A REVIEW ON MAMMARY GLAND: AS A NON RENAL DRUG EXCRETION ROUTE

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ABSTRACT:
Milk is a mother's diet for her infant, comprising several physiologically active chemicals that play a vital role in newborn and adult nutrition. Nursing is the best type of infant nutrition for the first few months of a newborn's life, and the majority of healthy women start breastfeeding soon after their baby is born. Women on medicine, on the other hand, may resort to formula feeding or refrain from taking their medication for fear of exposing their infant to the medication through breast milk. Although the majority of drugs are thought to be compatible with breastfeeding, there have been reports of substantial baby toxicity, implying that a case-by-case risk assessment should be performed before the mother begins breastfeeding or drug therapy. The introduction of medications used in therapy, as well as environmental contaminants, into milk poses a risk to consumer health. The ability of medicines to transfer into milk is defined by the milk/plasma ratio. The M/P ratios of the medications are influenced by the content of the milk as well as the drug's physicochemical qualities. The drug concentration in milk is determined by drug variables (protein binding, ionisation, molecular weight, lipophilicity, drug-drug and drug-nutrient interactions) and organism (race, species, lactation period, parity, disease and nutrition). However, as our understanding of drug transfer pathways grows, it is becoming clearly obvious that carrier-mediated processes play a role in the excretion of a variety of pharmaceuticals into milk.

Keywords: Mammary gland, Milk, Breastfeeding, infant nutrition, Prolactin,

1. INTRODUCTION:

Mammary gland is an organ in female mammals that produces milk to feed young offspring. Mammals get their name from the word "mamary". The mammary gland has evolved from epidermal apocrine glands, the skin glands as an accessory reproductive organ to support postnatal survival of offspring by producing milk as a source of nutrition. The mammary gland develops as a rudimentary structure during embryogenesis and matures into an elementary branched ductal tree that is lodged in one end of a bigger mammary fat pad at birth. The basic ductal system undergoes substantial morphogenetic change with ductal elongation and branching with the initiation of ovarian function at puberty. During pregnancy, alveolar differentiation and tertiary branching are completed, and mature milk-producing glands finally develop during lactation. Mammary gland development is hormone independent in the early stages, but hormonal dependent throughout puberty and pregnancy [1,2,3,4].

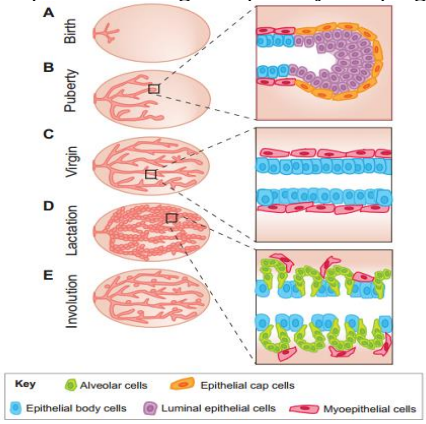

Fig. 1- The mammary gland development from the stage of birth to involution [1]

Anatomy and physiology: The mammary gland's development is unique in that the last stages occur postnatally during puberty under the influence of hormonal stimuli. Furthermore, the mammary gland can go through numerous rounds of enlargement and proliferation during a female's life. As a result, the mammary gland is a great model for understanding the'stem/progenitor' cells that allow for this repeated expansion and regeneration. The mammary glands are located in the breast of humans [5,6]. The alveoli, which are lined with milk secreting cuboidal cells and surrounded by myoepithelial cells, are the most basic component of a mammary gland. These alveoli combine together to produce lobules. Each lobule has a laciferous duct that empties into a nipple aperture. The myoepithelial cells contract under the stimulation of oxytocin, excreting the milk secreted by alveolar units into the lobule lumen toward the nipple [7,8].Initiation of lactation is mediated by hormone release. Progesterone prolactin, oxytocin & cortisol. Each has an impact on milk production and lactation.

• Progesterone - Progesterone is a hormone produced by the ovaries, adrenal glands, and placenta. By suppressing prolactin, high levels of rogesterone preserve pregnancy and reduce milk production. Progesterone levels fall after the baby is born and the placenta is delivered [9].
• Prolactin- Prolactin is a hormone generated by the anterior pituitary gland. Progesterone inhibits prolactin throughout pregnancy. Suckling stimulates prolactin production. Milk production is caused by prolactin secretion [10].

• Oxytocin - Oxytocin is a hormone generated by the posterior pituitary gland. Suckling and nipple stimulation stimulate oxytocin secretion. Oxytocin causes milk ejection or let down.

• Cortisol- a stress hormone produced in the adrenal glands and released. High cortisol levels can delay lactogenesis, whereas low levels and reduced stress increase nursing quality. [11].

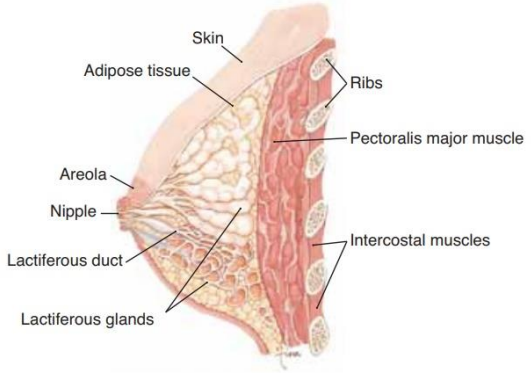

Figure Mammary gland shown in a mid-sagittal section.

Fig. 2- Structure of Mammary gland

2. MECHANISM OF DRUGS ENTRY INTO HUMAN MILK:

Drugs enter milk predominantly by diffusion in the early postpartum period. They travel from the maternal plasma compartment to the alveolar cell lining of the milk buds via capillary cells. To enter milk, they must normally travel through both walls of the alveolar cells. Large gaps between alveolar cells appear during the first 4 to 10 days of life [12,13]. Most medicines, many immunoglobulins, maternal lymphocytes, and other maternal proteins can enter the milk through these gaps. Soon after the first week, the alveolar cells enlarge, closing intracellular spaces and restricting access to the milk. Although there are exceptions, it is generally agreed that drugs permeate milk more during the newborn period than in mature milk. A frequently asked concern is why a medicine is safe for a pregnant woman but may not be safe for breastfeeding mothers [14]. Remember that in pregnant women, the mother's system is responsible for metabolising and removing medications, whereas in breastfed newborns, the infant must metabolise and eliminate the drug himself. This may be challenging for some infants, thus a comprehensive review is required to determine whether it is safe for a breast-feeding mother to take a specific drug [15].

3. PHARMACOKINETIC FACTORS:

Several relevant factors should be considered when determining whether a drug is compatible for breast feeding mother [16].
The amount of drug excreted into milk depends on a number of kinetic factors:

- Volume of distribution
- Percent of maternal protein binding Molecular weight of drug
- pH
- Log P
- T max
- Active transport
- Milk to plasma ratio
- T-half

3.1 Volume of distribution-Vd describes the extent to which the medicine is spread throughout the body. Drugs with a high Vd concentration may penetrate different compartments of the body, resulting in a decreased concentration in the blood. These medications may take longer to remove from the body than lower Vd pharmaceuticals. However, medicines with varying elimination half lives in plasma and peripheral compartments may cause lower milk levels. Drugs with Vd between 1 and 20 L/kg are generally safe to use while nursing [17,18].

3.2 Percent of maternal protein binding-Protein binding demonstrates how well a medicine binds to plasma albumin and other proteins. As a result, medications with high protein binding diminish the infant's exposure to the medication. Drugs with a protein binding rate greater than 90% are normally safe to use while nursing. Drugs can be present in the bloodstream in either free or bound form. Free medications can flow through tissue and biological fluids like milk, whereas bound drugs cannot. Milk contains specialised proteins (casein, lactalbumin, and lactoglobulins) that bind drug molecules and are produced by breast epithelial cells. Drugs that bind to milk proteins at high ratios are excreted quickly, and their distribution to tissues is minimal [19,20].

3.3 Molecular weight of drug-Medicine molecular weight is crucial in determining medication penetration into human milk. Medication having a low molecular weight can easily enter into the milk via the mammary epithelium's tiny pores. Drugs with a greater molecular weight Weight must be actively transported or dissolved in the lipid membranes of cells, making medications with a higher molecular weight less likely to transfer into breast milk. Drugs having a molecular weight greater than 800 Da are more easily excluded from the milk compartment than those with a molecular weight less than 800 Da, making them more suitable for breast feeding. Smaller molecular weight and molecule size drugs pass through milk more easily. For example Ethanol(molecular weight 120) passes rapidly from theplasma to milk and reaches a high concentration inthe milk. It is not possible for drugs of ≥ 600molecular weight to transition at high concentrationsinto the milk. Heparin (30.000) and insulin (6.000)molecules are not found in milk because theirmolecular sizes are high [21,22].

3.4 pH-Because breast milk is more acidic than plasma, medicines with high pH concentrations may be more concentrated in breast milk than plasma. Compounds with a low pH, on the other hand, may have a lower concentration in breast milk than in plasma. Although aspirin has a low pH, it can cause Reye's syndrome in children and is therefore not suggested while breastfeeding. The majority of non-ionic medicines are lipid-soluble and easily traverse the membrane. While the pH of plasma is constant, the pH of milk varies. Mastitis causes the pH of the milk to shift to alkaline, with the exception of gangrenous mastitis. The drug's ionisation ratio in milk is also affected by the severity of the infection. The pKa value and plasma concentrations of the drug, as well as the pH of the plasma and milk, determine the excretion of weak acid and basic medicines with milk. Weak base medications accumulate in milk more than weak acid drugs because the pH of milk is lower than the pH of plasma [23,24].

3.5 Log P-Water-soluble medication compounds are less likely to concentrate in breast milk. This happens because water-soluble compounds resist fatty substances, and breast milk contains more fat than plasma [23].

3.6 t-max-The concentration of a medication in breast milk and plasma usually approaches a proportionate equilibrium. When there is a larger drug concentration in plasma, the drug concentration in breast milk is usually higher as well. The mother can reduce the likelihood of exposing her newborn to the drug by not feeding the infant when the drug reaches its highest concentration in the plasma [25].

3.7 t-half- Pharmaceuticals with shorter half lives and consequently shorter peak intervals can be used to reduce infant exposure to drugs in breast milk. This allows the mother to time her feedings to coincide with trough levels. Approximately 97% of the medication is removed from breast milk after five half lives. If a drug's elimination half life is 12 to 24 hours or more, it has the potential to accumulate in breast milk over time [22,25].

3.8 Milk to plasma ratio- the milk to plasma ratio shows the proportion in the milk versus the plasma. The M/P of a drug and active metabolites is calculated by dividing the drug levels in the milk by the drug levels in the plasma. If M/P is less than 1, it is usually safe to breastfeed [23, 24]. The M/P rate is influenced by the composition of the milk as well as the physicochemical qualities of the medication. The M/P ratio can be calculated using the octanol/water partition rate, drug binding to plasma proteins, and drug pKa. Drugs that have a high M/P ratio are actively secreted into the milk. Drug concentration in milk is directly affected by maternal plasma drug concentration. However, the drug concentration in the blood is not simply controlled by the maternal dose; this ratio can also be influenced by maternal drug metabolism. In mammals, drug metabolism is genetically determined and varies. [19].

3.9 Active transport-Although most drugs are passively dispersed into breast milk, many medications do have active transport via carriers. Nitrofurantoin, cimetidine, ranitidine, iodides, and acyclovir are examples of medications that are actively transported [6, 15, 25].

4. DRUGS ARE CLASSIFIED FOR BREASTFEEDING

The following classifications are used in the list

4.1 Compatible with breastfeeding- Drugs are classified as compatible with breastfeeding if there are no known or theoretical contraindications for their use, and it is considered safe for the mother to take the drug and continue to breastfeed [26,27].

4.2 Monitor infant for side-effects- Drugs are classed in this fashion if they could theoretically induce adverse effects in the child but have not been documented to do so or have only caused minimal negative effects on rare occasions. Inform the mother of any potential adverse effects, reassuring her that they are unusual, and inviting her to return if they are necessary or if she is concerned. If adverse effects arise, discontinue the drug and, if required, find an alternative. If the mother is unable to discontinue the medication, she may be forced to discontinue breastfeeding and feed her baby artificially until her treatment is done. Help her express her breast milk to maintain a supply so that she can nurse again once she discontinues the medicine [26,27].

4.3 Induce side effects-Drugs are categorised in this manner if they have been reported to induce side effects in infants, particularly if the side effects are potentially significant. Use these drugs only when they are absolutely necessary for the mother's treatment and there are no safer alternatives. Allow the mother to continue breastfeeding, but give her specific instructions about observing the infant and setting up regular check-ups. If side effects arise, discontinue the medication. If it is not possible to

discontinue the medication, discontinue breastfeeding and feed the infant artificially until the treatment is completed. Assist her in expressing her breastmilk in order to maintain a sufficient supply so that she can resume breastfeeding once the medicine is discontinued [26,27].

4.4 May inhibit lactation- Drugs listed in this category may diminish breast milk production and should be avoided if feasible. If a mother needs to take one of these drugs for a short time, she does not need to give her infant artificial milk. She can compensate for the potential reduction in milk production by urging her infant to suckle more frequently [28-30].

4.5 Avoid- Drugs are classed in this manner if they have the potential to cause harmful adverse effects in the foetus. They should not be administered to a breastfeeding mother. If they are required for the mother's therapy, she should discontinue breastfeeding until the treatment is done. If her therapy is prolonged, she may be forced to discontinue breastfeeding. Apart from anticancer medications and radioactive chemicals, this area contains extremely few drugs [26,28].

4.6 Some Additional Considerations- Certain medications' safety also relies on the infant's age. Premature newborns and infants under one month old have a different potential for medication absorption and excretion than older infants. As a result, greater caution is required for these infants in general. Specific information regarding age is known for some medicines, and this is noted in the list. You may need to provide a medicine to a breastfeeding mother that is not on this list. Unless the drug is clearly contraindicated (for example, cytotoxic drugs), advise the woman to continue breastfeeding and ask her to return if she observes anything concerning about her infant [27,29,30].

Table 1- Breastfeeding and Mother's Medication [25-30]

S.No.	Drug category		Action	Example
1.	Anaesthetics		If a surgery necessitates anaesthetic, assist the mother in expressing her breastmilk ahead of time and storing it in the refrigerator so that her baby can be fed her expressed breastmilk by cup while she is receiving the procedure and recovering from the anaesthetic.	Ether, halothane, ketamine, bupivacaine
2.	Non-opioids analgesics and antipyretics and NSAID		Ibuprofen and paracetamol have the most research on their safety while nursing. Acetylsalicylic acid (ASA) In little amounts, it is safe to breastfeed. If at all feasible, avoid long-term therapy. Keep an eye on the baby for any negative effects (haemolysis, prolonged bleeding time and metabolic acidosis).	Ibuprofen and paracetamol
3.	Opioid analgesics		Most opioids are excreted in modest levels in breastmilk after a single intake. Accumulation in the baby may happen from repeated dosages. Avoid repeated dosages, especially if the newborn is premature or under the age of four weeks. If the infant has experienced an episode of apnea, bradycardia, or cyanosis, avoid medications in this category. If administered during delivery, the newborn may be sleepy at birth, which may hinder with nursing initiation.	
4.	Antineoplastic And Immunosuppressive Drugs		Breastfeeding is not recommended if a mother is taking a medicine in this group.	
5.	Cardiovascular Drugs	Antianginal drugs	If at all possible, avoid, particularly if the infant is premature or less than one month old. Keep an eye on the baby for any negative effects (bradycardia, hypotension and cyanosis)	Atenolol
		Antiarrhythmic drugs		Atenolol, Digoxin, lidocaine, lerapamil
		Antihypertensive drugs		Captopril (hydralazine
6.	Diuretics		Large dosages of short-acting thiazide diuretics, as well as standard doses of loop diuretics or long-acting thiazide diuretics, can suppress lactation and should be avoided if at all possible.	Spironolactone, mannitol

5. CONCLUSION:

The introduction of carcinogenic medications and substances into milk, such as environmental contaminants and mycotoxins (aflatoxins), causes significant health concerns and economic losses. The residue problem in animal meals is a global issue that can only be solved incrementally. In recent years, researchers have shown that not only passive diffusion, but also active transport and certain transmembrane proteins play a role in drug trafficking into milk. The pharmacokinetics of medicines change significantly during pregnancy and lactation. Diseases like as mastitis, in particular, can be blamed for changes in medication content in milk.It may be useful to explore the impact of pregnancy and lactation on drug transition to milk in all species, as well as whether other disorders influencing milk yield other than mastitis may affect drug behaviour in milk. Milk composition, which varies by species and breed, may also influence drug behaviour in milk. There is a BCRP-mediated interaction that can cause changes in the quantities of xenobiotics, biological molecules, and nutrients in milk. Combining BCRP substrate medicines used in the treatment of mastitis with a similar transmembrane protein generating chemical can boost clinical efficacy.

6. REFERENCE

1. Inman, J. L., Robertson, C., Mott, J. D., & Bissell, M. J. (2015). Mammary gland development: Cell fate specification, stem cells and the microenvironment. *Development (Cambridge)*, *142*(6), 1028–1042. https://doi.org/10.1242/dev.087643
2. Biswas, S. K., Banerjee, S., Baker, G. W., Kuo, C. Y., & Chowdhury, I. (2022). The Mammary Gland: Basic Structure and Molecular Signaling during Development. *International Journal of Molecular Sciences*, *23*(7). https://doi.org/10.3390/ijms23073883
3. Wilson JT, Brown RD, Cherek DR, Dailey JW, Hilman B, Jobe PC, Manno BR, Manno JE, Redetzki HM, Stewart JJ. Drug excretion in human breast milk: principles, pharmacokinetics and projected consequences. Clin Pharmacokinet. 1980 Jan-Feb;5(1):1-66. doi: 10.2165/00003088-198005010-00001. PMID: 6988135.
4. Ito, S., & Lee, A. (2003). Drug excretion into breast milk - Overview. *Advanced Drug Delivery Reviews*, *55*(5), 617–627. https://doi.org/10.1016/S0169-409X(03)00034-6
5. Gerk, P. M., Hanson, L., Neville, M. C., &Mcnamara, P. J. (2002). Sodium Dependence of Nitrofurantoin Active Transport across Mammary Epithelia and Effects of Dipyridamole, Nucleosides, and Nucleobases. *Pharmaceutical Research*, *19*(3), 299–305.
6. Hens, J. R., &Wysolmerski, J. J. (2005). Molecular mechanisms involved in the formation of the embryonic mammary gland. *Breast Cancer Research*, *7*(5), 220–224. https://doi.org/10.1186/bcr1306
7. Hovey RC, Goldhar AS, Baffi J, Vonderhaar BK. Transcriptional regulation of vascular endothelial growth factor expression in epithelial and stromal cells during mouse mammary gland development. Mol Endocrinol. 2001 May;15(5):819-31. doi: 10.1210/mend.15.5.0635. PMID: 11328861.
8. Kordon EC, Smith GH. An entire functional mammary gland may comprise the progeny from a single cell. Development. 1998 May;125(10):1921-30. doi:10.1242/dev.125.10.1921. PMID: 9550724.
9. Boulanger, C. A., Bruno, R. D., Rosu-Myles, M., & Smith, G. H. (2012). The Mouse mammary microenvironment redirects mesoderm-derived bone marrow cells to a mammary epithelial progenitor cell fate. *Stem Cells and Development*, *21*(6), 948–954. https://doi.org/10.1089/scd.2011.0148
10. Gianni, M. L., Bezze, E. N., Sannino, P., Baro, M., Roggero, P., Muscolo, S., Plevani, L., &Mosca, F. (2018). Maternal views on facilitators of and barriers to breastfeeding preterm infants. *BMC Pediatrics*, *18*(1). https://doi.org/10.1186/s12887-018-1260-2
11. Julie J. Kelsey, . (2016). Drug Principles in Lactation. In *PSAP* (Vol. 3, pp. 7–32).
12. Schadewinkel-Scherkl AM, Rasmussen F, Merck CC, Nielsen P, Frey HH. Active transport of benzylpenicillin across the blood-milk barrier. PharmacolToxicol. 1993 Jul;73(1):14-9. doi: 10.1111/j.1600-0773.1993.tb01950.x. PMID: 8234185.
13. Ito S, Alcorn J. Xenobiotic transporter expression and function in the human mammary gland. Adv Drug Deliv Rev. 2003 Apr 29;55(5):653-65. doi: 10.1016/s0169-409x(03)00031-0. PMID: 12706548.
14. Pérez M, Real R, Mendoza G, Merino G, Prieto JG, Alvarez AI. Milk secretion of nitrofurantoin, as a specific BCRP/ABCG2 substrate, in assaf sheep: modulation by isoflavones. J Vet PharmacolTher. 2009 Oct;32(5):498-502. doi: 10.1111/j.1365-2885.2008.01050.x. PMID: 19754918.
15. Ozdemir, Z., &Traş, B. (2018). Behaviours of drugs in the milk - A review. *Ataturk UniversitesiVeterinerBilimleriDergisi*, *13*(3), 364–372.https://doi.org/10.17094/ataunivbd.319443
16. Kumar S, Srivastava AK, Dumka VK, Kumar N, Raina RK. Plasma pharmacokinetics and milk levels of ceftriaxone following single intravenous administration in healthy and endometritic cows. Vet Res Commun. 2010 Aug;34(6):503-10. doi: 10.1007/s11259-010-9421-2. Epub 2010 Jun 24. PMID: 20571922.
17. Atkinson HC, Begg EJ, Darlow BA. Drugs in human milk. Clinical pharmacokinetic considerations. Clin Pharmacokinet. 1988 Apr;14(4):217-40. doi: 10.2165/00003088-198814040-00003. PMID: 3292101.
18. Abduljalil, K., Pansari, A., Ning, J., &Jamei, M. (2021). Prediction of drugconcentrations in milk during breastfeeding, integrating predictive algorithms within a physiologically-based pharmacokinetic model. *CPT: Pharmacometrics and Systems Pharmacology*, *10*(8), 878–889. https://doi.org/10.1002/psp4.12662
19. Jonker JW, Merino G, Musters S, van Herwaarden AE, Bolscher E, Wagenaar E, Mesman E, Dale TC, Schinkel AH. The breast cancer resistance protein BCRP (ABCG2) concentrates drugs and carcinogenic xenotoxins into milk. Nat Med. 2005 Feb;11(2):127-9. doi: 10.1038/nm1186. Epub 2005 Jan 30. PMID: 15685169.
20. Gehring R., Smith G., 2006. An overview of factorsaffecting the disposition of intramammarypreparations used to treat bovine mastitis. J VetPharmacolTher, 29, 237-241.

21. Agatonovic-Kustrin S, Ling LH, Tham SY, Alany RG. Molecular descriptors that influence the amount of drugs transfer into human breast milk. J Pharm Biomed Anal. 2002 Jun 20;29(1-2):103-19. doi: 10.1016/s0731-7085(02)00037-7. PMID: 12062670.
22. GarcíA-Lino, A. M., Álvarez-Fernández, I., Blanco-Paniagua, E., Merino, G., & Álvarez, A. I. (2019). Transporters in the Mammary gland—contribution to presence of nutrients and drugs into milk. *Nutrients*, *11*(10). https://doi.org/10.3390/nu11102372
23. Shennan, D. B., & Peaker, M. (2000). Transport of Milk Constituents by the Mammary Gland. *PHYSIOLOGICAL REVIEW*, *80*(3), 925–951. www.physrev.physiology.org
24. Otero J., Garcia-Mateos D., de la Fuente A., PrietoJ., Alvarez A., Merino G., 2016. Effect of bovineABCG2 Y581S polymorphism on concentrations inmilk of enrofloxacin and its active metaboliteciprofloxacin. J Dairy Sci, 99, 5731-5738.
25. Abo El Sooud K. Influence of albendazole on the disposition kinetics and milk antimicrobial equivalent activity of enrofloxacin in lactating goats. Pharmacol Res. 2003 Oct;48(4):389-95. doi: 10.1016/s1043-6618(03)00179-8. PMID: 12902210.
26. *BREASTFEEDING AND MATERNAL MEDICATION Recommendations for Drugs in the Eleventh WHO Model List of Essential Drugs*. (2002).
27. Hotham Neil, & Hotham Elizabeth. (2015). Drugs in breastfeeding. *Australian Prescriber*, *38*(5), 156–159.
28. Walters Burkey, B., & Holmes, A. P. (2013). Continuing Education Evaluating Medication Use in Pregnancy and Lactation: What Every Pharmacist Should Know. *J PediatrPharmacolTher*, *18*. www.jppt.org
29. Spencer, J. P. (2001). Medications in the Breast-Feeding Mother. *Am Fam Physician*, *64*(1), 119–145. www.aafp.org/afpAMERICANFAMILYPHYSICIAN119
30. Gomes, N. T. N., Haslett, M. I. C., Alves, A. J. S. E., Percio, J., Duarte, M. M. S., Malta, J. M. A. S., Carvalho, F. C. de, Almeida, W. A. F. de, Gava, C., Souza, L. R. de O., Fantinato, F. F. S. T., & Santos, E. D. dos. (2021). Breastfeeding and risk classification of medications used during hospitalizationfor delivery: 2015 Pelotas Birth Cohort. *Brazilian Journal of Epidemiology*, *24*, e200026. https://doi.org/10.1590/1980-549720200026