DOI: 10.1590/1413-812320212610.30702020

Breastfeeding and drug use: what is the orientation found in drug package inserts of contraceptives and anti-infective agents?

Tatiane da Silva Dal Pizzol (https://orcid.org/0000-0002-7566-7745) [1]
Alessandra Nunes Pinto (https://orcid.org/0000-0002-8280-1244) [1]
Marysabel Pinto Telis Silveira (https://orcid.org/0000-0002-6453-8534) [2]
Maria Carolina de Campos Caetano (https://orcid.org/0000-0001-5809-7464) [3]
Camila Giugliani (https://orcid.org/0000-0002-2652-5214) [4]

Abstract *This article aims to evaluate the conformity between drug package inserts (DPIs) and evidence-based bibliographic sources regarding the presence of contraindications to the use of contraceptives and anti-infective agents during breastfeeding. Contraceptive and anti-infectives were selected, according to ATC, with the updated record in the ANVISA and present in the bibliographic sources Breastfeeding and Use of Medicines and Other Substances, Medications and Mother's Milk, LactMed®, Micromedex® and UpToDate®. Information was extracted from the DPI "Contraindications" and "Warnings and precautions" sections and compared with the information in the bibliographic sources. The contraindication of the drug during breastfeeding was evaluated. Contraindications were found in the DPIs of five (55.5%) of the nine contraceptives. The contraindication percentage ranged from 0 to 55.5% among the bibliographic sources, depending on the source. The percentage was 46.3% in the DPIs, ranging from 0 to 12.9% in the bibliographic sources for anti-infectives. There is an agreement between the DPIs and the bibliographic sources regarding contraceptives; regarding anti-infectives, the DPIs are more often contraindicated for use during breastfeeding.*

Key words *Breast Feeding, Drug package inserts, Drug utilization, Contraceptives, Anti-infective agents*

[1] Faculdade de Farmácia, Universidade Federal do Rio Grande do Sul (UFRGS). Av. Ipiranga 2752, sala 203, Santana. 90610-000 Porto Alegre RS Brasil. tatiane.silva@ufrgs.br
[2] Departamento de Fisiologia e Farmacologia, Instituto de Biologia, Universidade Federal de Pelotas. Pelotas RS Brasil.
[3] Universidade Federal de Ciências da Saúde de Porto Alegre. Porto Alegre RS Brasil.
[4] Faculdade de Medicina, UFRGS. Porto Alegre RS Brasil.

Introduction

Breastfeeding has well-established benefits for the baby's health, being a safe and complete nutritional source. The impact of breastfeeding on children's health (protection against respiratory infections, diarrhea and future development of overweight/obesity and diabetes)[1] and on women's health (protection against diabetes, breast and ovarian cancer and increase in the interval between births)[1,2] is well known and demonstrated by overwhelming evidence. The World Health Organization (WHO) recommends breastfeeding up to 2 years or more, with exclusive breastfeeding for the first six months of the child's life[3]. Despite this, in Brazil only 37% of children under six months of age are exclusively breastfed, and 32% continue to be breastfed between 20 and 23 months of age[4].

During breastfeeding, the use of medications is a widespread practice[5-7], and the most often prescribed therapeutic classes are contraceptives, anti-infectives, antidepressants and analgesics[8,9]. In general, medications can influence milk production[10], and can be excreted in breastmilk, resulting in the child's exposure to drugs, which may or may not harm the infant.

Most studies that assess the effects of medications on breastfeeding are carried out on animal models[11]. Even with the scarcity of studies in nursing mothers, understanding the pharmacokinetic principles and mechanisms of drug excretion in breast milk can help the physician to make appropriate decisions about the prescription of a particular drug, maintaining breastfeeding while the health problem is treated[8]. The child's exposure to the drug can be minimized if the mother takes it soon after the feedings or during the baby's sleep, in an attempt to prevent the child from breastfeeding during the maternal peak plasma concentration. In addition, the current knowledge indicates that few drugs are known to be harmful to the child when consumed by the breastfeeding mother[12].

However, the belief that medication use is incompatible with breastfeeding, generated by a perception of risk that is often mistaken and reinforced by information without evidence-based recommendations, increases the risk of early weaning or non-use of medication, even when there is a precise indication for it[5]. Few studies have investigated the agreement of information between drug package inserts (DPIs) from different laboratories[13], or between DPIs and scientific evidence[14-16].

This study aimed to assess the agreement between DPIs and literature sources based on scientific evidence regarding the presence of contraindications for the use of contraceptives and anti-infectives during breastfeeding.

Method

A descriptive study with a quantitative approach was carried out, complemented by qualitative aspects related to the bibliographic sources' characteristics. The drug classes selected for this analysis were anti-infectives and contraceptives, as they are commonly prescribed drugs during the breastfeeding period[8,9], and because they represent different drugs in terms of time of use, with acute and chronic use, respectively.

Contraceptive and anti-infective drugs from standard DPIs intended for health professionals were included. Drugs without an active registration at the Brazilian Health Regulatory Agency (ANVISA, *Agência Nacional de Vigilância Sanitária*) or absent from at least one of the bibliographic sources used in this analysis, described below, were excluded.

First, all drugs indexed as contraceptives and anti-infectives, at the Anatomical Therapeutic Chemical Classification (ATC/DDD Index 2018) of the WHO[17] were selected, regardless of the administration route. According to the ATC, drugs are classified into therapeutic, pharmacological and chemical groups and subgroups. All drugs included in the ATC classification were screened, starting from level 1, which corresponds to the main anatomical/pharmacological group, aiming to locate anti-infectives present not only in group J (anti-infectives for systemic use) and in group P (antiparasitic), but also in other groups, where some anti-infective drugs could be present, isolated or in combination with other drugs. Regarding the contraceptives, all drugs present in the therapeutic subgroup G03 (sex hormones and modulators of the genital system) belonging to group G (genitourinary system and sex hormones) were screened. Based on this initial list of drugs, it was verified which ones had an active registration at ANVISA, a regulatory and health control agency for the production and consumption of medications, including the establishment of standards for the text of DPIs and their approval. The databases available on the ANVISA website[18] were consulted to obtain information on the active registration of medications. After confirming the active registration at ANVISA,

the reference drugs were identified for each of the medications listed in ANVISA's "List of Reference Drugs", and the standard professional's DPIs were extracted from the ANVISA Electronic Drug Package Insert[19]. The identification of medications with an active registration at ANVISA and the extraction of information from the DPI took place between March and April 2018.

Information on the compatibility of the drug use during breastfeeding was searched for in the "Contraindication" or "Warnings and Precautions" sections of the DPIs, which correspond to the parts where this type of information must be provided in the DPIs, following Resolution No. 47 of ANVISA[20].

The information from the DPI of each drug was compared with the information present in the following bibliographical reference sources: Breastfeeding and Use of Medicines and Other Substances (2nd edition), a manual published by the Ministry of Health[21], Medications and Mother's Milk (16th edition)[12], Lactmed®[22], UpToDate®[23] and Micromedex®[24]. The bibliographic sources selected for this study were defined based on previous studies[14,25] and by consulting specialists, in addition to their availability in our country.

The manual Breastfeeding and the Use of Medicines and Other Substances[21] contains a review on drugs and other substances that can be excreted in breast milk and their possible effects on the infant and/or lactation, using as reference the publications of the American Academy of Pediatrics (AAP), the WHO, and the book 'Medications and Mothers' Milk' (2008 edition). It has a three-level classification system.

The book *Medicines and Mother's Milk*, by T.W. Hale[12], features monographs on a wide variety of medications and natural substances, including relevant pharmacological characteristics, primary research, as well as the AAP classification. It uses a five-point numerical rating system for each drug and is updated every two years.

UptoDate®[23] is an online resource, widely used in clinical practice by healthcare professionals in hospital and outpatient settings. It is considered one of the most up-to-date information sources, making an overview of the available evidence to support the professional's decision-making, which will also consider each clinical situation's uniqueness. It does not have a classification system but rather a descriptive summary of the drug use during breastfeeding and conduct recommendations.

Micromedex®[24] is an online resource, consisting of monographs containing indications approved by the United States Food and Drug Administration (FDA) agency, off-label drug uses and information on drug safety, among other information. It has its own classification on the safety of medication use in breastfeeding, divided into four categories, according to the available evidence and/or expert consensus. It features AAP rating.

LactMed®[22] is an online resource, created by an expert panel based on scientific literature, updated monthly. This source includes information on drug levels in breast milk, effects on the child, breastfeeding and on breast milk. It does not have a classification system but rather a descriptive summary of the drug use during breastfeeding.

The primary outcome evaluated was the presence of information contraindicating the drug during breastfeeding ("yes" or "no"), considering the specificities of each bibliographic source, whose risk classification systems are presented in Chart 1. The information was classified as "yes" when the information clearly contraindicated use during breastfeeding (or indicated the suspension of breastfeeding while using the drug), and "no", in other situations, whereas phrases such as "a decision must be made to discontinue breastfeeding or discontinue treatment", were classified as "yes". They were classified as "no" in other situations (compatible use or risk/benefit assessment). As previously mentioned, the Ministry of Health manual, the book *Medications and Mother's Milk* and the Micromedex®[12,21,24] database have their own classification systems. In turn, Lactmed® and UpToDate®[22,23] bring the incompatibility information in text form; in these sources, the presence of information contraindicating the use of the drug during breastfeeding was classified as "yes" when the use was clearly contraindicated and "no" in the other situations (compatible use or risk/benefit assessment). In Lactmed®[22], when the database recommended using an alternative drug, without clearly mentioning the possibility of concomitant use, the drug was classified as contraindicated. In UpToDate®[23], when it was mentioned that certain information came from the manufacturing laboratory, this was considered in the drug classification.

The classification of information as "yes" or "no" was independently performed by two reviewers (ANP and MCC), and disagreements were resolved by a third reviewer (TSP). The third reviewer, a pharmacist, has experience in information on drugs, having coordinated a Medication Information Center for several years. Only

Chart 1. Classification of drug use compatibility during breastfeeding in each of the surveyed bibliographic sources[a].

Source of information	Risk Rating[b]
Technical Manual on Breastfeeding and Use of Medicines and Other Substances, Brazil	1. Compatible with breastfeeding: Drugs that are potentially safe to use during lactation, as there are no reports of significant pharmacological effects for the infant
	2. Judicious use during breastfeeding: Medicines whose use during lactation depends on the risk/benefit assessment. When used, they require clinical and/or laboratory monitoring of the infant, and should be used for the shortest time and at the lowest possible dose. New drugs whose safety during breastfeeding has not yet been properly documented are in this category
	3. Contraindicated for use during breastfeeding: Medicines that require the interruption of breastfeeding, due to evidence or significant risk of important side effects in the infant
Medications and Mothers' Milk, United States	L1 Compatilble: This is a drug that has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote, or the product is not orally bioavailable in an infant
	L2 Probably Compatible: A drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant and/or the evidence of a demonstrated risk that is likely to follow use of this medication in a breastfeeding woman is remote
	L3 Probably Compatible: There are no controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal non-threatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant. (New medications that have absolutely no published data are automatically categorized in this category, regardless of how safe they may be)
	L4 Potentially Hazardous: There is positive evidence of risk to a breastfed infant or to breast milk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective)
	L5 Hazardous: The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant
Micromedex®, United States	1. Infant risk cannot be ruled out: Available evidence is inconclusive or is inadequate for determining fetal risk when used in pregnant women or women of childbearing potential. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding
	2. Infant risk has been demonstrated: Evidence and/or expert consensus has demonstrated harmful infant effects when used during breastfeeding. An alternative to this drug should be prescribed or patients should be advised to discontinue breastfeeding
	3. Infant risk is minimal: The weight of an adequate body of evidence and/or expert consensus suggests this drug poses minimal risk to the infant when used during breastfeeding

[a]The categories in which the drug was considered contraindicated during breastfeeding were highlighted in grey; [b]LactMed® and UpToDate® do not have a classification system.

Source: Elaborated by the authors.

anti-infectives and hormonal contraceptives containing standard package inserts and present in the five bibliographic sources were analyzed. The agreement between the classifications of the two reviewers was verified for each class of drugs. The total number of drugs that received the same classification by the two reviewers was calculated, divided by the total number of drugs belonging to that class, using the Kappa test. The agreement criterion by Landis and Koch[26] was used to inter-

pret the value found in the Kappa test, according to the following values: < 0.40, reasonable agreement; from 0.41 to 0.60, moderate agreement; from 0.61 to 0.80, substantial agreement; and from 0.81 to 1.00, excellent agreement.

Frequency measures were calculated using the Excel 2013 program, and the Kappa test was performed using the SPSS 18.0.0.0 statistical program for Windows (SPSS Inc., Chicago, IL, USA).

Results

In total, 54 anti-infectives and nine contraceptives, present in the five bibliographic sources, were evaluated. The following drugs were excluded due to lack of information about the drug in one or more bibliographic sources or lack of registration in Brazil: benzathine benzylpenicillin (J01CE08), cephalothin (J01DB03), oxytetracycline (J01AA06), teicoplanin (J01XA02), sulbactam (J01CG01), vancomycin (J01XA01), valaciclovir (J05AB11), secnidazole (P01AB07), meglumine antimoniate (P01CB01), artesunate and mefloquine (P01BF02), levamisole (P02CE01), lincomycin (J01FF02), thiabendazole (P02CA02), ertapenem (J01), meropenem (J01DH02), griseofulvin (D01BA01), silver sulfadiazine (D06BA01), chlormadinone acetate and ethinylestradiol (G03AA15), desogestrel (G03AC09), medroxyprogesterone acetate and estradiol cypionate (G03FA12 ethinylestradiol), gestodene, norethisterone enanthate and estradiol valerate (G03FA01), etonogestrel and ethinylestradiol (G03AC08), norethisterone acetate and ethinylestradiol (G03AA05) and nomegestrol acetate/estradiol (G03AA14).

The agreement between the two reviewers (ANP and MCC) when evaluating the drug package inserts was 77.8% for contraceptives (Kappa 0.564; p=0.10) and 85.2% for anti-infectives (Kappa 0.602; p<0.001). Disagreements were resolved by a third reviewer (TSP), taking into account the criteria for classification as "yes" or "no".

Graph 1 shows the frequency of contraindication for medication use in the package inserts and the five bibliographic sources. It was found that 55.5% of contraceptive inserts contraindicated them during breastfeeding. The same frequency was observed in three of the five sources evaluated for this therapeutic group. In contrast there was no contraindication, in one of the other two sources. Concerning anti-infectives, contraindication was identified in the inserts of 46.3% of the medications, while in the bibliographic sources the frequencies varied between 0% and 12.9%.

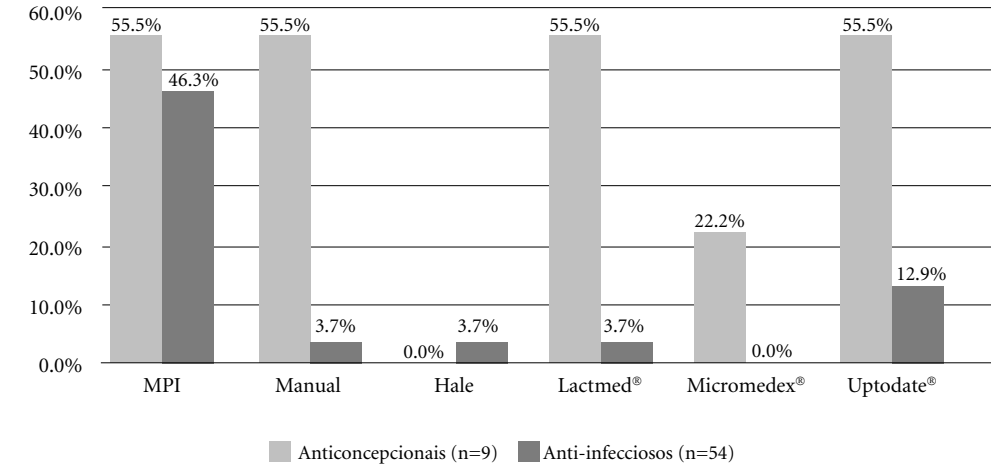
According to the DPIs and bibliographic sources, Tables 1 and 2 show the classifications for each evaluated drug. Regarding contraceptives (Table 1), a complete agreement was observed between the DPIs and the sources of information regarding the compatibility of using preparations containing isolated progestins during breastfeeding. For contraceptives that contain estrogen associated with progestin, there was an agreement between the package inserts and the manual of the Ministry of Health, Lactmed® UptoDate®. The source *Medications and Mothers' Milk* did not contraindicate the use of any of the analyzed contraceptives.

For the anti-infectives (Table 2), total agreement was observed regarding the non-contraindication between the DPIs and the sources, for the following anti-infectives: chloramphenicol, amoxicillin, piperacillin, oxacillin, all analyzed cephalosporins, meropenem, sulfamethoxazole and trimethoprim, erythromycin, clarithromycin, gentamicin, norfloxacin, nitrofurantoin, itraconazole, rifampicin, acyclovir, lamivudine, oseltamivir, chloroquine, mebendazole, praziquantel, ivermectin, and nystatin. Disagreements are observed in the contraindication, as the DPIs contraindicates a greater number of anti-infectives, except for linezolid and aztreonam, which do not have contraindications in the DPIs, but one of the sources contraindicates them. The anti-infective that showed the greatest contraindication agreement between the sources was ganciclovir, which was contraindicated in three of the five sources of information.

Discussion

This study aims to assist in the decision-making, both in clinical practice and in the regulation of medications, considering that the DPIs can be consulted by the health professional as a source of information on the compatibility between breastfeeding and the use of the prescribed medications.

For every two evaluated medications, considering both anti-infectives and contraceptives, one had a DPI contraindicating their use during breastfeeding. For anti-infectives, the agreement between the DPIs and sources was low (46.3% of the inserts contraindicated them, compared with 0% to 12.9%, depending on the source). For



Graph 1. Frequency of contraindication for the use of contraceptives and anti-infectives during breastfeeding in the DPIs and bibliographic sources[a].

[a]We evaluated 77 DPIs for anti-infectives, corresponding to 54 medications, and 17 DPIs for contraceptives, corresponding to 9 medications. Of two azithromycin DPIs, one included a contraindication. Of three tobramycin DPIs, one included a contraindication. In these cases, the drug was considered contraindicated.
Manual: Technical Manual on Breastfeeding and Use of Medicines and Other Substances, Ministry of Health (2010); Hale: Medications and Mothers' Milk, by Hale & Rowe (2014).

Source: Elaborated by the authors.

Table 1. Classification of contraceptives present in all sources (n=9) according to the contraindication for use during breastfeeding in the DPIs intended for professionals and in the bibliographic sources.

Drugs (number of DPIs evaluated)[a]	ATC	Hale	Manual[b]	Hale[c]	Lactmed®	Micromedex®	Uptodate®
Progestogens and estrogens, fixed combinations (G03AA)							
Levonorgestreland and Ethinylestradiol (4)	G03AA07	X	X		X		X
Esogestrel and Ethinylestradiol (4)	G03AA09	X	X		X	X	X
Drospirenone and Ethinylestradiol (2)	G03AA12	X	X		X		X
Norelgestromin and Ethinylestradiol (1)	G03AA13	X	X		X	X	X
Progestogens (G03AC)							
Norethisterone (1)	G03AC01						
Levonorgestrel (1)	G03AC03						
Medroxyprogesterone (2)	G03AC06						
Etonogestrel (1)	G03AC08						
Progestogens and estrogens, sequential preparations (G03AB)							
Dienogest and Estradiol (1)	G03AB08	X	X		X		X

[a]17 DPIs were evaluated, corresponding to 9 medications; [b] Technical Manual on Breastfeeding and Use of Medicines and Other Substances, Ministry of Health (2010); [c] Medications and Mothers' Milk, de Hale & Rowe (2014). X - Contraindicated drug.

Source: Elaborated by the authors.

Table 2. Classification of anti-infectives present in all sources (n=54) according to the contraindication for use during breastfeeding in the DPIs intended for professionals and in the bibliographic sources.

Drugs (number of DPIs evaluated)[a]	ATC	DPI	Manual[b]	Hale[c]	Lactmed®	Micromedex®	Uptodate®
Antibacterials for systemic use (J01)							
Doxycycline (1)	J01AA02	X					
Minocycline (1)	J01AA08	X					
Chloramphenicol (2)	J01BA01						
Ampicillin (1)	J01CA01	X					
Amoxicillin (2)	J01CA04						
Piperacillin (1)	J01CA12						
Amoxicillin and Clavulanate (1)	J01CR02						
Oxacillin (1)	J01CF04						
Cefalexin (3)	J01DB01						
Cefazolin (1)	J01DB04						
Cefuroxime (1)	J01DC02						
Ceftazidime (1)	J01DD02						
Ceftriaxone (1)	J01DD04						
Cefepime (1)	J01DE01						
Aztreonam (1)	J01DF01						X
Meropenem (1)	J01DH02						
Imipenem and Cilastatin (1)	J01DH51	X					
Sulfamethoxazole and Trimethoprim (2)	J01EE01						
Erythromycin (1)	J01FA01						
Clarithromycin (2)	J01FA09						
Azithromycin (2)[d]	J01FA10	X					
Clindamycin (3)	J01FF01	X					
Tobramicyn (3) [d]	J01GB01	X					
Gentamicin G (3)	J01GB03						
Amikacin (1)	J01GB06	X					
Ofloxacin (1)	J01MA01	X					
Ciprofloxacin (5)	J01MA02	X					
Norfloxacin (1)	J01MA06						
Levofloxacin (3)	J01MA12	X					
Moxifloxacin (2)	J01MA14	X					
Daptomycin (1)	J01XX09	X					
Linezolid (1)	J01XX08		X				
Metronidazole (2)	J01XD01	X					X
Tinidazole (1)	J01XD02	X					X

it continues

contraceptives, there was more significant agreement in the classification between the DPIs and the sources.

The identification of inconsistent information in the DPIs has been reported in previous studies, either between DPIs from different laboratories[13], or between DPIs and scientific evidence[14-16]. In an analysis of 23 DPIs for antidepressant medications and bibliographic sources, da Dal Pizzol et al.[14] found that in most DPIs (62.5%), the antidepressant was contraindicated in breastfeeding, whereas, among the bibliographical sources, the percentage ranged from 0% to 25%. Arguello et al.[27] assessed the com-

Table 2. Classification of anti-infectives present in all sources (n=54) according to the contraindication for use during breastfeeding in the DPIs intended for professionals and in the bibliographic sources.

Drugs (number of DPIs evaluated)[a]	ATC	DPI	Manual[b]	Hale[c]	Lactmed®	Micromedex®	Uptodate®
Nitrofurantoin (1)	J01XE01						
Tetracycline and Amphotericin B (1)	J01AA07	X					
Antimycotics for systemic use (J02)							
Amphotericin B (1)	J02AA01	X					X
Ketoconazole (3)	J02AB02	X					X
Fluconazole (1)	J02AC01	X					
Itraconazole (1)	J02AC02						
Antimycobacterials (J04)							
Rifampicin (1)	J04AB02						
Antivirals (J05)							
Aciclovir (1)	J05AB01						
Ganciclovir (1)	J05AB06	X	X		X		X
Saquinavir (1)	J05AE01	X		X			
Lamivudine (1)	J05AF05						
Nevirapine (1)	J05AG01	X		X			
Oseltamivir (1)	J05AH02						
Antiprotozoals (P01)							
Chloroquine (1)	P01BA01						
Antihelmintics (P02)							
Albendazole (1)	P02CA03	X					
Mebendazole (1)	P02CA01						
Praziquantel (1)	P02BA01						
Ivermectin (1)	P02CF01						
Others							
Amantadine (1)	N04BB01	X			X		
Nystatin (1)	D01AA01						

[a] 77 DPIs were evaluated, corresponding to 54 medications; [b] Technical Manual on Breastfeeding and Use of Medicines and Other Substances, Ministry of Health (2010); [c] Medications and Mothers' Milk, de Hale & Rowe (2014); [d] Of two azithromycin DPIs, one presented a contraindication. Of three tobramycin DPIs, one presented a contraindication. In these cases, the drug was counted as contraindicated. X - Contraindicated drug.

Source: Elaborated by the authors.

pleteness of information on drug use during pregnancy and lactation in European DPIs. Of 534 evaluated DPIs, only 16.5% contained information that the drug was excreted in breast milk, 0.6% that it was not excreted in milk and 61.4% stated that this information was not known, whereas 21.5 % of the DPIs did not provide any information regarding the excretion of the drug in milk. The authors warn that if the regulatory agency considers the information insufficient, more data should be requested from the laboratory during the authorization process[27]. Taken together, the cited studies reveal a lack of information on the subject and that this situation does not occur only in Brazil.

The more remarkable agreement observed in the group of contraceptives, compared to anti-infectives, was already expected, in part because the variety of the analyzed drugs was smaller (9 versus 54). Considering that contraception is a more frequent necessity than anti-infective drug use, at least among nursing mothers, it is to be expected that contraceptives have greater potential for use than anti-infective drugs. Furthermore, in most cases, the use of contraceptives is continuous and long-lasting, unlike anti-infectives, which

are predominantly used in acute conditions and for a limited period of time. These factors can contribute to a more significant accumulation of evidence about their effects on this population.

Progestins combined with estrogens were contraindicated in all DPIs and most bibliographic sources. The contraindication is due to the potential of estrogens to reduce milk production due to the inhibitory effect on prolactin[20], although this effect depends on the drug dose and on each individual. However, it is noteworthy that the source *Medications and Mother's Milk* does not contraindicate any contraceptive during breastfeeding. This source ranks all combinations of contraceptives containing ethinylestradiol as L3 (limited data - probably compatible), probably because the effects on decreased milk production are dose-dependent[12]. Thus, in most cases, the option has been to use contraceptives that contain progestin only. In general, the high agreement observed between the DPIs and the bibliographic sources suggests that the DPIs for contraceptives would be consistent in their recommendations regarding their use during breastfeeding, providing greater security and tranquility for the nursing mothers.

On the other hand, the agreement between the DPIs and the used sources was lower for anti-infectives. The high number of anti-infectives whose DPI contraindicated breastfeeding (approximately one in two DPIs) contrasts with the classification verified in the bibliographic sources. The sources consistently contraindicated a few anti-infectives. The only anti-infective with more sources classifying it as contraindicated (three of the five sources) was ganciclovir.

When the anti-infectives were evaluated by chemical subgroup (ATC classification level 4), containing two or more representatives per subgroup, the total disagreement that was observed between the DPI and the sources for tetracyclines and fluoroquinolones stands out. Although some sources point to the judicious use of tetracyclines during breastfeeding, none contraindicates them. *Medications and Mother's Milk*, for example, classifies doxycycline and minocycline as L3 – probably compatible[12]. The Ministry of Health manual points out the judicious use of doxycycline, warning of the possibility of stains on teeth, and compatible use of minocycline when used for a period of less than three weeks[21]. The contraindication in the DPIs may be associated with possible staining of tooth enamel or bone deposition of tetracyclines. However, Lactmed® emphasizes that there is no likelihood of harm after short-term use of minocycline and doxycycline, because levels in milk are low, and absorption by the child is inhibited by the calcium in breast milk. A short-term use of minocycline by breastfeeding mothers is acceptable[22].

A similar pattern is seen with fluoroquinolones. In the Lactmed® database, the use of ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin during breastfeeding is acceptable. The recommendation is to monitor the child for possible adverse effects on the gastrointestinal flora (such as diarrhea or candidiasis) and to breastfeed only 3 to 6 hours after drug administration[22].

Given the disagreement identified between the recommendations of the DPIs and the sources for these two subgroups of anti-infectives, we can suggest that, with any risk, even if minimal or controlled by a judicious use (with use for a limited time or control of the time between breastfeeding and drug administration), pharmaceutical companies choose to contraindicate the use to differentiate the levels of risk and conditions of drug use during breastfeeding. The inclusion of conservative information in DPIs seems to reflect a position of self-protection by the pharmaceutical industry against possible legal actions, as already pointed out in a previous study[14]. This protectionist position by the pharmaceutical industry can be illustrated by the frequent presence of generic phrases, such as "The decision between discontinuing the drug or breastfeeding must be made taking into account the potential benefits of the drug for the mother" and mentioning the lack of clinical studies. This position can be questioned when reference sources point to the safe use of the drug during this period. Limited information about the effect of the medication on breastfeeding can lead, on the one hand, to early weaning or, on the other hand, to the reduction or discontinuation of medication use by nursing mothers, both with consequences for the health of the mother and child[28]. More than a legal requirement for product registration, DPIs are an official source of information about medications, and this defensive position by the industry does not contribute to DPIs providing adequate information to professionals in the health field[27].

Ultimately, the DPIs are the main official documents that Brazilian health professionals have to use as a source of information because, in addition to the unavailability of an updated National Formulary, it does not include all medications marketed in the country, being limited to those included in the National List of Essential Medications (RENAME). Specialized books and

other non-Brazilian sources are not always accessible and include drugs prescribed and used in Brazil. Therefore, there is a lack of fast, accessible and reliable information for the professional and the DPI, which could exercise this role, does not do it adequately.

Among the anti-infectives, the high agreement between the DPIs and bibliographic sources for penicillins and cephalosporins is noteworthy. This finding is likely to reflect the more significant number of studies on these drugs, with more evidence on their safety. Much of the disagreement between DPIs and the sources may be a consequence of the limited available pieces of evidence, especially good quality ones, on drug use during breastfeeding. Most studies in humans are observational, and there are also a large number of case reports. Thus, in general, the level of evidence for the safety of drugs and other substances during pregnancy and breastfeeding is low or very low, contributing to the conservative position of pharmaceutical industries[29].

Some aspects of the bibliographic databases used in this analysis are noteworthy. The evidence used for risk classification and the classification system itself can differ significantly between sources. When there are doubts about the risk of breastfeeding, without sufficient evidence to contraindicate the concomitant use, the Ministry of Health manual and LactMed® encourage breastfeeding, supported by the literature. On the other hand, those sources that base their recommendations on the manufacturer's data, such as UptoDate®, contribute to a more conservative decision, similar to Brazilian DPIs[14]. In addition, some sources are updated more frequently than others, a fact that can lead to different classifications.

DPI legislation in Brazil was developed throughout the 20th century, especially from the 1980s onward, with the publication of ordinances and resolutions that gradually added mandatory information items and improved aspects related to the formatting and language of package inserts[30,31]. However, we observe that the information regarding the drug's compatibility during lactation, required by these standards, is quite limited. In Ordinance 110, of 1997, only the inclusion of the phrase "should not be used during pregnancy and lactation" was required, when applicable. The RDC Resolution 140, of 2003, established the description of warnings and recommendations about the acceptable use of the medication by risk groups, including infants. The current RDC 47 adds advice on monitoring and dose adjustment, when applicable. However, the resolution does not require specific information about the excretion of the drug in breast milk and its adverse effects on the baby. Results of clinical or preclinical studies, when they exist, or even information about the inexistence of these studies would contribute to the health professional's decision-making to prescribe or not the drug. However, Brazilian regulations do not establish this type of information either, which is required, for example, in the European Medicines Agency[32]. Despite this, we observe that many DPIs only inform about whether the drug is excreted in breast milk or not, without including additional information necessary for decision-making, such as, for example, if the amount excreted is clinically relevant, what are the possible damages to the infant, and what evidence is available.

One limitation of the study is that, as not all drugs listed in the WHO ATC are registered in Brazil, and some were not present in one or more bibliographic sources, it was not possible to evaluate a greater number of anti-infectious and contraceptive agents. As a hierarchy was not established between the bibliographic sources, given the characteristics of each one, we decided to exclude the drug that was absent from any of the sources without differentiating between them. However, as at least one drug of each class was registered in Brazil, it is believed that the results found would not have been very different, as the incompatibility of use, in most cases, was linked to the therapeutic class and not to the drug itself. Another limitation concerns the moderate agreement between reviewers in the classification of information present in the DPIs. The main reason for disagreements between the reviewers occurred regarding the phrase "it must be decided to discontinue breastfeeding or discontinue treatment" and variations thereof but containing the same central idea. One of the reviewers understood it as a contraindication, whereas the other did not. In the tie-breaker, it was considered a contraindication, as this information did not allow the possibility of concomitant use.

In conclusion, this analysis reveals that for every two medications, one had a DPI contraindicating its use during breastfeeding and that there is a low agreement between the information available in the DPIs of the evaluated anti-infectives and the consulted information sources. In the case of contraceptives, the agreement was more significant. Data on anti-infectives, in general, suggest greater caution related to the use of information about breastfeeding provided by the

DPIs. Before making any decision involving the prescription and advice regarding the use of these medications by nursing mothers, the prescribers should seek more reliable information in bibliographic sources based on up-to-date scientific evidence. Finally, a review of Resolution RDC 47 is recommended regarding the content and format of the information required for the "Contraindication" or "Warnings and Precautions" sections of the standard DPIs. The information should not be limited to the drug excretion in breast milk, but it should also indicate whether it has clinical significance and specify the effects that may be harmful to the infant or to breastfeeding and the need to carry out post-marketing studies that provide evidence about these effects.

Collaborations

TS Dal Pizzol: designed the study, analyzed and interpreted the results, wrote the manuscript, reviewed the literature and approved the final version of the manuscript. AN Pinto: collected the data, reviewed the literature, wrote the manuscript and approved the final version of the manuscript. MCC Caetano: collected the data, reviewed the literature and approved the final version of the manuscript. MPT Silveira: analyzed and interpreted the results, wrote the manuscript, reviewed the literature and approved the final version of the manuscript. C Giugliani: analyzed and interpreted the results, wrote the manuscript, reviewed the literature and approved the final version of the manuscript.

References

1. Victora CG, Bahl R, Barros AJD, França GVA, Horton S, Krasevec J, Murch S, Sankar MJ, Walker N, Rollins NC, Lancet Breastfeeding Series Group. Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* 2016; 387(10017):475-490.
2. Chowdhury R, Sinha B, Sankar MJ, Taneja S, Bhandari N, Rollins N, Bahl R, Martines J. Breastfeeding and maternal health outcomes: a systematic review and meta-analysis. *Acta Paediatr* 2015; 104(467):96-113.
3. World Health Organization (WHO). *Infant and young child feeding: model chapter for textbooks for medical students and allied health professionals*. Genebra: WHO; 2009.
4. Boccolini CS, Boccolini PMM, Monteiro FR, Venâncio SI, Giugliani ERJ. Breastfeeding indicators trends in Brazil for three decades. *Rev Saude Publica* 2017; 51:108.
5. Schirm E, Schwagermann MP, Tobi H, Jong-van den Berg LTW. Drug use during breastfeeding. A survey from the Netherlands. *Eur J Clin Nutr* 2004; 58(2):386-390.
6. Chaves RG, Lamounier JA, César CC. Self-medication in nursing mothers and its influence on the duration of breastfeeding. *J Pediatr (Rio J)* 2009; 85(2):129-134.
7. Lutz BH, Bassani DG, Miranda VIA, Silveira MPT, Mengue SS, Dal Pizzol TS, Silveira MF, Bertoldi AD. Use of Medications by Breastfeeding Women in the 2015 Pelotas (Brazil) Birth Cohort Study. *Int J Environ Res Public Health* 2020; 17(2):568.

8. Rowe H, Baker T, Hale TW. Maternal Medication, Drug Use, and Breastfeeding. *Child Adolesc Psychiatr Clin N Am* 2015; 24(1):1-20.
9. Matheson I, Kristensen K, Lunde PKM. Drug utilization in breast-feeding women. A survey in Oslo. *Eur J Clin Pharmacol* 1990; 38(5):453-459.
10. Paricio Talayero JM, Díaz-Gómez NM, Rivera LL, Palomares MS, Cholbi LE. Medicamentos y lactancia materna. *An Pediatría Contin* 2014; 12(5):239-243.
11. Sachs HC, Committee on Drugs. The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update on Selected Topics. *Pediatrics* 2013; 132(3):e796-e809.
12. Hale TW, Rowe HE. *Medications and Mother's Milk*. 16ª ed. Texas: Hale Publishing; 2014.
13. Bjerrum L, Foged A. Patient information leaflets-helpful guidance or a source of confusion? *Pharmacoepidemiol Drug Saf* 2003; 12(1):55-59.
14. Dal Pizzol TS, Moraes CG, Diello MV, Campos PM, Pletsch JT, Giugliani C. Uso de medicamentos antidepressivos na amamentação: avaliação da conformidade das bulas com fontes bibliográficas baseadas em evidências científicas. *Cad Saude Publica* 2019; 35(2):e00041018.
15. Colaceci S, Giusti A, Chapin EM, Notarangelo M, De Angelis A, Vellone E, Alvaro R. The Difficulties in Antihypertensive Drug Prescription During Lactation: Is the Information Consistent? *Breastfeed Med* 2015; 10(10):468-473.
16. Chaves RG, Lamounier JA, César CC, Corradi MAL, Mello RP, Gontijo CM, Drumond JM. Amamentação e uso de antiinflamatórios não esteróides pela nutriz: informações científicas versus conteúdo em bulas de medicamentos comercializados no Brasil. *Rev Bras Saude Materno Infant* 2006; 6(3):269-276.
17. WHO Collaborating Centre. *WHOCC - ATC/DDD Index* [Internet]. [acessado 2018 dez 6]. Disponível em: https://www.whocc.no/atc_ddd_index/.
18. Agência Nacional de Vigilância Sanitária (ANVISA). *Consulta a Medicamentos e Hemoderivados* [Internet]. [acessado 2020 ago 12]. Disponível em: http://portal.anvisa.gov.br/medicamentos/consultas.
19. Agência Nacional de Vigilância Sanitária (ANVISA). *Bulário Eletrônico* [Internet]. [acessado 2016 out 11]. Disponível em: http://portal.anvisa.gov.br/bulario-eletronico1.
20. Agência Nacional de Vigilância Sanitária (ANVISA). Resolução - RDC nº 47, de 8 de setembro de 2009. Estabelece regras para elaboração, harmonização, atualização, publicação e disponibilização de bulas de medicamentos para pacientes e para profissionais de saúde. *Diário Oficial da União*; 2009.
21. Brasil. Ministério da Saúde (MS). *Amamentação e uso de medicamentos e outras substâncias*. 2ª ed. Brasília: MS; 2010.
22. U.S. National Library of Medicine. *Drugs and Lactation Database (LactMed)* [Internet]. [acessado 2018 nov 13]. Disponível em: https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm.
23. Wolters Kluwer. *Search - UpToDate* [Internet]. [acessado 2018 nov 12]. Disponível em: https://www.uptodate.com/contents/search.
24. IBM Corporation. *Drug Result Page - MICROMEDEX* [Internet]. [acessado 2018 nov 12]. Disponível em: https://www.micromedexsolutions.com/micromedex2/librarian/PFDefaultActionId/evidencexpert.DoIntegratedSearch#.
25. Akus M, Bartick M. Lactation Safety Recommendations and Reliability Compared in 10 Medication Resources. *Ann Pharmacother* 2007; 41(9):1352-1360.
26. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33(1):159-174.
27. Arguello B, Salgado TM, Fernandez-Llimos F. Assessing the information in the Summaries of Product Characteristics for the use of medicines in pregnancy and lactation. *Br J Clin Pharmacol* 2015; 79(3):537-544.
28. Davanzo R, Copertino M, De Cunto A, Minen F, Amaddeo A. Antidepressant Drugs and Breastfeeding: A Review of the Literature. *Breastfeed Med* 2011; 6(2):89-98.
29. Schüler-Faccini L, Sanseverino MTV, Giugliani C. Medicamentos e Outras Exposições na Gestação e na Amamentação. In: *Medicina Ambulatorial: Condutas de Atenção Primária Baseadas em Evidências*. 4ª ed. Porto Alegre: Artmed; 2013.
30. Caldeira TR, Neves ERZ, Perini E. Historical evolution of package inserts in Brazil. *Cad Saude Publica* 2008; 24(4):737-743.
31. Cruz F, Caldeira T, Rediguieri C. Bulas e Rótulos. In: *A regulação de medicamentos no Brasil*. Porto Alegre: Artmed; 2013.
32. European Medicines Agency (EMEA). *Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling* [Internet]. EMEA; 2008 [acessado 2020 ago 12]. Disponível em: https://www.ema.europa.eu/en/risk-assessment-medicinal-products-human-reproduction-lactation-data-labelling#current-effective-version-section.

Article submitted 09/10/2019
Approved 25/08/2020
Final version submitted 27/08/2020

Chief editors: Romeu Gomes, Antônio Augusto Moura da Silva