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Determining the exposure of maternal medicines through breastfeeding: the UmbrelLACT study protocol—a contribution from the ConcePTION project

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ABSTRACT

Introduction Breastfeeding is beneficial for the health of the mother and child. However, at least 50% of postpartum women need pharmacotherapy, and this number is rising due to the increasing prevalence of chronic diseases and pregnancies at a later age. Making informed decisions on medicine use while breastfeeding is often challenging, considering the extensive information gap on medicine exposure and safety during lactation. This can result in the unnecessary cessation of breastfeeding, the avoidance of pharmacotherapy or the off-label use of medicines. The UmbrelLACT study aims to collect data on human milk transfer of maternal medicines, child exposure and general health outcomes. Additionally, the predictive performance of lactation and paediatric physiologically based pharmacokinetic (PBPK) models, a promising tool to predict medicine exposure in special populations, will be evaluated.

Methods and analysis Each year, we expect to recruit 5–15 breastfeeding mothers using pharmacotherapy via the University Hospitals Leuven, the BELpREG project (pregnancy registry in Belgium) or external health facilities. Each request and compound will be evaluated on relevance (ie, added value to available scientific evidence) and feasibility (including access to analytical assays). Participants will be requested to complete at least one questionnaire on maternal and child's general health and collect human milk samples over 24 hours. Optionally, two maternal and one child's blood samples can be collected. The maternal medicine concentration in human milk will be determined along with the estimation of the medicine intake (eg, daily infant dose and relative infant dose) and systemic exposure of the breastfed child. The predictive performance of PBPK models will be assessed by comparing the observed concentrations in human milk and plasma to the PBPK predictions.

Ethics and dissemination This study has been approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204). Results will be published in peer-reviewed journals and presented at (inter)national scientific meetings.

Trial registration number NCT06042803.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ There is still an extensive information gap regarding medicine exposure and safety during breastfeeding. Few case studies on selected medicines have been conducted. However, a diversity of study methods have been used for these investigations.

WHAT THIS STUDY HOPES TO ADD

⇒ This prospective observational study aimed to obtain a generic protocol (umbrella approach) for clinical lactation studies to generate more knowledge on medicine safety during lactation. The presence of ethics and biobank approvals can facilitate rapid patient inclusion and study performance in terms of logistics and feasibility.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The data collected will provide new insights into the transfer of medicines to human milk and support the desired interplay between case reports and physiologically based pharmacokinetic predictions in this research field. Despite centre-specific regulations, the protocol provides a general workflow that can be used as a guide for future clinical lactation studies in and outside our institution.

INTRODUCTION

Breastfeeding is highly recommended by the WHO, more specifically exclusive breastfeeding up to 6 months after birth and continued partially, in combination with complementary feeding, until 2 years of age. This is because breastfeeding has a positive impact on the development and general health of children. Breastfed children are less likely to suffer from childhood infections, at least in part due to antibodies in human milk, and have a lower risk of being overweight.[1] According to Castro *et al*[2] breastfeeding is also related to higher

intelligence, with a possible increase up to seven intelligence quotient points and a reduction in child morbidity and mortality.[2] In addition, breastfeeding is also beneficial for maternal health, for example, by reducing the risk of developing breast or ovarian carcinoma.[3]

At least 50% of women need pharmacotherapy in the postpartum period, and this proportion has been rising due to the increasing prevalence of chronic diseases and later-age pregnancies.[4] Meanwhile, an immense information gap regarding the safety of medicines during lactation still exists today, complicating evidence-based decisions on the use and selection of medicines during breastfeeding.[5 6] This often results in unnecessary cessation of breastfeeding or poor adherence to or avoidance of pharmacological treatment.[4 7] Furthermore, the majority of medicines are used off-label during breastfeeding, which may put the child at risk for unknown side effects.[8]

To assess the transfer of medicines in human milk, the relative infant dose (RID) and the milk-to-plasma (M/P) ratio are commonly used as parameters in clinical lactation studies. M/P ratios reported in the literature are often based on single time point assessments. However, as the concentration profiles in human milk and plasma vary individually over time and may not be exactly the same, the M/P ratio may differ significantly depending on the timing of sampling. Ideally, the M/P ratio should be based on the (24-hour) area under the concentration-time curve (AUC) in human milk and plasma.[9] Assuming that only the unbound and unionised medicine fraction will cross the blood–milk barrier, the M/P ratio can be calculated based on the physicochemical properties of a medicine (eg, pH partitioning, protein binding and distribution into milk lipid), for instance, using the non-clinical phase distribution model.[10 11]

Koshimichi *et al*[12] have developed an empirical model to predict the in vivo M/P ratio based on the physicochemical properties of the medicine (ie, polar surface area, molecular weight, lipophilicity as logP and $logD_{7.4}$ and hydrogen bond donors). However, medicines that are dependent on transporters (efflux and uptake) for their active secretion into human milk are not sufficiently well captured by this method.[12] Moreover, an issue with approaches using exposure indexes such as the RID is the arbitrary cut-off point (typically 10%), indicating safe versus non-safe exposure.[9] Importantly, the safety of the child does not only depend on the dosage that the child receives via human milk but also on the toxicity of the medicine and its major metabolites, as well as the absorption, distribution, metabolism and excretion (ADME) profile of the medicine and its metabolites in the child.

Besides the above-mentioned methods to study medicine transfer in human milk, non-clinical (in vitro and in vivo animal) experiments have been developed. Unfortunately, these experiments were often not successful in predicting human milk medicine concentrations due to species-specific differences.[13 14]

Recently, some studies on the prediction of medicine exposure in the child via breastfeeding have been performed using an in silico method, that is, physiologically based pharmacokinetic (PBPK) modelling.[15 16] PBPK modelling allows bottom-up predictions of pharmacokinetics (PK) based on the integration of population-specific physiology data with medicine-specific data on ADME and physicochemistry. These models have been accepted by regulatory authorities and the pharmaceutical industry to predict drug–drug interactions and population-specific PK.[17] Although there are limitations, these models indicate that PBPK modelling is a feasible approach predicting child exposure to maternal medicine via breastfeeding.[18] Lactation and paediatric PBPK models are currently being developed within the Innovative Medicine Initiative (IMI) project ConcePTION[i], a European public–private partnership aiming to establish an ecosystem to generate evidence-based information on the exposure and effects of medicines during pregnancy and lactation.

Breastfeeding women and their breastfed children are often excluded from clinical trials due to ethical and practical reasons, which result in a therapeutic orphan population and a huge knowledge gap.[19] Due to this existing information gap, performing clinical lactation studies is highly needed and can provide valuable information. However, a broad variability in conducting and reporting on clinical lactation studies exists where, for example, essential PK data might be missing, such as dosage or time of medicine intake relative to the sampling time.[20 21] In addition, obtaining ethics approval for samples of each individual woman and each specific compound makes conducting clinical lactation studies time-consuming, while the breastfeeding period is generally limited in time. However, the collection of in vivo human data is essential for the evaluation of lactation PBPK models. These thoroughly evaluated PBPK models will lead to a generic set of breastfeeding-specific population parameters, enabling the construction of structural PBPK frameworks for breastfeeding women and breastfed infants. Such frameworks might subsequently be applied with increasing certainty to similar medicines for which in vivo data are still lacking.

The UmbrelLACT study is a prospective, observational, clinical lactation study to collect data on human milk transfer of maternal medicines and, subsequently, data on child intake and systemic exposure through human milk and the general health outcome of the child. In addition, the results will be used to evaluate the predictive performance of lactation and paediatric PBPK models.

METHODS AND ANALYSIS

Study design

This UmbrelLACT protocol, listing the generic steps of recruitment, sampling, sample storage and data management, has been developed within an interdisciplinary team with the aim of including lactating cases using medicines for which only limited safety information during breastfeeding is available in the literature.

[i]https://www.imi-conception.eu/

Distribution of the study awareness and information may occur via different channels, that is, the University Hospitals Leuven, the BELpREG pregnancy registry in Belgium (www.belpreg.be) or external health facilities, so that interested breastfeeding women are able to contact the study team.[22] Each request and compound is evaluated on relevance (ie, added value to available scientific evidence) and feasibility (including timely access to analytical assay). Optionally, available cases in the literature or data from other biobanks with a similar sampling method can be pooled with new data achieved from the current study protocol while respecting all guidelines and regulations in the relevant biobanks to generate more insights from the pooled available observations.

This prospective observational study will evaluate the presence and transfer of medicines in human milk, along with systemic concentrations and health outcomes of the child, without interfering with the maternal pharmacological therapy as previously initiated by the women's treating physician(s). This means lactating women will not be asked by the researchers to initiate or use medicines for research purposes while breastfeeding or expressing milk. In addition, this study does not interfere with the decision to give human milk to the child through breastfeeding or expressed milk.

Due to the umbrella approach, defining a predefined sample size is challenging. We anticipate to enrol about five cases, with a maximum of 15 lactating women, per year, according to feasibility. This will provide evidence of the achievability of implementing the UmbrelLACT protocol in practice.

Inclusion and exclusion criteria

Breastfeeding women can be included when they are at least 18 years old and are exclusively or partially breastfeeding (or expressing milk) at the time of milk sampling. Eligible cases are using medicines, for any indication, for at least five half-lives of the medicine (ie, to be at a steady-state concentration of the medicine) and are willing to express and collect human milk during at least 24 hours. Mothers of twins are excluded. Their breastfed neonate (from birth up to 28 days postnatal age), infant (1 month–23 months) or preschool child (2–6 years) can be included if the gestational age is at least 24 weeks and if written informed parental consent is obtained.

Study visits

Screening visit

Study information and contact details of the study team are distributed to individual, eligible mothers in the University Hospitals Leuven via the BELpREG initiative or external health facilities.[22] Interested breastfeeding women can contact the study team. Subsequently, a screening visit (by phone, video call or at an already planned real-life consultation for medical follow-up) will be planned to explain the study and discuss informed consent in case of interest for participation (see online supplemental file 1) (table 1).

Characteristics from the mother and child and the maternal pharmacotherapy, such as listing medicine intake during the 3 days prior to sampling, will be collected via a self-reported questionnaire, according to the Food and Drug Administration (FDA) guidelines on clinical lactation studies and PBPK analyses.[23 24] This includes medical data to interpret maternal medicine exposure (eg, confounding factors such as smoking, alcohol and renal function), child exposure (eg, maturational factors, medicine, etc) and to adequately evaluate the PBPK models (eg, maternal biometry, renal and liver function). The medical data to be collected can be found in the online supplemental file 2.

Sampling day

After inclusion, a sampling day is planned at least 2 weeks postpartum (non-colostrum phase). Steady-state intake of the medicine and the possibility of milk expression over 24 hours are requested. If the participant gives consent for additional sampling days, the interval should be at least 1 week and preferably 2–3 months for chronic treatment (see table 1). Human milk sampling is performed at the patient's home or during hospitalisation for medical reasons, with self-directed sampling instructions provided (see online supplemental file 3). A member of the study team is generally present during the first human milk sample collection to assist with the procedure and is afterwards available during the 24-hour collection period. Blood sampling is performed at the patient's home or outpatient clinic at the University Hospitals Leuven by a trained member of the study team.

Human milk

The total available milk volume of one feed is collected from both breasts by using an electric pump each time the woman would normally breastfeed her child. For each sampling moment, the total volume of milk (determined using a measurement cup) and sampling time are noted to simulate the child's milk intake of a feeding session. Subsequently, 5–10 mL is transferred in a test tube for analysis (maximum 10% of the collected volume of each feed). The participant decides how the remainder of the collected milk is used.

Maternal blood

Blood collection (6–10 mL EDTA or another tube, depending on the compound) will be performed within a 1-hour interval from the first feeding (expressing) after medicine intake and 24 hours after medicine intake (preferably with milk collection within 1 hour of blood sampling).

Children's blood

Blood collection from the child will be performed on the same day as maternal sampling if parental consent is obtained. A maximum of 5% of the total blood volume of the child[25] will be collected in an EDTA or another tube, depending on the type of compounds.

Table 1 Overview of the timing of the study visits and investigations of included patients.

	Screening visit	Sampling day 1	Sampling day 2 (optional*)	Sampling day 3 (optional*)	Follow-up children †
Signed informed consent from mother with parental informed consent for child	X				
Collecting medical data of the mother and child	X	X	(X)	(X)	
Collecting medicine list with last intake and medicine data during 3 days prior to the sampling day	X	X	(X)	(X)	
Collecting medicine-specific information (formulation, timing, dose and confounders)		X	(X)	(X)	
Collecting 24-hour human milk samples, starting at the time of medicine intake		X	(X)	(X)	
Collecting two maternal blood samples: one at the time of the first milk pumping session after medicine intake and one at the last pumping session of the 24-hour period		(X)	(X)	(X)	
Collecting a single child's blood sample within the 24-hour period of milk collection, if approval of the parent(s) is obtained		(X)	(X)	(X)	
Questionnaire-1 about the general health of the child until the day of sampling (see online supplemental file)		X	(X)	(X)	
Questionnaire-2 about the general health of the child (see online supplemental file)					X

Investigations, which are optional, are mentioned between brackets.
*In the case of multiple sampling days, a minimum lag time of 1 week between sampling days will be maintained. For chronic treatment, second or third sampling can be performed with a lag time of 2 months.
†Two weeks after the last sampling day in the case of an acute treatment; and 2 months after the last sampling day in the case of a chronic treatment. In the case of a combination of acute and chronic treatment, the questionnaire will be sent 2 weeks and 2 months after the last sampling day.

Milk samples will be stored in the fridge (4°C) at the patient's home for a maximum of 24 hours, transported on ice, together with the optional blood samples, and finally stored at −80°C until bioanalysis. Blood samples will be centrifuged (10 min, 3000×g and 4°C) and the plasma (supernatant) will be frozen at −80°C until bioanalysis. Specific additional sample handling can be added, depending on the compound(s) of interest. If the participant is taking a second compound of interest, the samples can be analysed for that compound as well.

Variables related to the general health of the child, such as growth, hospital admissions and medicine intake, will be questioned. The first questionnaire will be given to the parents on the sampling day and the second will be given 2 weeks (in the case of short-term treatment) or 2 months (in the case of chronic treatment) after the milk and/or blood collection (see online supplemental files 4,5). If an acute and chronic treatment is combined, the participants will be asked to complete the questionnaire at 2 weeks and 2 months after the last sampling day.

Biochemical analysis

For the quantification of the concentration of medicines in the milk and blood samples, liquid chromatography with tandem mass spectrometry (LC-MS/MS) will mainly be used, or a different method depending on the compound(s), at a facility where the requested assay(s) is/are or will easily become available for human milk or another matrix. The exploration of the required method of bioanalysis and its availability is part of the feasibility assessment. If a sensitive LC-MS/MS method, or a different method depending on the compound(s), needs to be developed, the recovery, specificity, linearity, precision and accuracy of this method will be determined prior to determining the human milk and plasma concentrations of the milk samples.[21]

Healthy volunteers

Milk (100–300 mL) and plasma samples (15–20 mL) of healthy volunteers, breastfeeding women without pharmacotherapy for an underlying medical condition, are required for method development of new milk and plasma assays, validation of the analytical methods and development of improved PBPK models. According to the European Medicines Agency (EMA) guidelines on bioanalytical method validation, initial donations from six healthy volunteers are required, and for each new assay development, subsequent donations are needed.[26] Besides an informed consent form, a questionnaire will be used to identify the exposure of healthy volunteers to,

for example, nicotine, caffeine and alcohol at the time of sampling (see online supplemental files 6,7).

Biobank

All milk and blood samples collected from patients and healthy volunteers will be handled, transported and stored according to the developed standard operating procedures. Storage of the samples will occur at UZ/KU Leuven (biobank approval received on 25 November 2022). After bioanalysis, the leftover samples will be stored for 10 years at UZ/KU Leuven.

Outcomes

Outcomes will be reported by performing descriptive statistics using Microsoft Excel, R and Rstudio (R Foundation for Statistical Computing). Since this is an exploratory clinical study, results should be interpreted with caution. If feasible, we aim to collect several cases per compound.

Primary outcome

The primary outcome of the included cases will be the quantification of the concentration of medicines in human milk. Subsequently, the 24-hour AUC-based M/P ratio will be determined, if at least two paired plasma and milk concentrations are available or if the AUC in plasma can be extracted from the literature (Equation 1).

$$\text{M/P ratio} = \frac{\text{AUC}_{\text{human milk}}}{\text{AUC}_{\text{plasma}}} \quad (1)$$

However, the M/P ratio for a single time point will be calculated using the paired milk and plasma samples. Furthermore, milk and plasma PK parameters of medicines and relevant metabolites will be estimated, such as the area under the milk concentration–time curve, the average concentrations (Cave, ie, AUC divided by collection and/or dosing interval), mean milk concentration, peak and trough milk concentration and time to reach peak milk concentration (if available, depending on dosing and lactation regimen). The plasma PK parameters, such as AUC, (time to) peak plasma concentration, plasma clearance (CL) or apparent oral CL, apparent volume of distribution and terminal half-life, will be compared with scientific literature results, if available.

Secondary outcomes

First, an estimation of the child's exposure to maternal medicine via human milk will be calculated using the daily infant dosage (DID, mg/kg/day) for the mother–child pair (Equation 2).

For the mother–child pair:

$$DID\left(\frac{\frac{mg}{kg}}{day}\right) = \sum_{i=1}^{n}\left(\frac{Milk\ Concentration_i\left(\frac{mg}{L}\right) * Milk\ Volume_i\ (L)}{Infant\ weight\ (kg)}\right) \quad (2)$$

Furthermore, the DID (mg/kg/day) will be calculated for an exclusively breastfed child with a milk intake of 150 mL/kg/day and, to estimate the child's risk, of 200 mL/kg/day (Equation 3), as well as the RID (%) (Equation 4).[24]

For an exclusively breastfed child:

$$DID\left(\frac{\frac{mg}{kg}}{day}\right) = Average\ Steady-State\ Milk\ Concentration\left(\frac{mg}{L}\right) \times Infant\ Milk\ Intake\left(\frac{\frac{L}{kg}}{day}\right) \quad (3)$$

$$\text{RID}\ (\%) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Daily\ Maternal\ Dose\left(\frac{mg}{day}\right)/Maternal\ Weight\ (kg)} \times 100 \quad (4)$$

The estimated DID via human milk will further be compared with, and divided by, the approved therapeutic dose in children, resulting in the relative infant therapeutic dose ($\text{RID}_{\text{therapeutic}}$) (Equation 5).

$$\text{RID}_{therapeutic}\ (\%) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Daily\ Therapeutic\ Infant\ Dosage\left(\frac{\frac{mg}{kg}}{day}\right)} \times 100 \quad (5)$$

Moreover, the average infant medicine plasma concentration at steady state (Css, ave) will be estimated (Equation 6).

$$Average\ Infant\ Medicine\ Plasma\ Concentration\left(\frac{mg}{L}\right) = \frac{DID\left(\frac{\frac{mg}{kg}}{day}\right)}{Apparent\ Oral\ Clearance_{Infants}\left(\frac{\frac{L}{h}}{kg}\right) \times 24h} \quad (6)$$

The relative infant exposure via breastfeeding will be determined by calculating the child/maternal plasma ratio based on the paired mother–child plasma sample, upon availability of the child's plasma.

Third, maternal questionnaires will be used as an instrument to investigate the health outcome of the exposed children up to a maximum of 2 months after the last sampling day and will provide valuable, although limited, information on the potential side effects of maternal medicines' use in the breastfed child.

Finally, PBPK modelling according to Jones *et al*[27] will be explored.[27 28] Maternal PBPK models allow for predicting the concentration–time profile of the medicines in plasma and human milk and to predict PK parameters (eg, AUC and C_{max} in plasma and human milk, M/P ratio, DID and RID).[29] In addition, paediatric PBPK models can be used to predict the child's systemic exposure (eg, plasma concentration-time profile, AUC and C_{max}). The data acquired from this study could be used to evaluate and validate the predictive performance of the developed PBPK models by comparing the observed data to the predicted concentration and parameters (such as M/P ratio), as adequate evaluation of PBPK models can be achieved with relatively few data and cases. Consequently, the child's systemic exposure and the exposure-related child risks, such as the relative exposure, will be predicted by using this bottom-up approach and will be evaluated if data is available. This is done in accordance with the 'Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation' from EMA and 'Physiologically Based Pharmacokinetic Analyses—Format and Content' from the FDA.[23 30]

Research experiences

A screening and enrollment log will be used while conducting this UmbrelLACT study. Based on this screening log, we will be able to report on the experiences of the patients, such as reasons for not participating in this study or the feasibility of data and sample collection.

Patient and public involvement

This UmbrelLACT study protocol was created as part of the IMI ConcePTION project and finds its origin in the advice requests the (clinical) research team receives regarding medicine safety during breastfeeding. Furthermore, the feasibility of the 24-hour human milk collection period was successfully executed in a recently published case report of our group.[31] The project is compliant with the WHO breastfeeding recommendations.[1]

Ethics and dissemination

This study has been approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204; 20/01/2023). Patient data and samples will be pseudonymised.

To recruit participants, the UmbrelLACT study has been shared through the website (www.belpreg.be/borstvoeding/) and the social media accounts of the BELpREG initiative. Furthermore, this study has been shared with healthcare providers, such as paediatricians, obstetricians, midwives and lactation consultants.

Study results will be published in peer-reviewed journals and will be presented at (inter)national scientific meetings.

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Contributors MVN, NN, KA and AS conceived this project. MVN, NN, MC, KA and AS participated in the trial design. The first draft of the manuscript was written by MVN and NN and revised by MC, KVC, AE, PA, KA and AS. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Competing interests K.A. is deputy editor in chief and A.S. an Editorial board member of the journal BMJ PO. P.A. is co-owner of the company BioNotus GCV. The remaining authors declare no conflict of interest.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the Ethics Committee Research UZ/KU Leuven (internal study number S67204; 20/01/2023). Participants gave informed consent to participate in the study before taking part.

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