiotics.

MATERIALS AND METHODS

We searched the PubMed, Cochrane, and Embase databases on August 1, 2021, using the following MeSH terms combined by the Boolean operators "AND" and "OR": "anti-bacterial agents," "antibiotic," "cesarean section," "c-section," "pregnancy," "gastrointestinal microbiome," and "microbiome." We selected animal and human studies and included articles published from the day of the database creation until August 1, 2021. Only articles published in English or Dutch for which the full text was available were included. Articles on preterm neonates were excluded because of the possible impact of postnatal therapies, such as antibiotics and proton pump inhibitors, on the microbiome. The maximum age of the study population was 16 years. Editorial articles and comments were excluded from this review. A total of 609 potentially relevant articles were identified. The list of articles was reviewed by both authors and checked for relevance. After an initial screening based on the title and abstract, 96 articles were retrieved for a full-text evaluation. Studies reporting on the antibiotic intake of the child after birth were only included if relevant data on the pre- and/or perinatal antibiotic intake of the mother could be analyzed separately. Thirty-one relevant studies (**Table 2**) were selected and checked for confounding variables for several factors such as maternal age and body mass index (BMI), asthma, tobacco use during pregnancy, socioeconomic status, previous deliveries, past miscarriages, and delivery method (**Fig. 1**).

Table 1. Different phases of normal initial bacterial colonization

Phase 0	Partial colonization in the periuterine environment
Phase 1	Acquire maternal vaginal/colonic microbiota (full-term vaginal delivery)
Phase 2	Introduction of oral feedings (breast milk or formula)
Phase 3	Weaning to solid foods
Phase 4	Acquire complete mature colonization (12–18 mo)

Adapted from Walker et al. (Nestle Nutr Inst Workshop Ser 2017;88:23-33) with permission [5].

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Table 2. Summary of included publications

First author (year of publication)	Country (total n)	Study design	Population	Sample size	Timing of antibiotic exposure	Outcome	Result
Baron et al. [26], (2020)	United States (3), Denmark (2), Canada (2), Japan (1), Iran (1), the Netherlands (1), Sweden (1) and Finland (1)	Systematic review	0–5 years until 7–14 years	134 (minimum) to 910,301 participants (maximum)	Pre- and perinatal	Asthma	Positive
	Denmark (1), United States (1) and Belgium (1)	Systematic review	18 months up to 4 years of age	492 (minimum) to 62,560 participants (maximum)	Pre- and perinatal	Eczema	Positive
Higgins et al. [20], (2021)	Isle of Wight, UK	Prospective birth cohort	0–12 months	412 participants	Pre- and perinatal	Infant wheezing	Negative
Cassidy-Bushrow et al. [28], (2018)	Detroit, US	Retrospective	0–2 years	527 participants	Prenatal	Early BMI Index	Positive
Baron et al. [29], (2020)	United States (4) and Denmark (1)	Systematic review	2 years old up to of 7 years old	436 (minimum) to 39,615 mother-child pairs (maximum)	Pre- and perinatal	Overweight	Positive (under certain conditions)
Cunha et al. [14], (2021)	Portugal	Retrospective	0–4 years	7,459 participants	Pre- and perinatal	Different infections: tonsillitis, otitis, pneumonia, UTI, AGE, *H. pylori*	Tonsillitis: positive Otitis: negative Pneumonia: negative UTI: negative AGE: negative *H. pylori*: negative
Hamad et al. [36], (2019)	Manitoba, Canada	Population-based cohort	0–13 years old	214,834 participants	Pre- and perinatal	Autism spectrum disorders	Positive
Huang et al. [27], (2020)	Sweden (1), Poland (1), Belgium (2), South Korea (1), UK (1), Denmark (1)	Meta-analysis	0–1 years old	411 (minimum) to 62,560 participants (maximum)	Pre- and perinatal	Eczema	Positive only in first and second trimesters
Jess et al. [33], (2019)	Denmark	Population-based nationwide cohort	7–11 years old	43,365 mother-child pairs	Pre- and perinatal	Overweight	Negative
Leong et al. [32], (2020)	New Zealand	Cross-sectional national	0–4 years old	151,359 participants	Pre- and perinatal	Obesity	Negative
Loewen et al. [23], (2018)	Winnipeg, Canada	Population-based	0–9 years old	213,661 mother-child pairs	Pre- and perinatal	Asthma	Positive (and doseresponse association)
Metsälä et al. [21], (2015)	Finland	Population- and register-based nested case–control study	3–11 years old	6,690 case-control pairs	Prenatal	Asthma	Positive
Metz et al. [35], (2020)	USA	Retrospective cohort	2–5 years old	4,825 mother-child pairs	Perinatal	BMI	Negative
Metzler et al. [25], (2019)	Austria, Finland, France, Germany, and Switzerland	Prospective birth cohort	0–6 years old	1,080 participants	Prenatal	AD, food allergy, asthma, atopic sensitization and allergic rhinitis	AD: positive Food allergy: positive Asthma: negative Atopic sensitization: negative Allergic rhinitis: negative
Miller et al. [16], (2018)	Denmark	Population-based cohort	0–14 years old	443,546 participants	Pre- and perinatal	Infection-related hospitalization	Positive
Mor et al. [30], (2015)	Denmark	Prevalence	7–16 years old	9,886 participants	Pre- and perinatal	Overweight and obesity	Positive
Mulder et al. [22], (2016)	The Netherlands	Case-sibling and case-control	0–5 years old	2,456 participants	Pre- and perinatal	Asthma	Case-sibling: positive only 3rd trimester Case-control study: positive in any trimester
Örtqvist et al. [17], (2019)	Sweden	Population-based	0–6 years old	827,239 participants	Pre- and perinatal	IBD	Positive
Pedersen et al. [15], (2017)	Denmark	Birth cohort	0–3 years old	514 (OM) and 699 (VT) participants	Pre- and perinatal	OM and VT	OM: positive (and doseresponse association) VT: positive
Timm et al. [18], (2017)	Denmark	Birth cohort	18 months old	62,560 mother-child pairs	Prenatal	AD	Positive
Turi et al. [24], (2021)	Tennessee (United States)	Population-based cohort	0–8 years old	84,214 mother-child pairs	Pre- and perinatal	Asthma	Positive (and dose-response association)

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Table 2. (Continued) Summary of included publications

First author (year of publication)	Country (total n)	Study design	Population	Sample size	Timing of antibiotic exposure	Outcome	Result
Wan et al. [31], (2020)	Hungary, South Korea, Denmark, New Zealand, UK, Canada, United States, Finland, The Netherlands	Systematic review and meta-analysis	0–11 years old	1,253,035 participants total	Pre- and perinatal	Childhood overweight and obesity	Negative
Wohl et al. [19], (2015)	Pennsylvania (United States)	Retrospective analysis	0–2 years old	492 mother-child pairs	Prenatal	AD	Positive

OM: otitis media, VT: ventilation tubes, BMI: body mass index, UTI: urinary tract infection, AGE: acute gastroenteritis, AD: atopic dermatitis, IBD: inflammatory bowel disease, *H. pylori: Helicobacter pylori*.

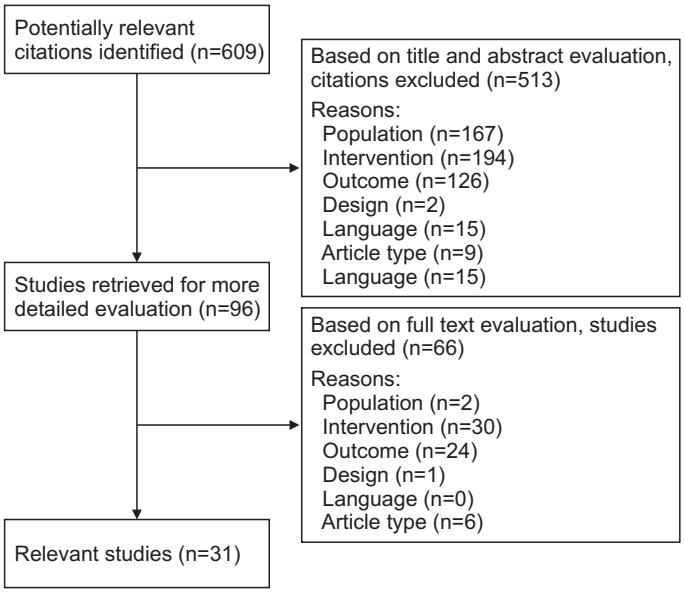

Fig. 1. Flow chart of literature review process.

RESULTS

Animals

Alhasan et al. [6] demonstrated that vancomycin intake in pregnant mice is associated with increased asthma severity in a dose-dependent manner. Moreover, mice with the highest antibiotic concentration showed reduced offspring weights and increased miscarriages [6]. When given a diet high in saturated fat later in life, low-dose antibiotics during pregnancy cause weight gain in newborn rat pups, eventually leading to obesity [3]. Maternal intake of the antibiotic neomycin during pregnancy was found to accelerate the development of diabetes mellitus (DM) in diabetic mice compared to the offspring of untreated control mice [7]. In neomycin-treated mice, immune-tolerant antigen-presenting cells with diminished specific autoantigen-presenting capability have been detected both in vitro and in vivo [7]. Tormo-Badia et al. [8] showed that a mixture of metronidazole, neomycin, and polymyxin ingested by pregnant mice is a potential risk factor for type 1 DM.

Male mice treated with prenatal penicillin developed long-lasting alterations in immune regulation, including a significant decline in T-reg cells and CD3+ CD4+ CD25+ lymphocytes

[9]. In another study, the offspring of mice treated with a combination of ampicillin, streptomycin, and clindamycin showed reduced interferon-γ production from CD8+ T cells and exhibited alterations in dendritic cell and natural killer cell populations during infection that could contribute to the poor antiviral immunity seen among them [10].

Multiple animal studies reported that antibiotics administered during pregnancy have a psychosocial impact on offspring [9,11-13]. In mice, Champagne-Jorgensen et al. [9] showed that the administration of low-dose penicillin during the last week of pregnancy had sex-specific long-term effects on the offspring. Female offspring of the treated group showed decreased anxiety-like behavior, whereas male mice showed abnormal social behavior on a sociability test. Furthermore, male offspring did not exhibit a strong preference for a mouse versus empty chamber compared with the control group [9].

Periconceptional exposure to succinylsulfathiazole in Wistar rats reduced social interactions, increased anxiety, and altered sensorimotor gating in male and female offspring [11]. Persistent alterations in anxiety (increased anxiety), sociability (deficits in social recognition), and cognitive behaviors (cognitive deficits) were observed in the offspring of mice when antibiotics were administered during pregnancy [12]. These effects were greater in the group of mice whose mothers were treated with a cocktail of ampicillin, vancomycin, metronidazole, ciprofloxacin, and imipenem than in the group treated with penicillin only [12]. Sulfamonomethoxine ingestion in pregnant mice reportedly increase anxiety among offspring, and spatial learning and memory were impaired more severely in male versus female offspring and control groups [13]. Furthermore, significantly increased blood glucose levels were observed in pups whose mothers received a high sulfamonomethoxine dose [13].

Human

1. Infections

In a Portuguese birth cohort of 7,459 children, Cunha et al. [14] found an association between prenatal antibiotic use in all trimesters and a higher occurrence of tonsillitis at 4 years of age even after controlling for potential confounders. However, this association could have been coincidental since no association was found with other infections (gastroenteritis, otitis, pneumonia, urinary tract infection, gastroenteritis) [14]. Prenatal antibiotic exposure in all trimesters was associated with an increased risk of otitis media [15]. The risk of ventilation tubes was particularly associated with antibiotic use during the third trimester. The risk of otitis media increases with a higher number of prenatal exposures to antibiotics; however, this association was not identified with ventilation tubes [15]. In a Danish population-based cohort study, all children were tracked from birth until the date of their first hospitalization due to an infection, death, 14th birthday, emigration, or December 31, 2009, whichever occurred first [16]. Antibiotic exposure during pregnancy is associated with a higher incidence of pediatric infection–related hospitalizations. This elevated risk persisted throughout childhood. Overall, hospitalization owing to infection was more likely to occur in boys [16]. When mothers received more antibiotic prescriptions throughout pregnancy and were closer to delivery, there was a higher risk of infection–related hospitalization [16]. A population-based study found a positive association between prenatal antibiotic exposure and very early onset IBD [17]. This increased risk was higher for Crohn's disease than for ulcerative colitis [17].

In summary, studies have shown positive associations between pre- and perinatal antibiotic use and different infections (tonsillitis, otitis media, and IBD) and an increased risk of childhood infection–related hospitalization.

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2. Allergy, asthma, atopic dermatitis, eczema, and wheezing

Timm et al. [18] investigated the association between atopic dermatitis (AD) and prenatal antibiotics among 18-month-old children within the Danish National Birth Cohort, which included 62,560 mother–child pairs. The authors found that prenatal antibiotic exposure throughout pregnancy was associated with an increased risk of AD, but only when the mother was atopic. In a study by Wohl et al. [19], perinatal antibiotic exposure for more than 24 hours before birth was found to be a risk factor for the development of AD by 2 years of age, whereas that for less than 24 hours before vaginal delivery did not increase the risk of AD.

A prospective birth cohort study showed no significant association between prenatal antibiotic exposure and wheezing (infectious and noninfectious) at 3, 6, and 12 months and prenatal antibiotic exposure [20]. According to a population- and register-based nested case-control study, the risk of asthma in the offspring was linked to maternal antibiotic use during pregnancy [21]. Cephalosporins and macrolides were the most strongly associated drugs. Antibiotics for gram-positive bacterial infections are associated with a higher risk of asthma [21]. In the Netherlands, a case-sibling study together with a case-control study was conducted to examine the association between prenatal antibiotic use and asthma in preschoolers [22]. The use of antibiotics during the third trimester of pregnancy has been linked to a higher incidence of asthma in preschool-aged children in both the case-sibling and case-control analyses [22].

Only one case-control study showed a significant association between antibiotic exposure during any trimester of pregnancy and the onset of asthma in preschoolers [22]. A population-based study in Canada found that children born to mothers who received antibiotics during pregnancy had significantly higher rates of asthma than their unexposed counterparts [23]. This association persisted after the adjustment for different confounding factors. Moreover, a dose-dependent increase in the risk of asthma was observed. However, the relationship between maternal antibiotic use and childhood asthma was unaffected by the timing of the mother's exposure [23]. Similar associations were observed for maternal antibiotic use during the first, second, and third trimesters, but also 9 months before and after pregnancy, suggesting that the association is either not directly causal or not specific to pregnancy [23].

Turi et al. [24] investigated the dose, timing, and spectrum of prenatal antibiotic exposure and the risk of developing childhood asthma in a population-based cohort study and found a significant dose-response association between the number of prenatal antibiotic courses and childhood asthma. Based on the trimester of prenatal antibiotic exposure, the odds of childhood asthma increased by 17% for first-trimester-only exposure, 9% for second-trimester-only exposure, 11% for third-trimester-only exposure, and 38% for multiple-trimester exposure compared with non-exposed children [24]. The effect of timing on the first course was moderated by the total number of maternal courses in children exposed to at least one treatment in utero. The timing of exposure had no effect on the likelihood of developing asthma of the offspring of pregnant women receiving a single course of antibiotics.

Among women who received more than one course of treatment, early exposure to the first course of treatment was linked to a higher chance of developing childhood asthma. A higher risk of childhood asthma was observed in the subgroup analysis of a specific number of courses when the first course was administered early in pregnancy. There was no significant association between the number and spectrum of prenatal antibiotic courses and the risk of

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developing asthma. Broad-spectrum antibiotics significantly increased the risk of childhood asthma compared with narrow-spectrum antibiotics among children exposed to only one course of antibiotics [24].

Data from 1,080 children who participated in a European birth cohort study (PASTURE), a prospective birth cohort of children living in rural regions of five European countries (Switzerland, Germany, France, Finland, and Austria), revealed an association between prenatal antibiotic exposure, AD, and food allergies [25]. Diseases that began within the first year of life were the most common. Asthma, atopic sensitization, and allergic rhinitis were not associated with prenatal antibiotic exposure [25].

A systematic review showed that, in most studies (9/12), a significant relationship was found between asthma and the prenatal use of antibiotics [26]. For eczema (three studies total), there was an overall significant effect in one study and in two other studies only when prenatal antibiotic exposure was prolonged (>24 hours) or when there was antibiotic exposure occurred in the first or second and third trimesters [26]. Prenatal antibiotic use in the first or second trimester was positively associated with eczema before 1 year of age according to a meta-analysis [27]. However, there was no association between third-trimester antibiotic exposure and infant eczema [27].

In summary, the role of antibiotics in the development of allergies indicates a moderate amount of evidence of the relationship between early life antibiotics and childhood asthma, AD, and eczema. The results were inconsistent; however, a positive association was generally found. Factors such as genetic predisposition or environmental exposure are possible confounding factors and merit additional studies addressing antibiotic use during pregnancy, including the role of family history of atopic disease, pollution, and socioeconomic factors.

3. Overweight and obesity

A growing body of research suggests that antibiotic use is associated with childhood BMI, possibly through processes mediated by gut microbiome alterations [28]. Five studies of prenatal antibiotic exposure and its effect on body weight were identified in a systematic review. All five studies indicated a positive correlation between prenatal antibiotic exposure and overweight/obesity [29]. Two studies reported a significant overall relationship, while the other three reported significant relationships when the frequency of antibiotic administration, antibiotic exposure only during the first or second trimester, and/or overweight status of the mothers were included [29]. Prenatal antibiotic use is reportedly associated with a higher mean BMI at 2 years of age [28]. Associations between prenatal antibiotic usage and childhood BMI varied by trimester of exposure, with first- or second-trimester exposure being more strongly associated with a higher BMI at age 2 years for overweight/obesity. A Danish prevalence study revealed a sex-specific adjusted prevalence with a higher prevalence of overweight and obesity in children with prenatal antibiotic exposure [30]. Among girls, the ratio was 1.16 for overweight and 1.27 for obesity. Among boys, the ratios were 1.37 and 1.29, respectively [30].

A systematic review and meta-analysis investigated whether antibiotic exposure during pregnancy and childhood was associated with childhood overweight or obesity [31]. The results of 23 observational studies of 1,253,035 participants showed that prenatal exposure to antibiotics was not significantly associated with childhood overweight or obesity, whereas an increased risk of overweight or obesity was observed in a subgroup analysis when antibiotics

were administered during the second trimester [31]. A dose-dependent relationship between prenatal antibiotic exposure and obesity at 4 years of age was discovered in a cross-sectional national study using covariate-adjusted analysis [32]. Despite evidence linking antibiotic exposure to an increased risk of obesity, subsequent investigations of twins and siblings with discordant results reported no correlation. Thus, antibiotics are unlikely to be major contributors to childhood obesity and these discordant results most likely reflect unmeasured confounding factors [32].

According to a population-based national cohort study, prenatal exposure to narrow-spectrum antibiotics was not associated with overweight in offspring until the age of 11 years [33]. By 7 years of age, exposure to broad-spectrum antibiotics was associated with a higher odds of overweight, but this association disappeared as the children aged. Antibiotic prophylaxis for group B streptococcus (GBS) was not associated with a higher BMI in young children [34,35].

In summary, the current literature shows inconsistent results regarding the relationship between prenatal antibiotic use, overweight, and obesity. These outcomes reflect unmeasured confounding factors and show that pre- and perinatal contact with antibiotics are small contributors to childhood obesity if at all. More well-designed studies are needed to address potential confounders.

4. Psychosocial effects

In a population-based cohort study conducted by Hamad et al. [36] of 214,834 children born in Canada, 37.6% of the individuals had prenatal exposure to antibiotics. There were no differences in the antibiotic dose. During follow-up, 2,965 children were diagnosed with autism spectrum disorder (ASD), and those exposed to antibiotics had a higher risk of ASD, with a hazard ratio of 1.10. An association was observed in women exposed to antibiotics during the second or third trimesters. Hence, exposure to prenatal antibiotics is associated with a slight increase in the risk of ASD.

DISCUSSION

Multiple animal and human studies evaluated the effects of pre- and perinatal antibiotic use on and outcomes of offspring. In animal studies, specific lymphocyte subset typing has shown long-term altered immune regulation [9,10] and profound alterations in the composition of the gut microbiota in mothers and infants [9]. Due to the altered gut microbiome, pathogens can interact with the intestinal surface, resulting in an inflammatory response. These factors may play a significant role in epigenetic and/or immunological alterations, another possible mechanism affecting long-term outcomes. There was also a positive association between autoimmune diseases and pre- and perinatal antibiotic use as a potential risk factor for type 1 DM. Human studies have shown positive associations between pre- and perinatal antibiotics and different infections; however, not all confirmed these associations [14,15,17]. A recent systematic review found that GBS perinatal antibiotic prophylaxis had profound effects on the intestinal microbiota of infants by diminishing beneficial commensals [34], although GBS prophylaxis was not associated with the risk of overweight [35]. Nevertheless, changes in the intestinal microbiota composition during early life may impact the development of the immune system.

Allergies, asthma, and eczema are serious public health issues whose prevalence is increasing worldwide. Animal and human studies reported a dose-dependent association between pre- and perinatal antibiotics and asthma severity. Human studies also reported a positive association between AD and eczema [26,27].

Limited data suggest a positive association between overweight/obesity and antibiotic use during pregnancy. One animal study found an increase in weight only when the offspring were fed a diet high in high saturated fat [5]. The results of human studies reflect unmeasured confounding factors and suggest that antibiotics are, if at all, small contributors to childhood obesity [28-35].

Many animal studies have analyzed the association between pre- and perinatal antibiotic use and psychological problems in offspring, showing that long-term effects can be sex-specific. Associations with abnormal social behavior, cognitive deficits, increased anxiety, and altered sensorimotor gating have been reported. To date, only a few human studies have analyzed the influence of pre- and perinatal antibiotics at the psychological level. One study reported that prenatal antibiotic exposure was associated with a low but increased risk of ASD [36].

This study had some limitations. However, these are association studies, and no human studies have shown causality. The importance of confounding factors cannot be underestimated. However, in animal studies, in which confounding factors can be easily eliminated and causality can be better investigated, multiple effects of antibiotic intake during pregnancy on various health aspects have been demonstrated. Due to interstudy heterogeneity, clear definitions such as childhood asthma and perinatal antibiotic use were not possible. However, this study provides a good summary of the different outcomes.

Given the high prevalence of maternal antibiotic intake during pregnancy [31], our findings have potentially significant translational relevance, particularly considering the implications for health from infancy to later life. This review emphasizes the possible consequences for the child, including an increased risk of asthma and atopy, increased susceptibility to infections with longer hospital stays, and a possible negative effect on the psyche. No or dubious associations were found between antibiotic use during pregnancy and overweight and obesity in childhood. More well-designed studies are needed to better address important potential confounders, such as environmental exposure, familial factors, or genetic predisposition. Other aspects to be addressed in future studies include the influence of different antibiotics, as some studies have shown different effects of specific antibiotics.

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