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The Most Common Medications Dispensed to Lactating Persons: An Electronic Health Record (EHR)-Based Approach

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Abstract

Purpose: Using a novel, electronic health record (EHR)-based approach, to estimate the prevalence of prescription medication use at 2, 4, and 6 months postpartum among lactating individuals.

Methods: We utilized automated EHR data from a US health system that records infant feeding information at well-child visits. We linked mothers who received prenatal care to their infants born May 2018-June 2019, and we required infants to have ≥1 well-child visit between 31–90 days of life (i.e., 2-month well-child visit with a +/− 1 month window). Mothers were classified as lactating at the 2-month well-child visit if their infant received breastmilk at the 2-month well-child visit. For subsequent well-child visits at 4 and 6 months, mothers were considered lactating if their infant was still receiving breastmilk.

Results: We identified 6,013 mothers meeting inclusion criteria, and 4,158 (69.2%) were classified as lactating at the 2-month well-child visit. Among those classified as lactating, the most common medication classes dispensed around the 2-month well-child visit were oral progestin contraceptives (19.1%), selective serotonin reuptake inhibitors (8.8%), first generation cephalosporins (4.3%), thyroid hormones (3.5%), nonsteroidal anti-inflammatory agents (3.4%), penicillinase-resistant penicillins (3.1%), topical corticosteroids (2.9%), and oral imidazole-related antifungals (2.0%). The most common medication classes were similar around the 4 and 6-month well-child visits although prevalence estimates were often lower.

Conclusions: Progestin-only contraceptives, antidepressants, and antibiotics were the most dispensed medications among lactating mothers. With routine collection of breastfeeding

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information, mother-infant linked EHR data may overcome limitations in previous studies of medication utilization during lactation. These data should be considered for studies of medication safety during lactation given the need for human safety data.

Plain Language Summary:

Purpose: The goal of the study was to identify the most commonly used prescription medications at 2, 4, and 6 months after delivery among lactating people. Methods: We used electronic health record (EHR) data from a US health care system that records information on the type of milk that is fed to infants at well-child health care visits. We linked data from mothers to their infants born between May 2018 and June 2019. We included infants who had ≥1 well-child visit between [1]31–90 days of life (i.e., around the 2-month well-child visit). Mothers were classified as lactating at the 2-month well-child visit if their infant received breastmilk at the 2-month well-child visit. Mothers were considered to be lactating at later well-child visits if their infant was still receiving breastmilk. Results: We identified 6,013 mothers meeting inclusion criteria, and 4,158 (69.2%) were classified as lactating at the 2-month well-child visit. Progestin-only contraceptives, antidepressants, and antibiotics were the most frequently dispensed medications among lactating mothers. Conclusions: These data should be considered for studies of medication safety during lactation given the need for human safety data.

Keywords

breastfeeding; Electronic health records; epidemiology; lactation; pharmacoepidemiology; prevalence

Introduction

There is a clear need for human data to guide decisions about medication use among lactating persons.[2–4] United States Food and Drug Administration's Pregnancy and Lactation Labeling Final Rule requires prescription drug and biologic product labeling to include narrative summaries of product risks during pregnancy and lactation.[5] The European Medicines Agency's Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation indicates that drug labeling should include the risks of drug exposures and recommendations for use during lactation.[6] Furthermore, the Task Force on Research Specific to Pregnant Women and Lactating Women has recommended increasing the quantity, quality, and timeliness of research on safety and efficacy of therapeutic products used by pregnant and lactating women.[7] However, lactating patients and their providers often lack data to support decisions regarding medication use. Of 290 newly approved medications during 2010–2019, as of March 2020 only 3% had lactation safety data from human studies.[3] Lack of safety information contributes to non-initiation or early cessation of lactation, inadequate treatment of acute or chronic conditions in lactating persons, and infant exposure to medications with potentially harmful effects through breastmilk.[1,4,8–11]

Experts have suggested that drugs that are commonly used among lactating people should be prioritized for lactation safety studies.[4] Unlike medications used during pregnancy,[12–14] there are few published studies on medication utilization among lactating people, with

even fewer using contemporary data from United States.[10,15] Prior studies have been limited by small size, volunteer bias, selection bias, or unclear timing of medication use relative to infant age.[10,11,15–18] Three of these studies assessed the frequency of calls to a teratogen information service about a particular potential medication exposure by a lactating individual, health care provider, family member, etc.[15–17] This approach relies on highly selective reporting and the lack of a denominator precludes medication prevalence estimates. Other studies relied on self-report of both breastfeeding status and medication use.[10,11,18] Using a novel approach to study medications during lactation with routinely collected information on infant feeding stored in electronic health records (EHR), we aimed to estimate the prevalence of medication use at 2, 4, and 6 months' postpartum among lactating patients within one health system. This approach could be used to identify commonly used medications among lactating people to help prioritize lactation safety studies.

Methods

We conducted this study using automated EHR data from an integrated health care delivery system based in the upper Midwest, USA (HealthPartners). A waiver of informed consent was approved by the HealthPartners Institutional Review Board.

Lactation information

At well-child health care visits between 0 to 25 months of age across the health system—including the first visit (typically during the first week of life) and at 2, 4, and 6-month visits— caretakers are asked by medical assistants during rooming, "What type of milk is your child currently getting?" Responses (breastmilk only; formula or other milk only; or both) are recorded in standardized flowsheets in the child's EHR. Previous research studies have used similar data, e.g., to classify breastfeeding status at time of intrauterine device insertion and breastfeeding persistence.[19,20] At postpartum visits, breastfeeding status (yes, no) is recorded in standardized flowsheets in the mother's EHR.

Inclusion criteria and follow up

We identified infants with a date of birth from May 1, 2018, to June 30, 2019 who had at least one well-child visit between 31 and 90 days of life (i.e., 2-month well-child visit; Figure 1). We focused on this timeframe because standardized infant feeding data collection at well-child visits was being implemented by May 2018 and June 2019 was approximately six months before the COVID-19 pandemic began, which potentially could have led to irregularities in care. Mothers were linked to infants using a hierarchy of methods: Birth certificate and EHR birth registry had the highest rank, followed by health plan contract linkage, then exact match on name, baby birth date and address, and probabilistic match on name, infant birth date and address had the lowest rank. We included infants linked to a mother with at least one prenatal care visit to help identify maternal comorbidities. We required mothers to have at least one health care visit or medication dispensing in the year after delivery to help ensure that the study population had medication information captured after delivery. We restricted the analysis to mothers of infants with milk type recorded at well-child visits between 31–90 days of life (i.e., 2-month well-child visits). Of 6,099 eligible infants, 96.3% had milk type recorded.

We prioritized specificity (i.e., minimize false positives) when classifying patients as lactating; therefore, those with discordant feeding information within an assessment window were classified as not lactating (Figure 1). We classified mothers as lactating if their infants received breastmilk at the 2-month well-child visit (i.e., 'breastmilk only' or 'both breastmilk and formula or other milk' recorded). To help ensure that those who discontinued breastfeeding during the assessment window were not classified as lactating, mothers of infants who also had 'formula or other milk only' recorded during the window were then reclassified as not lactating. In addition, mothers reporting no breastfeeding at postpartum visits between 0 and 90 days after delivery were reclassified as not lactating (to remove mothers whose infants were receiving breastmilk from donors, had stopped breastfeeding, or possibly had an error in breastmilk status at their well-child visit). Among patients classified as lactating at the 2-month well-child visit, we also assessed infant milk type at 91–150 days (i.e., 4-month well-child visits) and at 151–210 days (i.e., 6-month well-child visits). Mothers of infants who had no information available on milk type at the 4-month or 6-month well-child visits or who did not receive breastmilk (i.e., any report of 'formula or other milk only', even if breastmilk was reported at other visits during the timeframe of interest) were excluded from follow up at the respective well-child visit.

Medication information

Medication dispensing data are typically the preferred source of medication exposure information in pharmacoepidemiologic studies of drug safety, given that dispensing implies that the patient picked up their prescription and had the medication in their possession on the dispensing date. Dispensed prescription medication history data, including medication dispensing date, from pharmacy benefit managers and pharmacies is incorporated into the health system's EHR via Surescripts® health information network.[21] Medication dispensing history, including for medications prescribed outside of the health care system, is incorporated in the EHR when a patient has a health care encounter. Although dispensing information is missing when medications are dispensed from pharmacies not captured by Surescripts, the Surescripts network includes major retail and mail order pharmacies.[22] Nevertheless, we also explored the use of ordered prescription medications as well as active medication lists in EHR. Unlike dispensing data, ordered medications may not have been picked up by the patient, and active medication lists in the EHR may be out of date as reconciliation of the list with actual medication use is dependent on having a health care visit.

In a subset of patients with urinary tract infections or mastitis (n=52), we compared evidence of antibiotics around the 2-month well child visits from the three medication data sources (i.e., dispensed, ordered, active list) and found agreement to be 93% when we allowed a 2-week grace period before the well-child visit timeframe for the medication dispensing data. Chart review indicated that antibiotics, one of the most common medications in this study, dispensed just before the 2-month well-child visit window would not be identified without implementing the 2-week grace period. To help ensure capture of medications, we assessed dispensings for any medication between 17 and 90 days after delivery, which corresponded to a two-week grace period plus the 2-month well-child visit window. We also assessed dispensings for any medication between 91–150, and 151–210 days after delivery,

corresponding to 4 and 6-month well-child visits. This study did not assess intrauterine devices, contraceptive implants or medications administered during hospitalizations or health care visits (e.g., injections, infusions, intravenous medications).

We report the most frequently dispensed medication classes, defined as the classes dispensed to at least 1% of lactating mothers at any of the well-child visit windows. Furthermore, we report generic medications dispensed to at least 0.5% of those at each well-child visit.

Maternal characteristics

Maternal characteristics were identified from EHR. We classified comorbidities based on documentation of at least one inpatient or outpatient diagnosis code for the condition between 270 days before delivery (i.e., the average length of pregnancy) until 90 days after delivery. We used this broad timeframe to capture comorbidities and included those with postpartum onset to help characterize the population.

Results

Among the 6,099 infants with milk type recorded during the 2-month well-child visit, 4,198 (68.8%) infants were classified as receiving breastmilk (Figure 2). The 4,158 mothers linked to these infants comprised the study population for the 2-month assessment window. There were 3,189 mothers with infants classified as receiving breastmilk for the 4-month window, and 2,660 mothers with infants classified as receiving breastmilk for the 6-month window (Table 1). The median maternal age at delivery was 31 years, and a majority of patients were non-Hispanic White (63.2%). Maternal insurance payer at the time of delivery was most often commercial insurance (66.7%) followed by Medicaid (32.4%). The median gestational age at delivery was 39 weeks. Mental health comorbidities were common; 20.9% of mothers had an anxiety disorder and 11.6% had a mood disorder recorded in EHR in the 270 days before delivery through 90 days' postpartum.

Overall, 53.8% of patients had at least one medication dispensed during the 2-month assessment window (Table 2). This figure was 39.5% during the 4-month and 36.3% during the 6-month windows. The most common medication classes dispensed during the 2-month window were oral progestin contraceptives (19.1%), selective serotonin reuptake inhibitor (SSRI) antidepressants (8.8%), first generation cephalosporins (4.3%), thyroid hormones (3.5%), nonsteroidal anti-inflammatory drugs (NSAIDs) (3.4%), penicillinase-resistant penicillins (3.1%), topical corticosteroids (2.9%), oral imidazole-related antifungals (2.0%), topical antifungals (1.9%), and aminopenicillins (1.6%).

The most common medication classes were generally similar for the 4-month and 6-month assessment windows. Prevalence estimates for common medication classes were often lower at the 6-month assessment window than the 2-month window, e.g., alpha-beta blockers (i.e., labetalol), calcium channel blockers, oral contraceptives, anti-fungals, NSAIDs, opioids, cephalosporins, penicillins, and topical corticosteroids. However, prevalence estimates for other common medication classes were similar or higher at the 6-month assessment window compared with the 2-month assessment window, e.g., aminopenicillins (i.e., amoxicillin), antiviral herpes agents, oral glucocorticoids, pulmonary sympathomimetics (e.g., albuterol),

and nasal steroids. . The most frequently dispensed medications according to generic name are reported in Supplementary Tables 1–3. Norethindrone (between 19.1% and 8.2% depending on the window), a progestin-only oral contraceptive, and sertraline (between 5.8% and 5.4% depending on the window), an SSRI, were the first and second most frequently dispensed medications across the three windows.

Conclusion

In this study, we used EHR data from mothers and their infants to identify lactation status. More than half of lactating persons had at least one medication dispensed during the first assessment window, which was approximately 10 weeks long. Oral contraceptives (norethindrone, desogestrel and ethinyl estradiol), antidepressants (SSRIs, bupropion), antibiotics (cephalexin, dicloxacillin, amoxicillin, amoxicillin and potassium clavulanate, clindamycin, nitrofurantoin, azithromycin, doxycycline), thyroid hormones (levothyroxine), nonsteroidal anti-inflammatory agents (ibuprofen), topical corticosteroids (triamcinolone, hydrocortisone, betamethasone), oral antifungals (fluconazole), and inhaled and oral glucocorticoids (fluticasone, prednisone), were among the most commonly dispensed medications.

Prevalence estimates for some common medication classes were lower at the 6-month assessment window than at the 2-month window in part due to the 2-month window being 2 weeks longer because of the grace period. Additionally, lower prevalence estimates at later timepoints may be expected as patients discontinue medications for pregnancy, delivery, and early postpartum-related indications, e.g., labetalol and nifedipine prescribed for hypertensive disorders of pregnancy; NSAIDs and opioids prescribed for pain relief following delivery; cephalexin and dicloxacillin prescribed for lactational mastitis, which is most common during the first few months postpartum.[23] The decrease in prevalence of oral contraceptives at the 4 and 6-month assessment windows compared with the 2-month window may be due to multi-month packs resulting in less frequent refills.[24]

Oral norethindrone, the most commonly dispensed medication in this study, is the oral hormonal contraceptive recommended for lactating people[25] because it does not contain estradiol, which can suppress lactation and increase the risk of thromboembolism, especially after delivery.[26] Combination oral contraceptives (e.g., desogestrel and ethinyl estradiol) are not recommended during the first 6 weeks' postpartum.[27,28] In the current study, combination oral contraceptives were dispensed to 1.4% of patients during the first assessment window. Some patients receiving these medications may have had infants who were being weaned or were no longer receiving their breastmilk. Therefore, in some cases, combination oral contraceptives may be an indicator of misclassification of lactation status.

SSRIs were the second most commonly dispensed medication in this study, reflecting a high burden of postpartum mood and anxiety disorders. Sertraline, the most commonly dispensed SSRI and the second most commonly dispensed medication overall in this study, has been a preferred antidepressant for lactating individuals.[29] Fluoxetine was the second most commonly dispensed SSRI, however its pharmacokinetics are the least favorable for lactation among the SSRIs.[29] Short-term adverse effects in breastfed infants have been

reported for SSRIs, e.g., drowsiness and irritability;[30,31] however, data on effects on child development are limited.[32] The impact of antidepressant use on breastfeeding initiation and duration is unclear.[33–38]

Cephalexin, dicloxacillin, and other antibiotics often prescribed to treat mastitis were among the most used medications in this study. Infant exposure to antibiotics through human milk can disrupt gastrointestinal flora, causing diarrhea or thrush, although effects on infant growth have not been evaluated.[39,40] Among other commonly used medications, exogenous levothyroxine is not believed to be harmful for breastfed infants as endogenous levothyroxine (T4) is found in human milk and adequate levels are necessary for lactation.[41,42] Ibuprofen is often the analgesic or anti-inflammatory agent used by lactating individuals given low levels excreted in breastmilk.[43] Amounts of inhaled glucocorticoids or short-term application of glucocorticoids absorbed by the mother and excreted into breastmilk are believed to be too small to affect infants.[44,45] Levels of prednisone in breastmilk are low following maternal use, and there are no reported adverse events in infants receiving breastmilk from mothers who used oral corticosteroids.[46] A few studies suggest that high oral corticosteroid doses may temporarily reduce breastmilk supply, however the impact on breastfeeding duration is unknown.[46]

Breastfeeding status is entered into EHR to support clinical care, but these data may also be captured systematically in an extractable format for quality measures (e.g., to track breastfeeding duration). In this study, we used mother-infant linked EHR, including prescription dispensing data and routinely collected breastfeeding information from postpartum and well-child visit for a sizeable population. The potential limitations of this novel approach should be considered. First, misclassification of lactation status due to changes in breastfeeding practices between well-child visit or lack of well-child visits during follow up is a limitation, and validation studies comparing EHR data with self-report are needed to quantify misclassification. Future studies should consider classifying lactation status with greater granularity, e.g., monthly, and should explore imputation when breastfeeding information is unavailable during certain intervals. Second, exposure misclassification is possible as medication use dates could not be confirmed. The percent agreement we calculated between medication data sources for antibiotics does not necessarily apply to all medications, therefore additional validation of Surescripts data is warranted to better understand potential exposure misclassification. As the data source captured prescription medication dispensings, use of products also available over-the-counter (e.g., topical corticosteroids, topical antifungals, NSAIDs, nasal steroids, proton pump inhibitors) was underestimated. Third, we were only able to estimate medication prevalence for mothers of infants who attended prenatal care within the health system so our findings may not represent individuals who received care elsewhere.

The approach we describe represents a novel response to the call for data sources for conducting phamacoepidemiologic studies of medication use and vaccine safety among lactating individuals.[32] To increase sample size and generalizability, mother-infant linked data may be pooled across health systems that routinely collect breastfeeding information in EHR, similar to previous consortium studies of the safety of medication use and vaccination during pregnancy.[48,49] This approach may overcome limitations of small sample

size and volunteer bias in previous studies of medication utilization during lactation and may be considered for studies of maternal and child lactation-related outcomes following prescription medication and other maternal exposures.

Many of the commonly dispensed medications observed in this study have inadequate data available on the effects of the medication on breastfeeding practices and childhood outcomes. This includes SSRIs, which were dispensed to nearly 9% of patients during a two and a half month-window. Findings from this study and future studies like it can be used to rapidly identify commonly used medications among lactating people to help prioritize lactation safety studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points:

- There are few published studies on medication utilization among lactating people, including studies using contemporary data from the United States.
- We used a novel, electronic health record (EHR)-based approach, to estimate the prevalence of prescription medication among lactating individuals.
- In this study, progestin-only contraceptives, antidepressants, and antibiotics were among the most common prescription medications dispensed to lactating persons.
- The approach described may overcome limitations of previous studies of medication utilization during lactation and may be considered for studies of maternal and child lactation-related outcomes following prescription medication and other maternal exposures.
- In future studies, mother-infant linked data may be pooled across health systems that routinely collect breastfeeding information in EHR similar to previous consortium studies of medication use and vaccination during pregnancy.

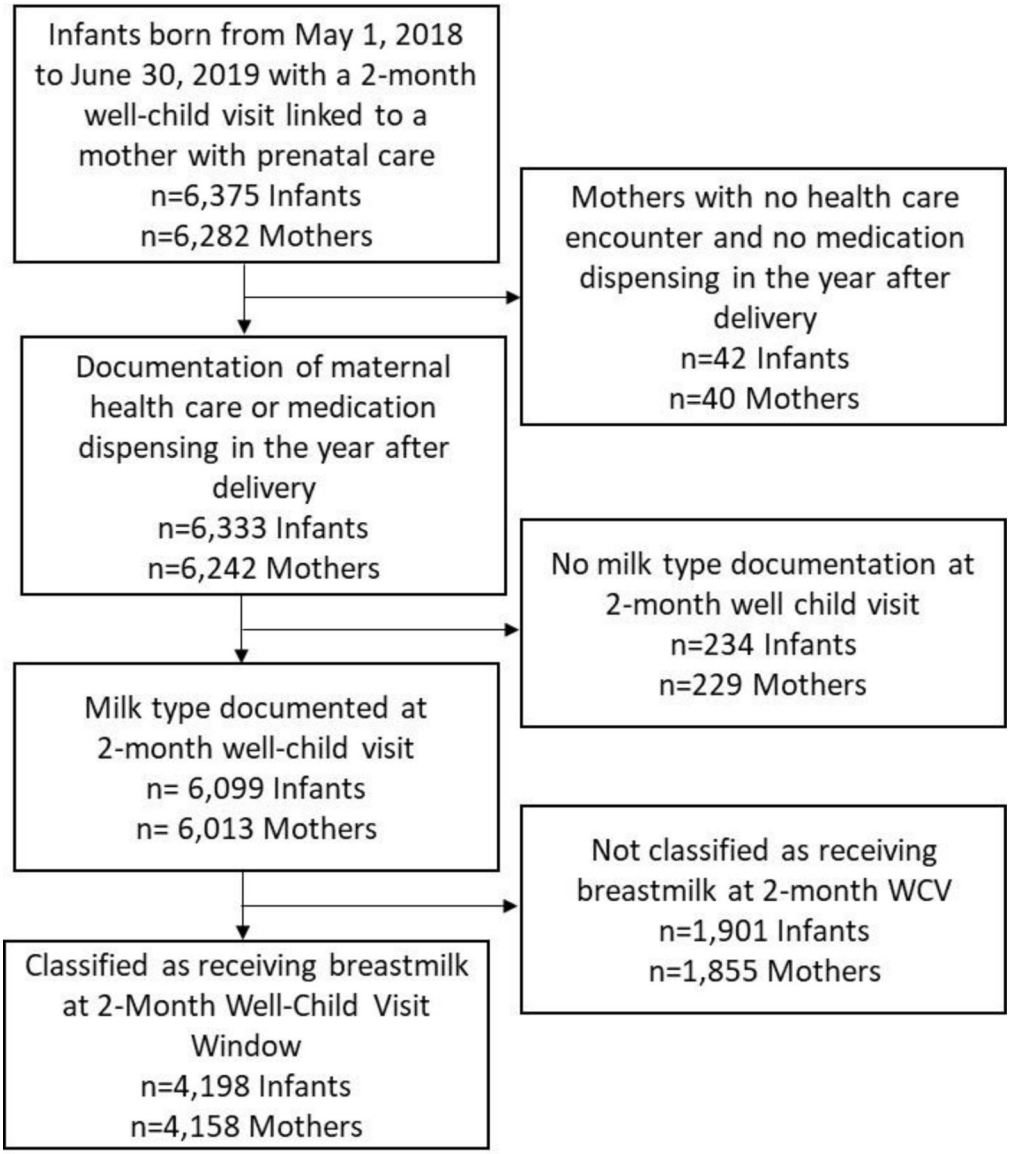

Figure 1.
Study population flow diagram.

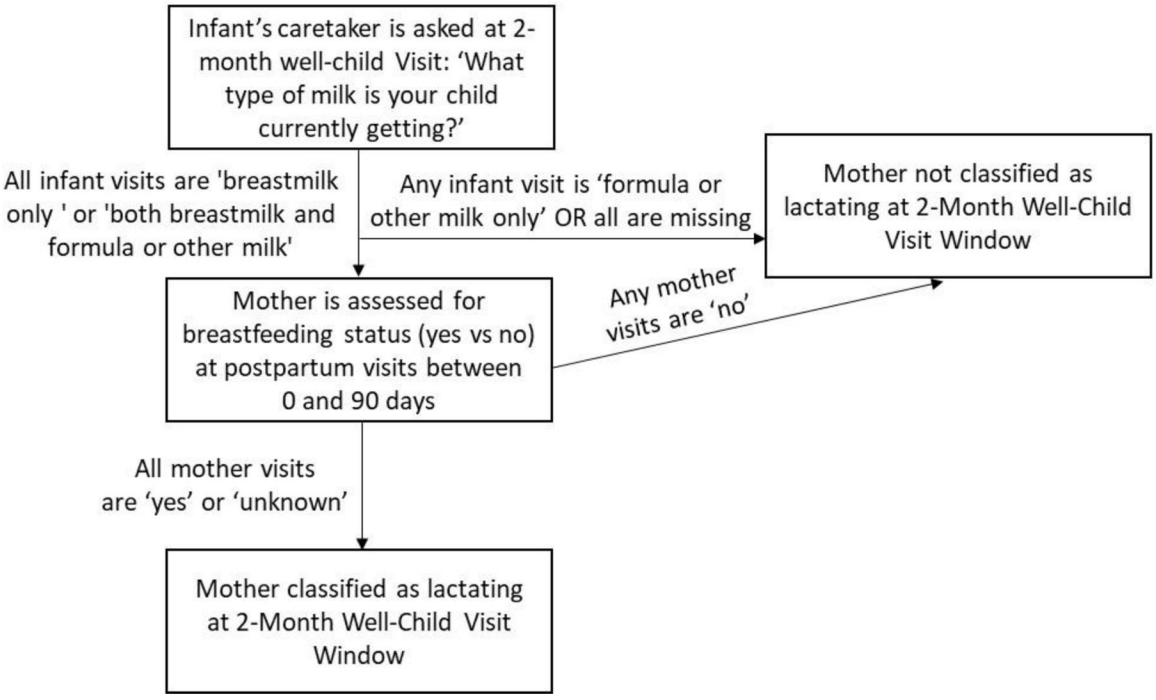

Figure 2.

Classification of lactation status during 2-Month Well-Child Visit Window based on well-child visit and postpartum visit information.

Table 1.

Characteristics of mothers linked to an infant classified as receiving breastmilk during the 2-month assessment window.

Characteristics	n=4,158
Infant classified as receiving breastmilk at 4-month well-child visit	3189 (76.7)
Infant classified as receiving breastmilk at 6-month well-child visit	2660 (64.0)
Maternal age at delivery (years), median (IQ range)	31 (6)
Maternal race and ethnicity[a], n (%)	
Non-Hispanic White	2608 (63.2)
Non-Hispanic Black	757 (18.4)
Non-Hispanic Asian	363 (8.8)
Hispanic	230 (5.6)
Multiple Races	48 (1.2)
American Indian	10 (0.2)
Different Race	113 (2.7)
Maternal insurance payer at delivery[b], n (%)	
Commercial	2671 (66.7)
Medicaid	1297 (32.4)
Other	38 (0.9)
Multiple gestation, n (%)	41 (1.0)
Gestational age at delivery (weeks), median (IQ range)	39 (2)
Maternal co-morbidities in the 270 days before delivery through 90 days' postpartum, n (%)	
Asthma	240 (5.8)
Type 1 or type 2 diabetes	46 (1.1)
Chronic hypertension	142 (3.4)
Mood disorder	482 (11.6)
Anxiety disorder	871 (20.9)

IQ, interquartile.

[a]34 with unknown race; % excludes unknown from denominator.

[b]Medicaid includes those with commercial and Medicaid payers at delivery; 152 with unknown insurance payer; % excludes unknown from denominator.

Table 2.

Most frequently dispensed medication classes among mothers linked to infants classified as receiving breastmilk during the 2-, 4-, and 6-month assessment windows. The five most frequently dispensed medications in each time-period are bolded.

	2-month n=4,158		4-month n=3,189		6-month n=2,660		
Medication Class	**n**	**%**	**n**	**%**	**n**	**%**	**Medication Observed Within Class**
Any Medication	2,238	53.8	1,260	39.5	966	36.3	
Alpha-Beta Blockers	45	1.1	13	0.4	10	0.4	labetalol
Aminopenicillins	65	1.6	49	1.5	**52**	**2.0**	amoxicillin
Antiviral Herpes Agents	47	1.1	29	0.9	29	1.1	acyclovir, valacyclovir
Calcium Channel Blockers	59	1.4	19	0.6	13	0.5	amlodipine, diltiazem, nifedipine, verapamil
Combination Oral Contraceptives	60	1.4	37	1.2	21	0.8	desogestrel-ethinyl estradiol, drospirenone-ethinyl estradiol, levonorgestrel-ethinyl estradiol, norethindrone-ethinyl estradiol, norgestimate-ethinyl estradiol, norgestrel-ethinyl estradiol
First Generation Cephalosporins	**178**	**4.3**	**66**	**2.1**	**51**	**1.9**	cefadroxil, cephalexin
Oral Glucocorticoids	44	1.1	27	0.8	33	1.2	dexamethasone, hydrocortisone, methylprednisolone, prednisone
Imidazole-Related Antifungals	83	2.0	37	1.2	23	0.9	fluconazole, miconazole
Nasal Steroids	37	0.9	30	0.9	32	1.2	beclomethasone, budesonide, fluticasone
Nonsteroidal Anti-inflammatory Agents	**140**	**3.4**	**52**	**1.6**	28	1.1	celecoxib, diclofenac, flurbiprofen, ibuprofen, ketorolac, meclofenamate, meloxicam, naproxen
Ophthalmic Anti-infectives	30	0.7	36	1.1	17	0.6	bacitracin-polymyxin B, ciprofloxacin, erythromycin, gentamicin, moxifloxacin, ofloxacin, polymyxin B-trimethoprim, tobramycin
Opioid Agonists	49	1.2	10	0.3	7	0.3	hydromorphone, oxycodone, tramadol
Opioid Combinations	57	1.4	24	0.8	13	0.5	hydrocodone-acetaminophen, oxycodone-acetaminophen
Oral Progestin Contraceptives	**793**	**19.1**	**400**	**12.5**	**221**	**8.3**	norethindrone
Penicillin Combinations	52	1.3	33	1.0	25	0.9	amoxicillin & potassium clavulanate
Penicillinase-Resistant Penicillins	127	3.1	22	0.7	13	0.5	dicloxacillin
Proton Pump Inhibitors	51	1.2	37	1.2	20	0.8	esomeprazole, lansoprazole, omeprazole, pantoprazole
Pulmonary Sympathomimetics	45	1.1	36	1.1	35	1.3	albuterol, budesonide-formoterol, fluticasone-vilanterol, fluticasone-salmeterol, ipratropium-albuterol, mometasone-formoterol
Selective Serotonin Reuptake Inhibitors	**367**	**8.8**	**245**	**7.7**	**222**	**8.3**	citalopram, escitalopram, fluoxetine, paroxetine, sertraline
Thyroid Hormones	**145**	**3.5**	**93**	**2.9**	**83**	**3.1**	levothyroxine, liothyronine, thyroid
Topical Acne Products	56	1.3	24	0.8	20	0.8	adapalene, azelaic acid, benzoyl peroxide, clindamycin, dapsone, erythromycin, metronidazole, sulfacetamide, tretinoin
Topical Antifungals	77	1.9	18	0.6	15	0.6	ciclopirox, clotrimazole, ketoconazole, miconazole, nystatin, nystatin-triamcinolone, terbinafine

Medication Class	2-month n=4,158 n	%	4-month n=3,189 n	%	6-month n=2,660 n	%	Medication Observed Within Class
Topical Corticosteroids	119	2.9	50	1.6	45	1.7	betamethasone, clobetasol, desonide, desoximetasone, fluocinolone, fluocinonide, hydrocortisone, mometasone, triamcinolone