



ANTIBIOTICS IN THE EARLY STAGES OF LIFE: A PRECURSOR TO CHILDHOOD OBESITY

ANTIBIÓTICOS NAS FASES INICIAIS DA VIDA: UM PRECURSOR DA OBESIDADE INFANTIL

ANTIBIÓTICOS EN LAS FASES INICIALES DE LA VIDA: UN PRECURSOR DE LA OBESIDAD INFANTIL

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RESUMO

Objetivo: integrar a produção científica sobre o uso de antibióticos nas fases iniciais da vida e sua relação com a obesidade infantil. **Metodologia:** trata-se de uma revisão sistemática integrativa. Os descritores estruturados no DeCS, *Pediatric Obesity*, *Antibiotic* e *Dysbiosis*, foram utilizados nas varreduras das seguintes bases de busca: BVS, Wiley; ScienceDirect; MEDLINE; Biblioteca VirtualSciELO e LILACS. O período de coleta dos dados compreendeu os meses de abril e maio de 2018. Adotaram-se como critérios de inclusão: texto completo (free); publicado nos anos de 2014 a 2018; dos tipos artigo original e de revisão, artigo na imprensa, recurso, editorial, perspectiva e pesquisa transacional. Enquanto que os critérios de exclusão foram: livros; monografias; Trabalho de Conclusão de Curso; resumos, teses e dissertações; além de artigos que não contemplavam a relação entre o uso materno, no pré-natal, e/ou infantil de antibióticos com o desenvolvimento da obesidade infantil. **Resultados:** analisaram-se 126 trabalhos. Entretanto, obedeceram aos critérios de inclusão, apenas, 23 artigos científicos, sendo submetidos às seis etapas da revisão integrativa, entre os quais 14 eram estudos primários e dez eram de revisão. As categorias temáticas desenvolvidas a partir da análise dos trabalhos foram: 1 - Efeitos benéficos da amamentação na microbiota intestinal e perda do efeito metabólico protetor do leite materno devido ao uso de antibióticos; 2 - Disbiose da microbiota intestinal induzida pelo uso de antibióticos e sua influência no desenvolvimento da obesidade na infância; 3 - Exposições aos antibióticos nas fases iniciais da vida e suas relações com o sobrepeso e com a obesidade. **Conclusão:** os médicos devem atentar para as consequências, como a obesidade infantil, da prescrição de antibiótico nas fases iniciais da vida e considerar este problema como uma nova e séria razão para avaliar, criteriosamente, os riscos em longo prazo e benefícios em curto prazo da antibioticoterapia voltada para o público infantil.

Descritores: Amamentação; Antibiótico; Disbiose; Obesidade Infantil.

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ABSTRACT

Objective: to integrate scientific production on the use of antibiotics in the early stages of life and its relation to childhood obesity. **Method:** it is a systematic integrative review. The structured descriptors in DeCS, Pediatric Obesity, Antibiotic and Dysbiosis, were used in the scans of the following search bases: BVS, Wiley; ScienceDirect; MEDLINE; Virtual Library SciELO and LILACS. The data collection period comprised the months of April and May 2018. Inclusion criteria were: full text (free); published in the years 2014 to 2018; original and review type articles, article in the press, feature, editorial, perspective and transactional research. While the exclusion criteria were: books; monographs; Final course work; abstracts, theses and dissertations; in addition to articles that did not contemplate the relationship between maternal, prenatal, and / or infantile use of antibiotics with the development of childhood obesity. **Results:** 126 papers were analyzed. However, only 23 scientific articles were included in the inclusion criteria, being submitted to the six stages of the integrative review, among which 14 were primary studies and ten were revision ones. The thematic categories developed from the analysis of the studies were: 1 - Beneficial effects of breastfeeding on the intestinal microbiota, and loss of the protective metabolic effect of breast milk due to the use of antibiotics; 2 - Dysbiosis of the intestinal microbiota, induced by the use of antibiotics and its influence on the development of childhood obesity; 3 - Exposure to antibiotics in the early stages of life, and their relationship with overweight and obesity. **Conclusion:** physicians should pay attention to the consequences, such as childhood obesity, of antibiotic prescription in the early stages of life and consider this problem as a new and serious reason to carefully evaluate the long-term risks and short-term benefits of antibiotic therapy for children.

Descriptors: Breast Feeding; Anti-bacterial Agents; Dysbiosis; Pediatric Obesity.

RESUMEN

Objetivo: integrar la producción científica sobre el uso de antibióticos en las fases iniciales de la vida y su relación con la obesidad infantil. **Metodología:** se trata de una revisión sistemática integrativa. Los descriptores estructurados en el DeCS, *Pediatric Obesity*, *Antibiotic* y *Dysbiosis* se utilizaron en las exploraciones de las siguientes bases de búsqueda: BVS, Wiley; ScienceDirect; MEDILINE; Biblioteca Virtual SciELO y LILACS. El período de recolección de los datos comprendió los meses de abril y mayo de 2018. Se adoptaron como criterios de inclusión: texto completo (free); publicado en los años de 2014 a 2018; de los tipos artículo original y de revisión, artículo en la prensa, el recurso, el editorial, la perspectiva y la investigación transaccional. Mientras que los criterios de exclusión fueron: libros; monografías; Trabajo de Conclusión de Curso; resúmenes, tesis y disertaciones; además de artículos que no contemplaban la relación entre el uso materno, en el prenatal, y/o infantil de antibióticos con el desarrollo de la obesidad infantil. **Resultados:** se analizaron 126 trabajos. Sin embargo, obedecieron a los criterios de inclusión, sólo, 23 artículos científicos, siendo sometidos a las seis etapas de la revisión integrativa, entre los cuales, 14 eran estudios primarios y diez eran de revisión. Las categorías temáticas desarrolladas a partir del análisis de los trabajos fueron: 1- Efectos benéficos de la lactancia materna en la microbiota intestinal y pérdida del efecto metabólico protector de la leche materna debido al uso de antibióticos; 2 - Disbiosis de la microbiota intestinal inducida por el uso de antibióticos y su influencia en el desarrollo de la obesidad en la infancia; 3 - Exposiciones a los antibióticos en las fases iniciales de la vida y sus relaciones con el sobrepeso y la obesidad. **Conclusión:** los médicos deben atender para las consecuencias, como la obesidad infantil, de la prescripción de antibiótico en las fases iniciales de la vida y considerar este problema como una nueva y seria razón para evaluar, cuidadosamente, los riesgos a largo plazo y beneficios a corto plazo de la antibioticoterapia orientada hacia el público infantil.

INTRODUCTION

The growing prevalence of childhood obesity is one of the greatest challenges faced by medical professionals who care for infants and children. According to the data obtained in the study of the prevalence of childhood and adult obesity in the United States in the 21st century, the National Nutrition and Health Examination Survey 2011-2012 was carried out. According to data from this survey, more than one in six children and young people, between the ages of two and nineteen, are obese and more than one in three are overweight. Overweight and obese children are at high risk of becoming obese adults. The harmful consequences of obesity for health - increased risk of metabolic and cardiovascular diseases, musculoskeletal problems and psychosocial problems such as bullying and bulimia - may manifest as early childhood and become more prevalent with increasing age.¹

Antibiotics are quite a few medicines given in childhood. Although it significantly reduces the morbidity and mortality of patients with bacterial infections and has enormous medical, social and economic advantages; their use may cause unwanted problems. Among them, the inadequate development of intestinal bacterial flora favoring the development of obesity.²

It is observed that the excessive use of broad spectrum antibiotics for conditions responsive to narrow spectrum agents has increased dramatically.³

A large number of highly diversified bacteria live in symbiosis with the human body. They are collectively called microbiota. The microbes that inhabit the human body outgrow the somatic cells of a human by an estimated ten times.⁴

Hours after birth, microorganisms from the vaginal, fecal and / or mother's skin and the environment are important colonizers of the baby's bowel. Several other factors, including prematurity, infant formula (milk or formula), hygiene and use of antibiotics will impact the composition of the infant intestinal microbiota.³

Studies indicate the influence of the intestinal microbiota on the regulation and development of energy metabolism, fat accumulation and susceptibility to

diet induced adiposity. This influence of dysregulated intestinal microbiota is termed dysbiosis-induced obesity.⁵

Bowel colonization begins in the intrauterine period, and continues throughout the child's life, and is influenced by a variety of dietary and environmental factors. A factor observed in the genesis of childhood obesity is the role of early imbalance of the intestinal flora, an imbalance caused by the action of bactericidal and / or bacteriostatic drugs that can transverse the placental barrier or act directly on the child's organism leading to a state of intestinal dysbiosis.⁶

Over the last decade, new evidence from animal and human studies has identified associations between intestinal microbiota imbalance, a condition called dysbiosis, dysregulation of host metabolism, and development of obesity.⁷ Maternal antibiotic use during the second and third trimesters of pregnancy was associated with an 84% increase in the risk of childhood obesity at age seven.⁸

Recently, a number of new problems related to intestinal microbiota dysbiosis have arisen. Of these, obesity appears to be of particular relevance. Obesity in children is increasing all over the world. Weight gain in the first years of life has been shown to be a significant risk for obesity that is difficult to treat in adulthood with the onset of type 2 diabetes, cardiovascular disease and a host of other serious comorbidities.²

It is known that breastfeeding protects against numerous infections early in life, and the long duration of breastfeeding also reduces the risk of overweight in children. The benefits of breastfeeding are related to the influence of breast milk in the initial development of the intestinal microbiota, which is strongly dependent on the baby's diet.⁵

In contrast to the mature intestinal microbiota of healthy adults, which seems relatively stable over time, the child's intestinal microbiota only establishes and matures in the early years of life. Thus, early childhood seems to represent a crucial age window in the prevention of diseases related to dysbiosis.⁹

In this context, the following guiding question emerged from this study: what is the influence of the development of childhood obesity after exposure to antibiotics in the prenatal and postnatal periods?

This study aims to integrate scientific production on the use of antibiotics in the early stages of life and its relationship with childhood obesity.

METHOD

It is a bibliographical review of the systematic integrative type, which followed the following steps (see Figure 1): 1) Definition of the theme, selection of the guiding question and choice of the search strategy, descriptors and databases more effective in the publications; 2) Choice of inclusion and exclusion criteria; 3) Identification of the pre-selected and selected studies by reading the indexing agents of the publications, such as summary, keywords and title, as well as organization of the pre-selected studies and identification of the selected studies; 4): Categorization of the selected studies, with elaboration and use of the synthesis matrix, besides information analysis, formation of an individual library and critical evaluation of the selected studies; 5) analysis, interpretation and discussion of results; 6) Presentation of the review in an article format, which includes proposals for future studies.¹⁰⁻¹¹

Figure 1 - Detail of the steps of the Systematic Integrative Review.

STEP	TOPICS OF EACH STEP	DETAILING OF EACH TOPIC
1	Theme	Antibiotics in the early stages of life: a precursor of childhood obesity.
	Guidingquestion	What is the influence of the development of childhood obesity after exposure to antibiotics in the prenatal and postnatal periods?
	General objective	Integrating scientific production on the use of antibiotics in the early stages of life and its relation to childhood obesity.
	Searchstrategies	1. Crossing of descriptors through the Boolean operator AND; 2. Use of quotation marks in polterms (descriptor with more than one term) so that the scan of scientific articles contemplates the exact term; 3. Use of date type of publication; 4. Use of English descriptors to expand the number of articles.
	Structureddescriptors in DECS	1. Pediatric Obesity (D000900) 2. Antibiotic (D063766) 3. Dysbiosis (D064806)
Virtual libraries	1. Virtual Health Library (VHL) - including the sources of information that compose its network: Latin American and Caribbean Literature in Health Sciences (LILACS), Medical	

		Literature Analysis and Retrieval System Online (MEDLINE), Virtual Library Scientific Electronic Library Online (SciELO); 2. Wiley; 3. ScienceDirect; 4. MEDLINE; 5. Virtual Library SciELO; 6. LILACS.
2	Period of data collection	April and May 2018
	Inclusion Criteria	1. Full text (available / free) of type: original article, review article, press article, feature, editorial, perspective and transactional research; 2. Publication (2014-2018).
	Exclusion Criteria	1. Books, monographs, Conclusion Work, Abstracts, Reports, Theses and Dissertations; 2. Articles that did not consider the relationship between maternal, prenatal, and / or infantile use of antibiotics with the development of childhood obesity.
3	Number of papers selected for integrative systematic review by reading the indexing agents of the publications (abstract, keywords and title) and results, which should contain the descriptors used in this study	23
4	Categories obtained with the analysis of the scientific works investigated	1. Beneficial effects of breastfeeding on the intestinal microbiota and loss of the protective metabolic effect of breast milk due to the use of antibiotics; 2. Dysbiosis of the intestinal microbiota induced by the use of antibiotics and its influence on the development of childhood obesity; 3. Exposures to antibiotics in the early stages of life and their relationship to overweight and obesity.
5	Analysis, interpretation and discussion of results	View in "Results and Discussion"
6	Presentation of the review in an article format, which includes proposals for future studies	This Complete Article

The methodological characteristics of the analyzed scientific papers were classified according to the level of evidence, according to the proposal of Melnyk and Fineout-Overholt¹² in: I - Evidence from a systematic review or meta-analysis of relevant data, randomized controlled trials, or from guidelines clinics based on systematic reviews of randomized controlled trials; II - Evidence derived from at least one well-delineated randomized controlled trial; III - Evidence obtained from well-designed clinical trials without randomization; IV -

Evidence from well-delineated cohort and case-control studies; V - Evidence from a systematic review of descriptive and qualitative studies; VI - Evidence derived from a single descriptive or qualitative study; and VII - Evidence from the opinion of authorities and / or report of expert committees.

RESULTS

Table 1 corresponds to the quantity of the scans performed in the main search databases.

Table 1. Total of publications and texts available in the VHL, Wiley, ScienceDirect, Virtual LibrarySciELO, LILACS and MEDLINE using crossword of structured descriptors.

Descriptor Crossing	Data base	Total of publications without the filter "Main subject"	Available full texts	Full texts available after applying filters	Texts used in Systematic Integrative Review
"PediatricObesity" andAntibiotic	BVS	36	32	18	4
	SciELO	0	0	0	0
	LILACS	0	0	0	0
	MEDLINE	16	7	7	3
	Wiley	6.886	1.980	34	3
	Science Direct	109	61	4	3
PediatricObesity" andDysbiosis	BVS	11	10	4	2
	SciELO	0	0	0	0
	LILACS	0	0	0	0
	MEDLINE	22	21	10	3
	Wiley	376	341	9	3
	Science Direct	392	345	40	2
TOTAL		7.848	2.797	126	23

7,848 scientific publications were detected in the databases, 126 were scientific articles available after the use of the filters. However, 23 scientific articles (see Table 2) followed the inclusion criteria and were submitted to the stages of the integrative review (see Table 1). Of these, 14 were primary (original) studies and ten were secondary (secondary) studies. As for the year of publication, three studies were published in the year 2018, five studies were published in the year 2017, nine in the year 2016, six in 2015 and in 2014, which proves to be a current theme. All articles were written in English.

Table 2. Survey of scientific publications according to the inclusion criteria.

Nº	QUOTE	THEME	YEAR	LEVEL OF EVIDENCE	OBJECTIVE OF THE STUDY	CONCLUSION OF THE STUDY	TERMINOLOGY CROSSING
1	Scottet al.	Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity.	2016	IV	To assess the association between exposure to antibiotics before two years of age and childhood obesity.	Administration of three or more cycles of antibiotics before children reach the age of TWO years is associated with an increased risk of obesity in early childhood.	"Pediatric Obesity" and Antibiotic
2	Lemas et al.	Exploring the contribution of maternal antibiotics and breastfeeding to the development of the infant microbiome and pediatric obesity.	2016	V	Describe maternal factors such as feeding practices and antibiotic use as mechanisms that may unbalance the baby's intestinal microbiota and raise the risk of childhood obesity.	The complex components of human milk have many nutritional benefits for the baby; however, the microbiome in human milk can be an important factor in helping to regulate baby's weight .	"Pediatric Obesity" and Antibiotic
3	Korpella et al.	Association of Early-Life Antibiotic Use and Protective Effects of Breastfeeding: Role of the	2016	IV	To analyze whether the early use of antibiotics in children interferes with the beneficial effects of breastfeeding on	The use of antibiotics in a child during breastfeeding may weaken the beneficial long-term effects of	"Pediatric Obesity" and Antibiotic

		Intestinal Microbiota.			weight gain and to investigate whether duration of breastfeeding is associated with the development of the long-term microbiota.	breastfeeding	
4	Turta,Rautava.	Antibiotics, obesity and the link to microbes - what are we doing to our children?	2016	II	Investigate the potentially harmful long-term metabolic consequences of early exposure to antibiotics.	The prudent use of antibiotics is critical not only to reduce the spread of antibiotic-resistant organisms but also to minimize the potentially harmful long-term metabolic consequences of early exposure to antibiotics.	"PediatricObesity" andAntibiotic
5	Magsariliet al.	Making a Case for Pediatric Antimicrobial Stewardship Programs.	2015	II	To describe the currently available evidence on antimicrobial management, with a focus on the pediatric public, in order to avoid possible future side effects that this family of drugs can cause	In general, interventions resulted in decreased antimicrobial use, reduced costs, and fewer errors in antibiotic prescribing.	"PediatricObesity" andAntibiotic

6	Schwartz et al.	Antibiotic use and childhood body mass index trajectory.	2016	I	Carry out a large-scale longitudinal study of the entire age range among children, noting whether the use of antibiotics in early life has been associated with weight gain during growth and development	The results suggest that the use of antibiotics influences weight gain throughout childhood and not only during the first years of life.	"PediatricObesity" andAntibiotic
7	Yallapragada, Nash, Robinson.	Early-Life Exposure to Antibiotics, Alterations in the Intestinal Microbiome, and Risk of Metabolic Disease in Children and Adults.	2015	II	To explore the natural evolution of the intestinal microbiota, from the perinatal period to infancy, and the effect of antibiotics on physiological microbial ecology.	Alterações na composição da microbiota devido a antibióticos podem levar a efeitos negativos a longo prazo, incluindo obesidade e diabetes mellitus	"PediatricObesity" andAntibiotic
8	Moret al.	Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study.	2015	I	Conduct a prevalence study among Danish schoolchildren aged 7-16 years, using data from routine school anthropometric assessments conducted during 2002-2013, investigating	Prenatal exposure to systemic antibiotics is associated with an increased risk of overweight and obesity at school age, and this association varies according to birth weight.	"PediatricObesity" andAntibiotic

					whether there is a link between the early and / or irregular use of antibiotics and obesity in childhood.		
9	Mueller et al.	Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity.	2016	I	To demonstrate that the use of antibiotics during gestation can alter the normal exchange of the maternal-offspring microbiota, contributing to the aberrant microbial colonization of the infant gut and greater susceptibility to obesity later in life	Exposure to antibiotics in the second or third trimester were associated with increased risk of childhood obesity.	"PediatricObesity" andAntibiotic
10	Bailey et al.	Association of antibiotics in infancy with early childhood obesity.	2014	IV	To assess the impact of antibiotics prescribed in childhood (ages 0-23 months) on obesity in infancy (ages 24-59 months).	Repeated exposure to broad spectrum antibiotics between zero and 23 months is associated with early childhood obesity.	"PediatricObesity" andAntibiotic
11	Shao et al.	Antibiotic Exposure in Early Life Increases Risk of Childhood Obesity: A Systematic	2017	V	Conduct a systematic review to comprehensively and quantitatively understand the risk of childhood obesity	It was observed that there was a dose dependent relationship of antibiotic used with the	"PediatricObesity" andAntibiotic

		Review and Meta-Analysis			caused by exposure to antibiotics in early life.	development of childhood obesity.	
12	Koleva, Bridgman, Kozyrskyj.	The Infant Gut Microbiome: Evidence for Obesity Risk and Dietary Intervention	2015	V	To summarize current research on the association between childhood intestinal microbiota and obesity.	Abuse of antibiotics may cause dysbiosis of the infant intestinal microbiota, and this factor is associated with a greater chance of excessive gain of body mass throughout life.	"Pediatric Obesity" and Dysbiosis
13	Forrest, Block, Bailey.	Antibiotics, infections, and childhood obesity.	2017	II	To analyze a possible exposure-response association between the number of episodes of antibiotic treatment during the first two years of life and the development of obesity in late childhood	An association between the frequency of antibiotic use and childhood obesity was identified, and this effect was more pronounced for those with broad spectrum antibiotics.	"Pediatric Obesity" and Dysbiosis
14	Lu, Ni.	Gut microbiota and the development of pediatric diseases.	2017	IV	Highlight recent studies on the relationships between intestinal microbiota and diseases, among them early obesity, from a pediatric	Dysbiosis plays an important role in various diseases in childhood and in adult life: obesity and atopic diseases are	"Pediatric Obesity" and Dysbiosis

					perspective.	some examples.	
15	Riva et al.	Pediatric obesity is associated with an altered gut microbiota and discordant shifts in Firmicutes populations	2017	V	To characterize the composition of the intestinal microbiota in obese and normal children aged six to 16 years.	Our results suggest that intestinal microbiota dysbiosis may be involved in the etiology of childhood obesity.	"PediatricObesity" andDysbiosis
16	Vangay et al.	Antibiotics, pediatric dysbiosis, and disease.	2015	IV	To synthesize the current knowledge on the relationship between antibiotics, dysbiosis and diseases related to metabolism and propose a knowledge to study antibiotic-related dysbiosis in children.	It was identified that the use of antibiotics during childhood induces imbalances in the intestinal microbiota, called dysbiosis. And that the responses of the intestinal microbiota to antibiotics have potential connection with disease development, such as obesity.	"PediatricObesity" andDysbiosis
17	García-Mantranet al.	Perinatal nutrition: how to take care of the gut microbiota?	2016	V	To update the nutritional recommendations, including the use of antibiotics for the perinatal period, and	Maternal nutritional status, environment, diet, lifestyle and microbes are associated with	"PediatricObesity" andDysbiosis

					to analyze the influence of maternal microbiota and nutrition on the development of the intestinal microbiota in infants, since changes in this process have recently been associated with specific diseases in the future.	the risk of developing childhood diseases, such as obesity, which may persist into adulthood.	
18	Moscetti, Pronk.	Invisible seams: Preventing childhood obesity through an improved obstetrics-pediatrics care continuum.	2017	V	Explore prenatal and early childhood factors that predispose children to excessive fat accumulation and present obstetric and pediatric care measures as a means of preventing childhood obesity.	A more attentive obstetric-pediatric clinical practice could better address, and avoid, the early origins of obesity, a condition we are finding to have consequences throughout life.	"PediatricObesity" andAntibiotic
19	Fleming-Dutra et al.	Prevalence of inappropriate antibiotic prescriptions among US ambulatory care visits, 2010-2011.	2016	VI	To estimate the antibiotic prescription rates per patient in the outpatient age by age and diagnosis, and the estimated portions of antibiotic use that may be inappropriate in	In the United States in 2010-2011 there was an estimated annual antibiotic prescription rate per thousand inhabitants of 506, but only an estimate of 353	"PediatricObesity" andAntibiotic

					adults and children in the United States.	antibiotic prescriptions was probably appropriate, supporting the need to set a goal for better outpatient antibiotic management, given the negative consequences of antibiotic therapy, especially in children.	
20	Emmanouil, Raoult.	Gut microbiota modifications and weight gain in early life.	2018	V	To review the effects of the administration of probiotics and antibiotics in early life on the intestinal microbiota and discuss their effects on weight gain	The composition of the intestinal microbiota is quite sensitive and has played a key role in human health. It was evident that early administration of antibiotics may have long-term implications, including disturbances of the intestinal flora and possible chronic	"PediatricObesity" andAntibiotic

						conditions such as obesity.	
21	Leong et al.	Antibiotics, gut microbiome and obesity.	2018	V	To focus the association between antibiotics and obesity, and the role of intestinal microbiota in this relation.	There is strong evidence to support the role of antibiotics in the development of obesity in well-controlled animal models. Association studies suggest that young children may be particularly vulnerable to the weight-promoting effects of antibiotics through changes in the intestinal microbiota.	"PediatricObesity" andAntibiotic
22	López-Contrera et al.	Composition of gut microbiota in obese and normal-weight Mexican school-age children and its association with metabolic traits.	2018	VI	To compare the composition of the intestinal microbiota in obese and normal weight children and to associate the intestinal microbiota profiles with serum amino acid levels and metabolic characteristics related to obesity.	No significant differences were observed in the abundance of phyla or Firmicutes / Bacteroides ratios between normal weight and obese children. However, the abundance of	"PediatricObesity" andAntibiotic

						Bacteroides Eggerthii was significantly higher in obese children and correlated positively with the percentage of body fat.	
23	Van Best et al.	On the origin of species: factors shaping the establishment of infant's gut microbiota.	2015	V	To study the origin of the pioneer bacteria and the factors that influence the development of the intestinal microbiota in infants.	Colonization of essential bacteria in the neonatal gut is important, since its lack may result in an increased risk of metabolic or disorders, such as obesity and / or allergy.	"Pediatric Obesity" and Antibiotic

The WordArt website was used to obtain the most frequent terms in the abstracts of the 23 articles selected. The most prevalent terms were: obesity (n=178), childhood (n=155), intestinal microbiota (n=153), antibiotics (n=151), dysbiosis maternal (n=28), breastfeeding (n=22).

DISCUSSION

Below, the thematic categories elaborated from the systematic integrative review:

Beneficial effects of breastfeeding on the intestinal microbiota and loss of the protective metabolic effect of breast milk due to the use of antibiotics.

Exclusive breastfeeding practices are linked to babies' healthy postnatal growth through optimal nutrition and health protection; this evidence led to the recommendation of 6 months of exclusive breastfeeding by WHO.¹³

It is known that breastfeeding also protects against numerous infections in early life, and that prolonged breastfeeding also reduces the risk of overweight in children. The benefits of breastfeeding are probably related to the initial development of the intestinal microbiota, which is strongly dependent on the baby's diet.¹⁴

After birth, breastfeeding is the most important determinant of infant colonization. Human milk contains trillions of live bacteria per liter and is a source of staphylococci, streptococci, lactic acid bacteria and, mainly, Bifidobacterium essential in the intestinal microbiota balance.⁸ Early microbial colonization plays a decisive role in human health and changes in this process have been lately associated with specific diseases in the future, such as obesity.¹³

The baby's intestine is initially colonized by Proteobacteria, Bacteroides and Firmicutes, followed by a gradual increase of Bifidobacterium, producer of short chain fatty acids that are against the process of obesity due to the introduction of breast milk. At six months of age, Bacteroides and Firmicutes dominate while Proteobacteria and Bifidobacterium gradually decline, which can be attributed to the weaning period. By the end of the first year of life, the baby's gut is dominated by bacteria from the Bacteroides, Firmicutes and

Bifidobacterium phyla. The baby's healthy bowel continues with dramatic composition changes throughout the first two years of life before becoming indistinguishable from an adult intestinal microbiota at three years of age.³

Breast milk provides substrates that are used as sources of energy by bacteria species, such as Bifidobacterium, which are abundant in the intestine of the infant, have probiotic action and are essential for the proper physiological functioning of infant energy metabolism, as they produce fatty acids of short chain.⁵

Children who are breastfed have better regulation of satiety and appetite than formula-fed children, as a healthy microflora results in a higher production of short-chain fatty acids, which are associated with increased satiety and decreased food intake.⁶

Short-chain fatty acids favor the production of some types of peptides (GLP-1, GLP-2 and PYY), which act on the hypothalamus by activating mechanisms responsible for increased satiety and decreased food intake, improving glycemic and insulinemic response, and decreasing metabolic endotoxemia, commonly present in obese and DM2 patients.¹⁵

Bifidobacterium species, with reduced presence in the intestinal microbiota of infants without breastfeeding, reduced breastfeeding time or who have made early use of antibiotics, are known for the intimate relationship with the future health of the being. The adequate presence of these bacteria in the intestinal lumen of the infant has been associated with protection against obesity induced by diet and metabolic effects. The beneficial metabolic effects of these species are thought to arise from the improvement of the permeability function of the intestinal barrier that reduces metabolic endotoxemia, which is responsible for increasing insulin resistance and for the development of obesity.²

A retrospective cohort study² made the association between the protection of the intestinal microbiota by breast milk and the use of antibiotics by children, with the body mass index in a cohort of 226 healthy children aged two to six years. The collection of these data allowed a detailed and controlled analysis of the associations between duration of breastfeeding, formation of the intestinal microbiota and health indicators.

This study made it clear that breastfed children have better regulation of satiety and appetite than formula-fed children, and this was explained by

differences in the intestinal microbiota of children with different types of nutrition.

The children with the highest Bifidobacterium population in the intestinal microbiota composition were the ones that were exposed to the mother's milk, and it was this group that presented a lower growth of the body mass index. Obesity is associated with an increase in the abundance of Firmicutes bacteria and a decrease in Bifidobacterium.¹

Irregular infant nutrition during the period in which breast milk should be the sole source of nutrition is able to increase the number of Firmicutes bacteria responsible for non-production of short-chain fatty acids and to decrease the Bifidobacterium population.⁶

It was observed that the protective effects of breastfeeding against infections and obesity were weakened or completely eliminated by the early use of antibiotics, and that in addition, the apparent impression of a protective microbiota by prolonged breastfeeding was also eliminated by the use of antibiotics during breastfeeding.⁵

These results suggest that the metabolic benefits of breastfeeding are transmitted by the beneficial effects of breast milk in the intestinal microbiota that can be positively stimulated by breast milk and negatively by antibiotics.

Thus, it is understood that the metabolic benefits of breastfeeding, as the main and exclusive diet until six months of age, are caused by the growth and development of a healthy and age-appropriate intestinal microbiota, and that breastfeeding also provides an excellent protection against elevated body mass index over the life of the child.

Disorders of intestinal microbiota induced by the use of antibiotics and their influence on the development of childhood obesity.

The human intestinal microbiota is a complex and dynamic ecosystem, consisting of hundreds to thousands of distinct bacterial species. In the last decades, knowledge about the role of the intestinal microbiota and its development, as well as on host-microorganism interactions in human health and disease, has increased rapidly due to the advance of molecular technologies. The intestinal microbiota plays a complex role in its host, providing a barrier against invading pathogens, using indigestible food components by the host enzymes,

producing essential metabolites of systemic action and modulating the responses of the immune system.⁹

The etiology of obesity is a unique interaction between genetics, socioeconomic factors and environmental conditions. Researchers and practitioners are rightly giving more attention to the origins of early obesity and demonstrating important roles for intestinal microbiota dysbiosis in the development of this condition.¹⁴

Until recently, the fetus and the intrauterine environments were believed to be sterile and thus the development of the intestinal microbiota began after birth through the vaginal canal or by cesarean section in contact with the microbiota of the skin. However, studies have found evidence of microbes in amniotic fluid, umbilical cord blood, meconium, and fetal membranes. Thus allowing the hypothesis that maternal-fetal exchange of bacteria occurs before birth, through placental changes, sowing the intestinal microbiota of the fetus.¹⁶

The initial development of the infant microbiota depends on the transmission of bacteria and metabolites in the prenatal (umbilical and amniotic fluid) and postnatal periods (vaginal flora at birth, breastfeeding, skin to skin, contact with the environment). And the microbiota evolves rapidly in early life.¹⁷

A healthy intestinal microbiota is useful to the host in many ways, including nutrient delivery, pathogen protection, and maturation of immune responses. Dysbiosis plays an important role in various diseases in childhood and in adult life, among them obesity is a very prevalent.⁴

A study was carried in which 67 children with normal weight and 71 obese children, aged between six and 12 years, were evaluated in order to compare the intestinal microbiota composition of obese and normal weight children.¹⁸ It was observed that there are bacterial species associated with obesity, since they correlated positively with the percentage of body fat. This study indicates that obese children present a bacterial microbiota in the state of dysbiosis.

The mechanisms by which antibiotics modulate weight gain are not fully elucidated, but several hypotheses have been proposed which include the following: 1- increased capacity of intestinal bacteria to extract energy from indigestible polysaccharides; 2- reduction in the number of bacteria that are metabolically protective against obesity; 3- altered hepatic lipogenesis; 4 - altered metabolic signaling; 5- deficiency of intestinal defense and immunity.¹⁹

The bacterial intestinal flora of a healthy child has bacteria capable of breaking down the undigested polysaccharides (fibers) into short chain fatty acids, which provide 80-200 kcal per day of energy. Dysbiosis (for example, a 20% increase in Firmicutes and a corresponding 20% decrease in Bifidobacterium) may result in an additional 150 kcal of energy harvested per day. Short chain fatty acids also modulate the secretion of intestinal hormones (glucagon-like peptide [GLP-1] and peptide YY), both of which directly influence the sensation of satiety.¹⁹

The sensitivity of the intestinal microbiota in the formation process to antibiotics is perceived even during the intrauterine life. Prenatal exposure to antibiotics may permanently deregulate fetal metabolic patterns.²⁰

The perinatal intestinal microbiota disturbance caused by the use of antibiotics seems to program the host for a metabolic phenotype prone to obesity, which persists after the antibiotics have been discontinued and the intestinal microbiota have recovered from the process of dysbiosis.¹

Exposure to antibiotics, especially broad spectrum antibiotics, in the early stages of infant development and growth, has a negative effect on the intestinal microbiota, and is a factor responsible for causing intestinal bacterial flora dysbiosis. The dysbiosis of the intestinal microbiota, in the first moments of life, is the key point for the genesis of metabolic imbalances that are factors inducing obesity.²¹

It is understood, therefore, that the intestinal microbiota plays an important role in the conditioning of body weight, and that the intestinal microbiota dysbiosis, related to the use of antibiotics, is associated with overweight and obesity throughout the life of the individual. It has also been observed that the change in the composition of the microbiota persists beyond the period of administration of antibiotics and leads to the emergence of several problems, including overweight and late obesity. Unfortunately, not all the mechanisms that could explain the relationship between intestinal microbiota modification and the development of obesity are defined, but it is already clear that an intimate relationship exists between antibiotic-induced dysbiosis in early life with the development of obesity.

Exposures to antibiotics in the early stages of life and their relationship to overweight and obesity.

A longitudinal study collected data from medical records of 257,729 children aged 2 to 18 years between January 2001 and February 2012.²² After applying the inclusion criteria, 163,820 children participated in the study. The association between exposure to antibiotics and the BMI trajectory throughout childhood was evaluated. This is one of the largest studies to date that analyzes the association between antibiotics and longitudinal trajectories of BMI in children. In conclusion we observed a combination of reversible, persistent and progressive associations in several classes of antibiotics, but all of them had an influence on obesity. The results suggest that the use of antibiotics influences weight gain throughout childhood and adolescence, not only during the first years of life.

A retrospective cohort study of 21,714 children in the UK Health Improvement Network was conducted through electronic medical records from 1995 to 2013. In the cohort, 1306 of the children (6.4%) became obese at four years of age. Exposure to antibiotics was associated with an increased risk of obesity at four years. The conclusion of the study was that administration of three or more cycles of antibiotics before children reach a two-year age is associated with an increased risk of obesity in early childhood.¹⁵

A study evaluated 436 mother-infant dyads, followed up to seven years of age with complete data.¹⁶ It was identified that children born to mothers who took antibiotics in the second or third trimester of pregnancy had an 84% higher risk of obesity at age seven when compared to children whose mothers did not report antibiotic exposure during that period.

A large study during the interval from 2001 to 2009, 89,057 children were analyzed in the primary care network of the Children's Hospital of Philadelphia, a large pediatric primary care network covering part of the eastern United States.²³ The cohort included 65,480 children. The results suggest that the use of broad-spectrum antibiotics before 24 months of life may be a favorable factor for excessive weight gain.

Using data from electronic records of 64,000 children,²⁴ identified an association exposure response between the number of episodes of antibiotic treatment during the first two years of life and development of childhood obesity, an effect that was more pronounced for broad-spectrum antibiotics.

A systematic review was conducted in order to comprehensively assess the impact of exposure to antibiotics on infant adiposity.²⁶ A literature review in

MEDLINE, Embase and Web of Science was conducted to find articles examining the impact of exposure to antibiotics on the risk of childhood adiposity. From the bibliographic research, a total of 1,294 abstracts were found, but only 26 studies were considered as potentially eligible. After detailed evaluation, 11 studies were chosen. This meta-analysis provides strong evidence for the association between exposure to antibiotics in early life and childhood adiposity. There is also an obvious dose-response relationship between exposure to antibiotics and childhood adiposity.

It follows from this data analysis that the prudent use of antibiotics is recommended for pregnant women, infants and children in order to reduce the risk of developing childhood obesity.

CONCLUSION

A thorough study is recommended to initiate any research, whether original or secondary, of the articles available in the databases of the virtual libraries, regarding the intended subject. However, the researcher needs the ability to manipulate terminology (descriptors) to make the search for scientific information effective. In the area of health, these terminologies are known as descriptors in health sciences and to obtain such structured vocabularies one must access the DeCS portal.

In this study, a survey of scientific publications about the influence of exposure to antibiotics, either in the prenatal period or in the postnatal period, was obtained with the development of childhood obesity. The contents arranged in the three categories of this research allowed to reach the objectives established in this research.

The Portals MEDLINE, Virtual Health Library (VHL), Virtual Library Scientific Electronic Library Online (SciELO), Latin American and Caribbean Literature in Health Sciences (LILACS), Wiley Online Library and Science Direct played a crucial role in the construction of the cited and discussed information, being considered essential tools of the object of study. In general, these portals met the main needs of the research, contemplating complete scientific texts in publications of various journals on the influence of antibiotics on the development of childhood obesity.

As for the increasing prevalence of childhood obesity, it is important to emphasize that this issue has become a major global health challenge, and

actions to reduce the prevalence of obesity in children and adolescents are urgently needed. Research into risk factors associated with childhood obesity can help us to develop effective preventive interventions. This systematic integrative review suggests that exposure to antibiotics may result in an increased risk of childhood obesity. The antibiotic therapy is able to change the intestinal microbiota to dysbiotic states, which can lead to the development and / or aggravation of obesity. This finding has important implications in the clinical setting, since antibiotics are among the most common drugs administered in infants and children.

As childhood obesity is a multifactorial condition, reducing prevalence depends on the identification and management of multiple risk factors, including early exposure to antibiotics. Promoting the natural development of the microbiota can be an effective way to improve children's long-term health.

Finally, medical professionals have to consider the dysbiosis caused by the use of antibiotics in the early stages of life as a new and serious reason for the judicious use of antibiotics in clinical practice, since the relationship between antibiotic therapy and obesity is indeed present and proven childlike.

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