

Breast feeding and infection control in premature newborns: an integrative review

Aleitamento materno e controle de infecções em recém-nascidos prematuros: revisão integrativa

Lactancia materna y control de infecciones en recién nacidos prematuros: revisión integrativa

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ABSTRACT

Background and Objectives: investigating the relationship between breast milk use infection control in premature newborns may provide a basis for continuing exclusive breastfeeding, reducing the rates of early introduction of formula and strengthening their immune system. In view of this, the objective was to analyze the relationship between breastfeeding and infection control in premature newborns. **Content:** an integrative review, which included original articles, available electronically and with a temporal cut of the last five years. Searches were carried out in August 2022 in the Medical Literature Analysis and Retrieval System Online, *Literatura Latino-Americana e do Caribe em Ciências da Saúde*, Scopus, Web of Science and Science Direct databases, using the descriptors Breastfeeding, Milk Human, Infection Control, Infection Control and Premature Newborn, concatenated with the search operators "AND" and "OR". The Rayyan digital tool was used to organize the study selection stages. A total of 490 studies were identified in the search, of which seven were selected. All studies were published in English between 2018 and 2022. Regarding design, three were case-control studies, one was a cohort, one was cross-sectional, and two were clinical trials. Regarding the level of evidence, studies classified as level IV predominated. **Conclusion:** human breast milk has the power to reduce the incidence of necrotizing enterocolitis and cytomegalovirus, reduce the worsening of inflammatory states and late-onset sepsis, prevent diseases, encourage the physical and cognitive development of premature newborns.

Keywords: Milk Human. Breast Feeding. Infection Control. Infant Premature.

RESUMO

Justificativa e Objetivos: a investigação da relação do uso de leite materno com o controle de infecções em recém-nascidos prematuros poderá fornecer embasamento para continuidade do aleitamento materno exclusivo, diminuindo os índices de introdução precoce de fórmula e propiciando o fortalecimento de seu sistema imunológico. Diante disso, objetivou-se analisar a relação do aleitamento materno com o controle de infecções em recém-nascidos

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prematuros. **Conteúdo:** revisão integrativa, que incluiu artigos originais, disponíveis eletronicamente e com recorte temporal dos últimos cinco anos (2018 a 2022). Foram realizadas buscas no mês de agosto de 2022 nas bases de dados *Medical Literature Analysis and Retrieval System Online*, Literatura Latino-Americana e do Caribe em Ciências da Saúde, Scopus, *Web of Science* e *Science Direct*, sendo utilizado os descritores Aleitamento Materno, Leite Humano, Controle de Infecções, Controle de Infecção e Recém-Nascido Prematuro, concatenados com os operadores de pesquisa "AND" e "OR". Foi utilizada a ferramenta digital Rayyan para a organização das etapas de seleção dos estudos. Foram identificados 490 estudos na busca, dos quais sete foram selecionados. Todos os estudos foram publicados em inglês entre 2018 e 2022. Quanto ao delineamento, três eram estudos de caso controle, um era coorte, um era transversal e dois eram ensaios clínicos. Em relação ao nível de evidência, predominaram os estudos classificados em nível IV. **Conclusão:** o leite humano materno tem o poder de diminuir a incidência de enterocolite necrosante e citomegalovírus, reduzir o agravamento de estados inflamatórios e de sepse tardia, prevenir doenças, estimular o desenvolvimento físico e cognitivo do recém-nascido prematuro.

Descritores: Leite Humano. Aleitamento Materno. Controle de Infecções. Recém-Nascido Prematuro.

RESUMEN

Justificación y Objetivos: investigar la relación entre el uso de la leche materna y el control de infecciones en los recién nacidos prematuros puede brindar una base para continuar con la lactancia materna exclusiva, reducir las tasas de introducción temprana de fórmula y fortalecer su sistema inmunológico. Ante ello, el objetivo fue analizar la relación entre la lactancia materna y el control de infecciones en recién nacidos prematuros. **Contenido:** revisión integradora, que incluyó artículos originales, disponibles electrónicamente y con un corte temporal de los últimos cinco años. Las búsquedas se realizaron en agosto de 2022 en las bases de datos *Medical Literature Analysis and Retrieval System Online*, *Literatura Latino-Americana e do Caribe em Ciências da Saúde*, *Web of Science* y *Science Direct*, utilizando los descriptores Lactancia Materna, Leche Humana, Control de Infecciones, Control de Infecciones y Recién Nacido Prematuro, concatenado con los operadores de búsqueda "AND" y "OR". Se utilizó la herramienta digital Rayyan para organizar las etapas de selección de estudios. En la búsqueda se identificaron 490 estudios, de los cuales se seleccionaron siete. Todos los estudios fueron publicados en inglés entre 2018 y 2022. En cuanto al diseño, tres fueron estudios de casos y controles, uno fue de cohorte, uno fue transversal y dos fueron ensayos clínicos. En cuanto al nivel de evidencia predominaron los estudios clasificados como nivel IV. **Conclusión:** la leche materna humana tiene el poder de reducir la incidencia de enterocolitis necrotizante y citomegalovirus, reducir el agravamiento de estados inflamatorios y sepsis tardía, prevenir enfermedades, estimular el desarrollo físico y cognitivo de los recién nacidos prematuros.

Palabras Clave: Leche Humana. Lactancia Materna. Control de Infecciones. Recién Nacido Prematuro.

INTRODUCTION

The neonatal period is considered critical due to hemodynamic instability and the immature physiological characteristics of low birth weight and premature newborns (NB). Furthermore, the immune system of this population is still developing, making them more susceptible to infections.¹

In addition to these factors, preterm and low birth weight newborns (PTNB) become more vulnerable to bacterial infections due to prolonged hospitalization, environmental exposures in the Neonatal Intensive Care Unit (NICU), need for invasive procedures and of treatments that compromise the defense mechanism.^{2,3}

The inflammatory process resulting from these infections is related to the development of complications that can induce neonatal sepsis, bronchopulmonary dysplasia, intraventricular hemorrhages and necrotizing enterocolitis. All of these diseases are considered risk factors for neonatal mortality, as they affect various organs such as the lungs, brain and intestine. Furthermore, they lead to a high number of neonatal deaths.⁴

According to data collected by the United Nations Children's Fund, infections account for approximately 21% of NB deaths worldwide, being considered a public health problem.⁵ In Brazil, infections are the third most prevalent cause of death among premature babies (18.5%).⁶

Therefore, it is essential to know the development of the microbiome, in addition to factors that can influence infection prevention, such as the type of food offered, especially human milk (HM).⁷

HM contains important properties for the development of NB, such as nutrients, a rich variety of vitamins, minerals, proteins, fats, carbohydrates, and a range of antibodies capable of protecting the immune system against pathological microorganisms.⁸ In the context of preterm infants, exclusive breastfeeding (EBF) is considered a strong ally in reducing infections and, consequently, neonatal morbidity and mortality.^{9,10}

Given that preterm infants face a greater risk of infections due to the immaturity of the immune system, identifying effective strategies to strengthen the immunity of these babies is essential to reduce morbidity and

mortality associated with neonatal infections. Considering the molecular composition of HM and its action on the NB's immune system, investigating the relationship between breastfeeding and infection control is crucial to understanding how this practice can positively impact the health of these babies. Gathering and synthesizing data on this topic provides a collection of information that can help health professionals make informed decisions, promoting evidence-based clinical practice. This is particularly relevant for guiding health policy and neonatal care practices.

Given this context, the following question arose: what is the relationship between breastfeeding and infection control in PTNB? The investigation of this scenario may provide a basis for continuation of EBF for PTNBs, reducing the rates of early introduction of formula in the ICU, enabling the strengthening of the immune system of these NBs, which may increase their survival, acting directly on reducing morbidity and mortality rates for this population. Therefore, this study aimed to analyze the relationship between breastfeeding and infection control in PTNB.

METHODS

This is an integrative literature review, carried out in six stages: 1) theme and guiding question definition; 2) definition of inclusion and exclusion criteria; 3) study extraction; 4) analysis of selected studies; 5) interpretation of results; 6) data synthesis.¹¹ Moreover, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used to organize and present the results.¹²

The guiding research question was formulated, based on the PICO strategy, an acronym for Patient, Interest and Context.¹³ Thus, PTNB was assigned to P, risks and benefits of breastfeeding to I and control and development of infections to Co. Therefore, the following question was elaborated: what is the relationship between breastfeeding and infection control in PTNBs? Therefore, this research included studies that dealt with the PTNB population, whose phenomenon of interest is the risks and benefits of breastfeeding in the context of infection control in prematurity.

Original articles that answer the guiding question, without language limits, available in full in open access journals and with a five-year time frame (2018 to 2022) were included. The temporal delimitation was made in an attempt to promote an ideal sample of original studies, given that a high sample of articles can make it difficult to conduct the integrative review, or cause biases in the stages.¹⁴ Duplicate articles and those that did not respond to the research object were excluded.

As for data extraction, it began by collecting articles online, which took place in August 2022, through access to five databases, via the Academic Community Federated on the Coordination for the Improvement of Level Personnel Higher Education (CAPES - *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior*) Journals Portal, such as Medical Literature Analysis and Retrieval System Online (MEDLINE) (via PubMed), Latin American and

Caribbean Literature in Health Sciences (LILACS) (via Virtual Health Library), Scopus, Web of Science and Science Direct.

To search for articles, we used the descriptors in Portuguese *Recém-Nascido Prematuro*, *"Aleitamento Materno"/"Leite Humano"*, *"Controle de Infecções"*, extracted from the Health Sciences Descriptors (DeCS), and its synonyms in English, "Infant, Premature", "Breast Feeding"/"Milk, Human", "Infection Control", obtained through Medical Subject Headings (MeSH). The descriptors were crossed with the Boolean operators "AND" and "OR".

As a result, search strategies were used according to the specificities of each database: MEDLINE - Breast Feeding OR Milk, Human AND Infection Control AND Infant, Premature; LILACS - *Aleitamento Materno* OR *Leite Humano* AND *Controle de Infecções* OR *Controle de Infecção* AND *Recém-Nascido Prematuro*; Scopus - Breast Feeding OR Milk, Human AND Infection Control AND Infant, Premature; Web of Science - (((ALL=(BreastFeeding)) OR ALL=(Milk, Human)) AND ALL=(InfectionControl)) AND ALL=(Infant, Premature); and Science Direct - Breast Feeding AND Infection Control AND Infant, Premature.

Study searches and selection was carried out in August 2022 independently by two reviewers, nurses and students from an academic master's program. The studies found were exported to Rayyan Web for identification, exclusion of duplicates and decision to remain the studies by the blind authors.¹⁵ Additional reference managers were not used, as the use of Rayyan was considered sufficient. Initially, the inclusion and exclusion criteria were analyzed, and the subject was screened, which included reading the title and abstract. Subsequently, eligible references were read in full. When differences of opinion were identified, a third reviewer was appointed to read and issue a conclusive opinion, with the aim of ensuring methodological rigor in the process of selecting and including studies.

The data extracted for the qualitative analysis of articles was based on an instrument previously prepared by the reviewers, adapted from the instrument constructed and validated in 2005 by Ursi and Gavão, which contains identification (authorship, title, place and year of publication), objective, methodological design, sample, main results, outcomes and level of scientific evidence variables.¹⁶ Adaptation is justified by the non-relevance, for the present study, of some items from the original instrument. Descriptive synthesis of the data in this review is presented according to the use of image resources, illustrated through a table and figure, organized into categories with subsequent discussion in the light of specialized scientific literature.

The following classification of levels of evidence was used: level I – systematic review or meta-analysis; level II – randomized clinical trial; level III – non-randomized clinical trial; level IV – cohort study or case-control study; level V – study resulting from a systematic review, descriptive and qualitative study; level VI – study derived from a single descriptive or qualitative study; level VII – expert opinion.¹⁷

As this was a review study, submission to the Rese-

arch Ethics Committee was not necessary. It is noteworthy that all ethical precepts were followed when carrying out the research.

RESULTS AND DISCUSSION

Initially, 490 studies were identified in the databases. In the first analysis, 26 articles were excluded due to duplication and 453 were removed for not answering the guiding question, after reading the titles and abstracts. In the second analysis, by reading the articles in full, four articles that did not answer the guiding question were excluded. Finally, seven articles made up the final sample (Figure 1).

Of the seven articles analyzed, all were published in English, with four (57.14%) developed in Europe and three (42.85%) in America. It can be suggested that the development of most research in Europe is an attempt by the academic and scientific community to raise awareness of people on the importance of breastfeeding, given the low rates of EBF on the continent.¹⁸⁻²⁴ In 2015, of the 21 countries in the region, only 13% of babies up to six months were exclusively breastfed with HM.²⁵

It is worth highlighting, however, the lack of data collected in Brazilian territory. Despite not matching Europe in terms of low breastfeeding rates, the country still needs to improve its numbers. According to research by the Ministry of Health carried out between 2019 and 2020, among the 14,505 children under five years old assessed, 45.7% of those under six months old were on EBF.²⁶

It was also found that three (42.85%) were case control studies, one (14.28%) was a cohort, one (14.28%) was cross-sectional and two (28.57%) were clinical trials - one

was not randomized and one randomized.¹⁸⁻²⁴ Regarding the level of evidence, studies classified with level IV evidence predominated (n=4; 57.14%), characterized by cohort/case control studies (Chart 1). Despite the diversification of the methodological approaches gathered, it was observed that the majority of studies demonstrate the effectiveness of HM against infections.

The main results of the studies analyzed showed that breastfeeding is related to infection control in PTNB by promoting several benefits to PTNBs that reduce the risk of the onset of this condition. Subsequently, in Chart 2, the benefits of offering HM in PTNB for infection control are presented, according to the articles analyzed.

When considering the findings that answer the guiding question of this work, it was observed that HM is related to infection control in PTNB by promoting several benefits to PTNB that reduce the risk of the appearance of this condition. This highlights the need to keep babies on HM, even when admitted to the NICU and given the difficulties presented for effective practice.²⁷

Mothers, however, may experience distress due to the fear of not being able to breastfeed, which therefore requires support from the multidisciplinary team to help these mothers adhere to and maintain breastfeeding.²⁸ Thus, it is observed that it is necessary for health professionals working in ICUs to view HM not only as a food, but as an essential infection prevention measure for the development of the newborn and hospital discharge.

It was seen that the benefits of breastfeeding for controlling infections in preterm infants most cited in studies include a reduction in the incidence of late-onset sepsis (28.57%), necrotizing enterocolitis (42.85%) and the inflammatory state (28.57%).

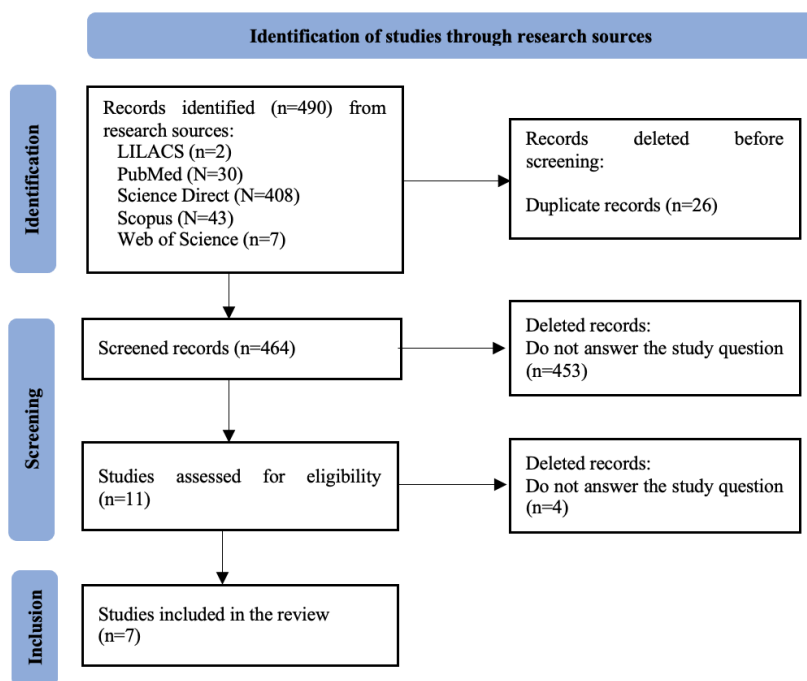


Figure 1. Flowchart for identification and selection of studies according to PRISMA, 2020

Chart 1. Synthesis of studies included in the final sample.

Code	Title	Authors and year	Location/sample	Objective	Design/LoE*	Main results
A1	Oropharyngeal Colostrum Positively Modulates the Inflammatory Response in Preterm Neonates	Martin-Álvarez et al., 2020 ¹⁸	Spain/ 100 NB [†]	Assess the effects of oropharyngeal breast milk administration on the inflammatory response of extreme preterm infants.	Case-control/ Level IV	The administration of oropharyngeal breast milk contributes to reducing the pre-inflammatory state of preterm infants [‡] and provides complete enteral nutrition earlier.
A2	Availability of Donor Human Milk Decreases the Incidence of Necrotizing Enterocolitis in VLBW Infants	Cohen et al., 2020 ²³	USA/ 9,400 NB [†]	Determine whether a project to promote HM feeding would be associated with a decrease in necrotizing enterocolitis.	Cross-sectional/ Level V	The incidence of necrotizing enterocolitis was reduced by 40% with the availability and supply of HM to NB.
A3	Team-Based Implementation of an Exclusive Human Milk Diet	Manthe et al., 2019 ²²	USA/ 225 NB [†]	Describe the teamwork, steps taken, and systems created to protect, implement, and maintain an all-HM diet.	Case-control/ Level IV	Administration of an exclusive HM diet significantly reduced the occurrence of late-onset sepsis, bronchopulmonary dysplasia, necrotizing enterocolitis and favored weight gain.
A4	Short-term Pasteurization of Breast Milk to Prevent Postnatal Cytomegalovirus Transmission in Very Preterm Infants	Bapistella et al., 2019 ¹⁹	Germany/ 87 NB [†]	Assess the effectiveness of pasteurization to prevent the transmission of cytomegalovirus via breast milk in preterm infants.	Cohort/ Level IV	The short-term supply of pasteurized HM reduced the incidence of cytomegalovirus infection through breast milk in the NICU [§] .
A5	Risk Factors for Late-Onset Sepsis in Preterm Infants: A Multicenter Case-Control Study	Hassani et al., 2019 ²⁰	Netherlands/ 755 NB [†]	Identify risk factors for late-onset sepsis in PTNB.	Case-control/ Level IV	Breast milk feeding has demonstrated a protective effect against the development of late-onset sepsis in PTNB, in addition to reducing the number of days of parenteral nutrition.
A6	Banked Human Milk and Quantitative Risk Assessment of <i>Bacillus cereus</i> Infection in Premature Infants: A Simulation Study	Lewin et al., 2018 ²⁴	Canada/ 1,000 NB [†]	Estimate the potential risk of <i>Bacillus cereus</i> infection in premature neonates caused by ingestion of contaminated pasteurized stored HM using different post-pasteurization release criteria.	Non-randomized clinical trial/ Level III	The risk of <i>Bacillus cereus</i> infection after ingesting pasteurized HM is small. Even so, the importance of bacteriological investigation before distributing HM to extremely premature babies is highlighted.
A7	Human milk feeding and cognitive outcome in preterm infants: the role of infection and NEC reduction	Lapidaire et al., 2022 ²¹	England/ 926 NB [†]	Investigate associations between early diet, infection and long-term cognitive outcome.	Randomized clinical trial/ Level II	HM, whether expressed raw or donated pasteurized HM, protects premature babies against infection and necrotizing enterocolitis. Furthermore, the absence of these is associated with better results in intelligence and performance coefficients.

* LoE: level of evidence; [†]NB: newborns; [‡]PTNB: premature newborns; [§]NICU: Neonatal Intensive Care Unit; HM – human milk.

Chart 2. Benefits of offering breast milk to premature newborns to control infections.

Effects of breastfeeding on premature newborns	Articles (n; %)
Decreased incidence of necrotizing enterocolitis	A2; A3; A7 (n=3; 42.85%)
Reduction of the inflammatory state	A1; A7 (n=2; 28.57%)
Late sepsis reduction	A3; A5 (n=2; 28.57%)
Promoting complete enteral nutrition	A1; A5 (n=2; 28.57%)
Increased weight gain	A1; A3 (n=2; 28.57%)
Decreased incidence of cytomegalovirus	A4 (n=1; 14.28%)
Risk of <i>Bacillus cereus</i> infection	A6 (n=1; 14.28%)

Regarding the reduction in the incidence of sepsis, a randomized double-blind clinical trial, carried out with 48 premature babies in Korea, presented similar data, by showing that oropharyngeal administration of colostrum can depress clinical sepsis, inhibit the secretion of pro-inflammatory cytokines as well as increase the levels of circulating immunoprotective factors in extremely

premature infants.²⁹

One hypothesis to answer this phenomenon caused by HM in the baby's body concerns its composition, rich in substances that act on the defense system, such as immunoglobulins, anti-inflammatory and immunostimulating factors. It is also rich in cytokines which, when in contact with receptors present in the mucosa of the gas-

trointestinal tract, contribute to defense mechanisms.³⁰

Based on this information, it is theorized that colostrum therapy is a protective action against neonatal sepsis, specifically through the following mechanisms: "1) interaction of milk cytokines with oropharyngeal immune cells, 2) absorption of protective biofactors by the mucosa, 3) barrier protection against pathogens, 4) local and systemic effects of oligosaccharides that modulate the intestinal microbiota and 5) beneficial effect of antioxidant protection".³¹

Regarding the reduction in the incidence of necrotizing enterocolitis, the data also prove true when comparing HM use with specific formula for premature babies, as, when assessing studies with more than 15,000 babies, a meta-analysis concluded that the use of 100% human milk can reduce by up to 4% in any type of disease, and by 2% in the most severe cases.³² It is also believed that, when ingesting colostrum, it starts to shape the intestinal microbiota, thus reducing the risks for the development of necrotizing enterocolitis.³³

Still talking about the diseases that can affect this public, the positive effects of HM on the lungs are also allies against bronchopulmonary dysplasia (BD). This is due to the antioxidant properties present in HM, which can contribute to a better prognosis of the disease, acting in oxidative stress prevention, one of the factors causing BD, and in the treatment of lung lesions.³⁴

However, it is necessary to clarify that it is not enough to simply keep the PTNB on a HM diet, as it is essential to achieve an adequate caloric balance in order to meet their energy needs. An inadequate supply of nutrients increases damage to the alveoli, while, if done properly, it allows for the development and maturation of the lungs as well as the repair of injuries already present.^{35,36}

Further, with regard to the reduction in the incidence of cytomegalovirus, despite the literature pointing out that its transmission is characterized as a common cause of maternal-fetal infection, it is consensual that, even if their mothers are seropositive for cytomegalovirus, full-term newborns must be breastfed.^{37,38}

This may be explained by the fact that the composition of HM varies depending on the stage of lactation and the mother's serological status. This biological property makes it possible to partially neutralize virus and bacterial particles; in this way, it reduces the risk of transmission of infectious viruses to PTNBs.³⁹

In this same paradigm, there is a risk of infection by *Bacillus cereus* when feeding the PTNB with stored HM, cited by an article (n=1; 14.28%). It was observed, in a French study, that this bacterium is the most frequent pathogen found in HM, stored in Human Milk Banks, being the main cause of discard⁴⁰. Therefore, bacteriological investigation is essential before distributing HM to extremely premature newborns.

In addition to acting against diseases, HM also acts in other essential areas that surround the life of PTNB, such as promoting complete enteral nutrition and increasing weight gain. HM has a high nutritional content, as it contains lipids, proteins, vitamins, enzymes and minerals,

making it the most suitable food for this audience, as it favors their physiological, biological and immunological development, enabling better results in intelligence and performance coefficients.²¹

The study has as a limitation the variety of methodological designs identified among the studies, such as case-control, cohort, cross-sectional studies and clinical trials, which does not allow for an in-depth comparison of their results.

In this scenario, it is essential that health services and professionals involved in practical and managerial activities develop policies and implement strategies capable of promoting the practice of breastfeeding in neonatal units aiming to prevent infections and, consequently, infant mortality.

CONCLUSION

It was evident that breastfeeding has a positive relationship with infection control in PTNB by promoting several benefits that reduce the risk of this condition appearing. The articles analyzed demonstrate that maternal HM is capable of reducing the incidence of necrotizing enterocolitis and cytomegalovirus, reducing the worsening of inflammatory states and late-onset sepsis, preventing diseases such as bronchopulmonary dysplasia as well as stimulating the physical development of PTNBs.

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AUTHORS' CONTRIBUTIONS

Raphaella Castro Jansen, Maria Rayssa do Nascimento Nogueira, Vitória Talya dos Santos Sousa, Vitoria Costa Oliveira contributed to article conception and design, data analysis and manuscript writing. **Anne Fayma Lopes Chaves** contributed to data analysis and interpretation.

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