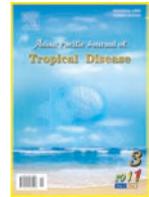




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Association between duration of breastfeeding and drug therapy

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ABSTRACT

Objective: To evaluate the existence of an association between the use of medication by nursing women and duration of breastfeeding in Itaúna, MG, Brazil. **Methods:** Longitudinal cohort study was carried out with 12-month follow-up, including 246 women admitted in the only Maternity Hospital of the city of Itaúna, MG, Brazil. The effect of medications on duration of breastfeeding was analyzed with the Cox regression model, with time-dependent covariables. Drugs were classified for safety during breastfeeding according to criteria established by the American Academy of Pediatrics (2001) and Hale (2004). **Results:** Ninety-eight percent of nursing women used medications after hospital discharge. The duration of breastfeeding was longer for mothers who did not use medications or who used drugs considering safety during lactation ($P < 0.05$). **Conclusions:** Health professionals should prescribe medications with well established safety for both infants and for the lactation process, so that maternal medication is compatible with breastfeeding.

1. Introduction

Human milk is considered as the ideal food for nourishing infants. Its important benefits include nutrient adequacy, high immunoprotective activity, and reduction of child mortality rates and morbidity due to infectious, allergic and immunomediated diseases[1]. Long-term beneficial effects of breastfeeding are also described, such as increasing mother–infant bonding[2], improving development of the oral motor system[3], better neurocognitive development and decreasing frequency of diseases such as arterial hypertension, type 2 diabetes, hypercholesterolemia and obesity[4]. Therefore, exclusive breastfeeding is recommended up to the age of 6 months[5], and breastfeeding should be continued for up to two years of age or longer.

Concurrent drug therapy in the nursing mother is

considered as one of the factors related to cessation of breastfeeding[6–8]. Medications used by the nursing mother may affect breastfeeding. The volume of milk may be increased or decreased, and many drugs are transferred into the milk, so that the infant is exposed to potentially harmful effects as well as the volume of milk also can be decreased. Nonetheless, most drugs indicated for use during breastfeeding, however, are considered safe[6], and the risk of infants exposed to maternal medication is minimal[9]. The association between the use of medication during breastfeeding and weaning needs further investigation and discussion.

Few reports are available showing an association between the use of medicines by the nursing mother and cessation of breastfeeding. Studies are generally concerned with the frequency of weaning due to the use of medication by the nursing mother, and do not investigate in greater detail the compatibility between the drugs and breastfeeding[10]. Data of literature have shown that most of the publications consist of isolated case reports on the use of medication during breastfeeding[11], description of harmful effects of

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drugs on infants^[12], investigation of specific pharmacological groups^[13–15] or nursing mothers groups^[16], classification of the short-term use of medication during breastfeeding^[17,18].

The present study investigated the duration of breastfeeding in women under medication involving possible risk for the infant or for lactation. There was also an association between the characterization of the drugs and the frequency of their use by nursing women after hospital discharge. Therefore, the present study can contribute to the knowledge of health professionals in the assistance to nursing women that need to receive drugs during breastfeeding.

2. Materials and methods

This longitudinal cohort study was conducted in the Maternity Ward of Hospital Manoel Gonçalves de Sousa Moreira, which is the only hospital in the city of Itaúna, Minas Gerais, Brazil. The sample was selected during the period between June 1st to September 4th 2003, and comprised mothers living in Itaúna and giving birth in that Hospital. After discharge, mothers and breastfed infants were followed up during the first 12 months or until weaning, by telephone contact or home visits.

Data were collected by the investigator, in collaboration with students of the School of Physical therapy of the University of Itaúna. In a pilot study, the students were trained in the application of questionnaires during interview with 20 mothers. For quality control of the study, meetings were performed weekly during the first eight weeks and every two weeks thereafter, until all data were collected. Data were also obtained from medical records. Mothers were interviewed immediately after delivery for collection of information on sociodemographic parameters, health care and maternal and child habits.

Due to the scarcity of literature parameters about duration of breastfeeding relative to the safety of drugs used by nursing women, and based on some literature suggestions about the prevalence of breastfeeding 12 months after delivery and the use of medication during the process, the size of sample was determined according to the following parameters: significance level (α) set at 5%; 90% power ($1-\beta$); sample recruitment period of three months; 12-month follow-up; 20% loss; a probability of 30% to be nursing at the end of the study, for the group of mothers under medication involving possible risk for the infant or for lactation, and of 70% for mothers without medication or using drugs known to be safe; and a probability of 25% for the use of drugs with adverse effect on the infant or the lactation. Based on these considerations, the sample was determined as 252 nursing mothers. The sample was later reduced to 246 women, as five of the mothers were not located after hospital discharge and in one case the infant died 40 hours after birth. Eight other mothers were excluded from the study for lack of follow-up,

due to change of residence in five cases and impossibility to contact in other three cases.

Data were processed with the EPI INFO™^[19], version 1.1.2 software, and transferred to the STATA™^[20], version 9 software for statistical analysis. Duration of breastfeeding according to the use of medication was described in Kaplan–Meier graphics. The associations between different classifications of drugs according to their safety during breastfeeding were determined by log–rank test. The effect of medication on duration of breastfeeding was analyzed with the Cox regression model, with time–dependent covariables^[21]. For each drug classification a model was adjusted, including as control maternal age (< 20 years), number of prenatal consultations (< 5 or > 9), interval from delivery to first feeding (> 6 hours), use of alcohol or smoking and use of a pacifier, which had shown in a previous study^[22] to be associated with duration of breastfeeding. The adequacy of the final model was evaluated with an analysis of residues.

Drugs were classified for safety during breastfeeding according to criteria established in the study The Transfer of Drugs and other Chemicals Into Human Milk, American Academy of Pediatrics (AAP)^[23] and on the book Medications and Mothers' milk, edited by Hale^[24]. The first report was chosen because of its high citation index in studies of medication and breastfeeding, whereas the book represents the most detailed and comprehensive publication on this subject. The classification reported in 2004 was selected, instead of the 2010 version, since it reflects more adequately the period when the present study was conducted.

Drugs were classified in three groups, according to safety during breastfeeding. According to AAP criteria^[23], drugs were classified in group A – “compatible with breastfeeding”, which also included nursing women not under medication; group B – “unknown effects, but may be of concern” and group C – medications not included in this classification.

According to Hale's^[24] criteria, drugs are classified in group 1 – drugs “safest” or “safer”, and no medication; group 2 – drugs “moderately safe” or “possibly hazardous”. and group 3 – other unclassified drugs. Drugs that may induce a reduction in milk production were also investigated for their effect on duration of breastfeeding. This project was approved by the Hospital and the Research Ethics Committee of Universidade Federal de Minas Gerais.

3. Results

A total of 98% of the nursing mothers were under medication after hospital discharge. According to the number of prescriptions or self-medication, painkiller/antipyretic drugs were more frequently used (336, 24.7%), followed by iron salts (186, 13.7%), NSAIDs (174, 12.8%), progesterone (139, 10.2%), multivitamin (90, 6.6%), antibacterial

(82, 6.0%), antihistamines (77, 5.7%), spasmolytic (41, 3.0%), antihypertensive (17, 1.3%), laxative (16, 1.2%), estrogen (15, 1.1%), hypnotic (11, 0.8%) and antifatulent (11, 0.8%). Other drugs were (164, 12.1%).

The pharmacological classes most often used, considering the number of days of intake reported, were progestogens (19 130, 55.8%), followed by iron salts (5 259, 15.3%), multivitamin (2 566, 7.5%), NSAIDs (1 465, 4.3%), painkiller/antipyretic (1 185, 3.5%), antihypertensive (872, 2.5%), estrogen (850, 2.5%) and antibiotic (667, 1.9%). Other drugs were also used (2 290, 6.7%).

The analysis of the safety of medications, according to AAP (2001) criteria, showed that 29 (30.8%) of the drugs used by the mothers were compatible with breastfeeding; 6 (6.4%) were in the class of unknown effects, but demanding concern; 2 (2.1%) possibly harmful to the infants, demanding care; and 57 (60.6%) unclassified drugs.

The univariate analysis showed an association between duration of breastfeeding and the classification of drugs according to AAP criteria with modifications ($P=0.0014$) (Figure 1).

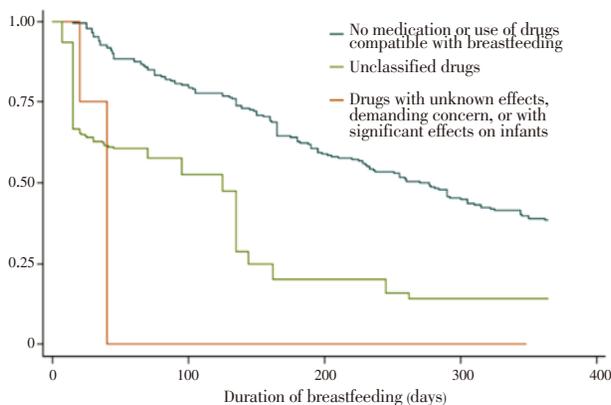


Figure 1. Relationship between duration of breastfeeding and type of medication used by the mother, classified according to AAP (2001) criteria, in Itaúna-MG (Brazil), in 2003.

Variables of the AAP (2001) classification were included in the final model of the previous study, which made use of the Cox multivariate regression model, to determine any possible association with weaning. As shown in Table 1, women on treatment with group A drugs breastfed for longer periods than mothers who used drugs from group B ($P=0.020$) and C ($P=0.019$).

According to the Hale (2004) classification 13 (13.8%) of the 94 drugs most frequently used by the mothers after discharge were included in the safest class (L1); 19 (20.2%) to the safe class (L2); 24 (25.5%) were classified as moderately safe (L3); 3 (3.2%) as possibly harmful (L4); and 35 (37.2%) were left unclassified. Medications considered as contraindicated during breastfeeding were not used.

As presented in Figure 2, the univariate analysis showed an association between duration of breastfeeding and the use of medications classified according to the Hale (2004) system with modifications ($P=0.0010$). The effect of drugs from groups 1, 2 and 3 on duration of breastfeeding was

determined by adjusting the model for the variables which, in this study, showed an association with breastfeeding. The residual analysis, however, showed that the effect was not proportional throughout the follow-up period. It was therefore necessary to include in the study a variable of interaction between the group of medications and time, so that its effect during follow-up could be better understood. As presented in Table 1, the multivariate analysis showed that women on treatment with group 1 drugs breastfed for longer periods than mothers who used drugs from groups 2 ($P=0.000$) and 3 ($P=0.000$), but the effect decreases with time.

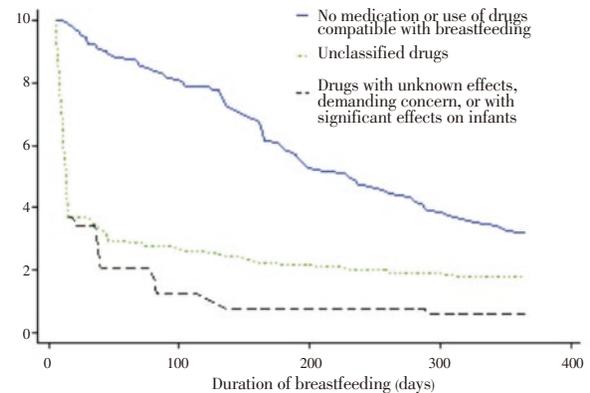


Figure 2. Relationship between duration of breastfeeding and type of medication used by the mother, classified according to Hale (2004), in Itaúna-MG (Brazil), in 2003.

The univariate analysis showed an association between duration of breastfeeding and the use of drugs with potential for suppressing lactation ($P=0.0014$) (Figure 3). This effect was also not proportional along time, so that a variable of interaction between this classification and time was included. The effect of these medications on duration of breastfeeding, according to this model, was presented in Table 1.

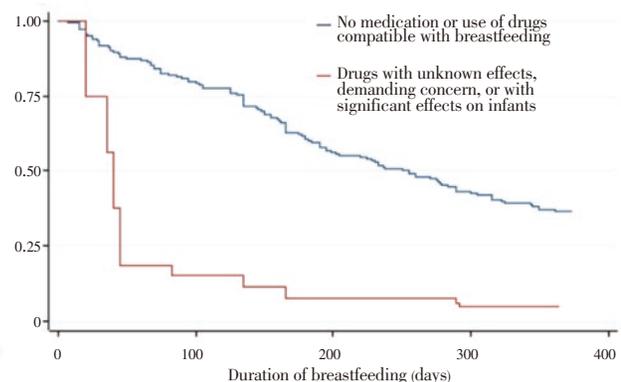


Figure 3. Relationship between duration of breastfeeding and type of medication with potential for suppressing lactation, in Itaúna-MG (Brazil), in 2003.

The inclusion of variables related to the use of drugs classified according to AAP (Groups A, B and C) or Hale (Groups 1, 2 and 3) criteria, or according to lactation-suppressing effect, did not modify the effect of variables associated to duration of breastfeeding in the statistical analysis of the data obtained in Itaúna.

Table 1

Relationship between weaning and medication, controlled for confounding variables[#], considering the classifications of AAP (2001), Hale (2004) and lactation-suppression drugs, in Itaúna-MG (Brazil), in 2003.

	Variable	RR (CI 95%)	P value
AAP criteria	Safety drugs (Group A)		
	Drugs with unknown effects or with significant effects in infants (Group B)	2.87 (1.02–8.11)	0.020
	Unclassified drugs (Group C)	1.79 (1.06–2.99)	0.019
Hale criteria	Safety drugs (Group 1)		
	Moderately safe or possibly harmful drugs (Group 2)	9.38 (3.12–28.19)	0.000
	Group 2 × time	0.99 (0.98–0.99)	0.027
	Unclassified drugs (Group 3)	11.37 (4.97–26.03)	0.000
	Group 3 × time	0.98 (0.98–0.99)	0.000
Lactation-suppression drugs		11.29 (3.60–35.44)	0.000
Lactation-suppression drugs × time		0.99 (0.98–0.99)	0.003

[#]Maternal age (< 20 years), number of prenatal visits (< 5 or > 9), interval from delivery and first feeding (> 6 hours), use of alcohol or smoking and use of a pacifier; RR: relative risk.

Cessation of breastfeeding was explained by 7 (4.5%) of the 155 women by the need of medication. Two of them reported the use of fluoxetine, and five described the use of celecoxib, cloxazolam, diazepam, metformin, metimazol. When weaning was due to the use of diazepam, mothers reported sleepiness in the infants. When in use of the other drugs, weaning followed medical recommendation. The use of medication was the fourth most frequent reason reported by mothers to cessation breastfeeding.

4. Discussion

After hospital discharge, 98% of the nursing women used medication. The most frequently used drugs, considering the number of prescriptions or self-medications, were painkillers/antipyretic, iron salts, NSAIDs and progestogens. Investigating the use of medication during the first four months after delivery, Olesen *et al*[25] observed that only 34% of the women, nursing or not, had received medical prescription, and that penicillin was the most frequently used drug. Another study, in the Netherlands, showed that 65.9% of nursing mothers were on medication during the first six months after delivery, with prescription of multivitamins (40.8%), painkillers (36.8%) and iron salts (20.2%)[26]. There are no studies found in the literature that evaluate the frequency of the use of medications by nursing women during 12 months after delivery.

The higher frequency of nursing women on medication after hospital discharge observed in the present study, as compared with other reports, may be explained by the longer follow-up. The frequent need for drug treatment during the nursing period stresses the importance of this discussion for health professionals involved with the care of nursing women and their infants. It also reveals the need for more detailed investigation on the effect of medications on infants and the lactation process.

No reports were found in the literature describing the frequency of use of medication considering the number of

days of intake. This kind of study is important for revealing the drugs to which infants are more exposed, through the mother's milk. In the present work, among drugs belonging to eight pharmacological classes, only estrogens called particular attention, due to their effect in reducing lactation[27].

The effect of medications used immediately after delivery on duration of breastfeeding was not analyzed, since all mothers left the hospital while still nursing. Furthermore, all mothers nursed until at least the second week after delivery, so that it is not probable that medications taken during hospitalization had any effect on duration of breastfeeding.

The analysis of the number of medications used, considering safety during breastfeeding, showed that most of them were not safe for use by nursing mothers, according to AAP[23] and Hale[24] classification criteria (60.6% and 37.2%, respectively). The non inclusion of drugs in these studies means that their safety was unknown at the time the reports were published.

In this study, the use of drugs not classified considering AAP (group C) and Hale (group 3) criteria was associated to shorter duration of breastfeeding, when compared to medications in groups A (AAP) and 1 (Hale). The lack of knowledge about the efficiency and safety of medications for children has led some authors to refer to them as "drug therapy orphans"[28]. Similarly, the lack of knowledge about the safety of drugs used during breastfeeding represents a risk for nursing women and infants.

A review on studies investigating the use of antidepressants during the nursing period showed that many mothers and physicians avoid breastfeeding during the use of these drugs, based on the lack of information about their safety[29]. Similarly, mothers may feel insecure about nursing when taking medication of unknown safety during breastfeeding. It is also possible that the drugs have harmful effects on the infants or the nursing process. These studies show the need for further research to better understand the effects of medications used by nursing women on infants and on milk production.

Mothers using medications with potential harmful effects on infants or on the lactation process, included in group B (AAP) or group 2 (Hale), nursed for shorter periods than non-medicated mothers or those using drugs considered compatible or safe during breastfeeding (AAP group A and Hale group 1). These results could be explained by the fear of using drugs potentially harmful for their babies. An alternative explanation, however, involves the induction of harmful effects on infants through drugs used by the nursing mother. Some of these drugs were used by the nursing women, including hypnotic drugs, barbiturates and benzodiazepines, which may induce sleepiness and decreased feeding frequency, with consequent weight loss^[6,30].

It is also possible that the use of medications with known effect on the reduction of milk production, such as ergotamine and ethinylestradiol, may have contributed to decreasing duration of breastfeeding^[6]. It is therefore important that mothers and health professionals are aware of harmful effects of medications on infants and on lactation itself. If these effects are suspected, medication should be interrupted or replaced for a safer equivalent, so that breastfeeding may be continued.

In the present study, we also investigated a possible association between the use of medication with a potential effect on suppressing lactation and duration of breastfeeding. This group of drugs included ethinylestradiol, ergotamine, dihydroergotamine, pseudoephedrine and furosemide. Alcohol and nicotine were not considered in this analysis, although both are possibly suppressors of milk production, due to lack of information on the frequency and exact period of use by the nursing women in our sample.

Mothers treated with drugs known to suppress milk production breastfed their infants for shorter periods than the remaining women. The reduction of milk supply, even when not significant, has been described as a determinant for weight gain in infants, increasing the probability of cessation of breastfeeding^[31]. This study did not consider the weight gain of infants whose mothers were on treatment with drugs possibly related to suppression of milk production. Further studies are necessary for the detailed investigation of possible effects of this group of drugs on weight gain in infants.

The effect of medication during the 12-month follow-up was more completely understood after an analysis of the interaction between variables and time. Since the effect of the interaction is smaller than one, the results showed that the effect of drugs potentially harmful for infants, according to a modification of Hale^[24] criteria, as well as drugs suppressing lactation, is stronger when they are used during the first months after delivery.

During exclusive breastfeeding, the growth of infants is entirely dependent on the amount of maternal milk received. Drugs with potential interference with milk production are therefore expected to have greater effect on weight gain during the first months of life. A review on studies of harmful effects of drugs used by nursing women showed that infants younger than two months are more susceptible (78%), whereas only 4% of these effects were observed in babies

older than six months, when the liver is more mature in terms of metabolic functions and milk intake decreases due to complementary feeding^[9]. Hale^[31] classified the risk of harmful effects on infants according to age as: low risk (six to 18 months), moderate risk (two to six months) and high risk (premature babies, newborns, and infants who are clinically unstable or present compromised kidney function).

Medications are used to relieve symptoms or to treat diseases. The evaluation of a possible association between use of drugs and duration of breastfeeding is therefore important to show if there is any relationship between maternal diseases and weaning. It should also be noted that nursing women may use medications to treat problems directly related to breastfeeding, such as plugged ducts and mastitis. In the present work, chronic diseases were not associated with duration of breastfeeding, but the mothers were not evaluated for acute diseases.

The prescribed dose and frequency of medication have an influence on their excretion in milk^[32]. It is therefore important to consider the dose of drugs used by the nursing women, and the interval of time between doses, for a better understanding of the effect of drugs on milk production and, as a consequence, on duration of breastfeeding. These parameters, however, are seldom evaluated in studies aiming to classify the level of safety of medications used during breastfeeding. The route of administration is another factor which is related to transfer of drugs into milk^[32]. Since topical medications used by the mother represent a much lower risk factor for infants, they were excluded in the present study.

The comparison of different studies investigating the role of medications as a direct cause of weaning is hampered by methodological differences. Some of the reports mention variables such as “medical orientation” or “diseases of the mother”, explanations that in theory could include the use of medication as a cause of weaning. Furthermore, most of the studies usually mention only the main causes of weaning and include, at the end of the list, the variable “other causes”, which could also include medications.

A total of 155 (4.5%) women explained cessation of breastfeeding by the use of medication. Schirm *et al*^[26], observed that 11.5% of the women who did not breastfeed explained the behavior by the need of medication. In a study by Pilviniene *et al*^[10], this situation was observed in 21% to 23% of the mothers. Large variations are seen in the literature, stressing the need for focal diagnosis of the importance of drug treatment of the mother as a cause of weaning. This analysis also shows that, in spite of the great number of reports mentioning a relationship between medications and cessation of breastfeeding, few studies have actually proven this association.

The use of medications by the nursing women is a frequent practice. The use of drugs with potentially harmful effects on infants, possibly suppressing milk production, or with no safety evaluation, has been associated with shorter periods of breastfeeding. The use of safe or moderately safe drugs was, according to reports of nursing women, directly responsible by cessation of breastfeeding. These evidences indicate that health professionals involved with

mother–infant care must keep updated on the field, aiming at improved compatibilization between the nursing process and treatment of the mother. In this context, drug therapies should consider the use of products already investigated and proved safe for the infant as well as for milk production.

Conflict of interest statement

We declare that we have no conflict of interest.

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