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Maternal drugs and breastfeeding: Risk assessment from pharmacokinetics to safety evidence – A contribution from the ConcePTION project

Short title: Maternal drugs and breastfeeding

Evelina Cardoso[1], Anaëlle Monfort[2,3,4], Ema Ferreira[3,4], Hedvig Nordeng[5,6], Ursula Winterfeld[7], Karel Allegaert[8,9,10,11], Peggy Gandia[12], Monia Guidi[13,14], Alice Panchaud[1,15]

[1] Service of Pharmacy, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

[2] Platform of Biopharmacy, Faculty of Pharmacy, University of Montreal, Montreal, H3T 1J4 QC, Canada.

[3] CHU Sainte-Justine, Montreal, H3T 1C5 QC, Canada.

[4] Faculty of Pharmacy, University of Montreal, Montreal, H3C 3J7 QC, Canada.

[5] Pharmacoepidemiology and Drug Safety Research Group, Department of Pharmacy, PharmaTox Strategic Initiative, Faculty of Mathematics and Natural Sciences, University of Oslo, 0316 Oslo, Norway

[6] Department of Child Health and Development, Norwegian Institute of Public Health, 0473 Oslo, Norway

[7] Swiss Teratogen Information Service, Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

[8] Child and Youth Institute, KU Leuven, Herestraat 49, 3000 Leuven, Belgium

[9] Department of Development and Regeneration, KU Leuven, 3000 Leuven, Belgium

[10] Department of Pharmaceutical and Pharmacological Sciences, KU Leuven, 3000 Leuven, Belgium

[11] Department of Hospital Pharmacy, Erasmus MC, 3000 GA Rotterdam, the Netherlands

[12] Laboratory of Pharmacokinetics and Toxicology, Purpan Hospital, University Hospital of Toulouse, 31073 Toulouse, France

[13] Service of Clinical Pharmacology, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

[14] Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, 1011 Lausanne, Switzerland

[15] Institute of Primary Health Care (BIHAM), University of Bern, 3012 Bern, Switzerland

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Corresponding author : Evelina Cardoso
Service de pharmacie, CHUV
Rue du Bugnon 46
1011 Lausanne, Suisse
Evelina.cardoso@chuv.ch

Abstract:

Human milk is the most appropriate form of nutrition for infants while taking medication during the postpartum period is common. Discontinuation of breastfeeding is sometimes wrongly recommended for fear of adverse effects in the breastfed infant whereas only a few drugs are strictly contraindicated while breastfeeding. Most drugs are transferred from the mother's blood to the milk, but the breastfed infant usually ingests a small drug amount through human milk. As population-based evidence is still scarce on safety of drugs during breastfeeding, risk assessment relies on the little clinical evidence available and on pharmacokinetic principles, as well as on specialized sources of information that are essential for clinical decision-making. Risk assessment should not only be based on the drug's potential risk for the breastfed infant but should always take into account the benefits associated to breastfeeding, the risks of untreated maternal disease and the maternal willingness to breastfeed. Identifying situations with potential for drug accumulation in the breastfed infant is decisive while assessing the risk. Health care providers should always assume that mothers will be concerned and use risk communication as a key to ensure medication adherence and prevent unnecessary interruption of breastfeeding. When a mother still expresses concerns, decision support algorithms may facilitate communication and some strategies can be offered to minimize the drug exposure in the breastfed infant even when clinically not justified.

Keywords: breastfeeding, drugs, pharmacokinetics, risk assessment, safety

List of abbreviations

C_{milk}	Drug concentration in human milk
M/P	Milk-to-plasma ratio
PK	Pharmacokinetics
RID	Relative infant dose
V_{milk}	Milk volume

Introduction

Human milk is the most appropriate form of nutrition for infants. Moreover, psychological and physical benefits of breastfeeding on the health of both the mother and the breastfed infant are numerous and well known [1,2]. For these reasons, several organizations, such as the World Health Organization (WHO) and the American Academy of Pediatrics (AAP), recommend exclusive breastfeeding for the first 6 months of life followed by continued breastfeeding up to 2 years as complementary food is introduced [3].

Drug therapy during the postpartum period is common. Some women may need to take a new medication during breastfeeding, while others are on a chronic medication and desire to breastfeed. A recent review reports that more than 50% of postpartum women take at least one drug [4]. For these women, the discontinuation of breastfeeding may be sometimes wrongly recommended for fear of adverse effects in the breastfed infant. In fact, only a few drugs are associated with a potential harm for the nursing infant and thus are strictly contraindicated while breastfeeding (e.g. radioactive compounds). According to the available evidence provided by clinical experience, pharmacological and pharmacokinetic (PK) reasoning, many drugs can be taken by breastfeeding mothers without significant risks for the infants. In absence of robust and clear recommendations in the medical literature, drug compatibility with breastfeeding must be assessed on a case-by-case basis to ensure that the benefits outweigh the risks for the breastfed infant, but also to avoid an unjustified interruption of breastfeeding. The potential consequences of a maternal treatment for the breastfed infant are almost always closely related to systemic drug exposure in the infant. Most drugs are transferred from the mother's blood to the milk, but the breastfed infant is generally only exposed to small amounts of the drug through human milk. Because of the absence of epidemiological studies on drug safety while breastfeeding, estimating drug transfer into human milk and infant's exposure are the usual approaches used to assess the safety of a drug intake while breastfeeding.

This article presents the PK principles governing the drug transfer from mother to infant through human milk and discusses several practical aspects to enable health care providers to make a rational risk assessment.

PK principles of human milk drugs transfer

The drug transfer from mother to infant can be represented by a three-compartment PK model: maternal plasma compartment, human milk compartment and infant plasma compartment (Figure 1).

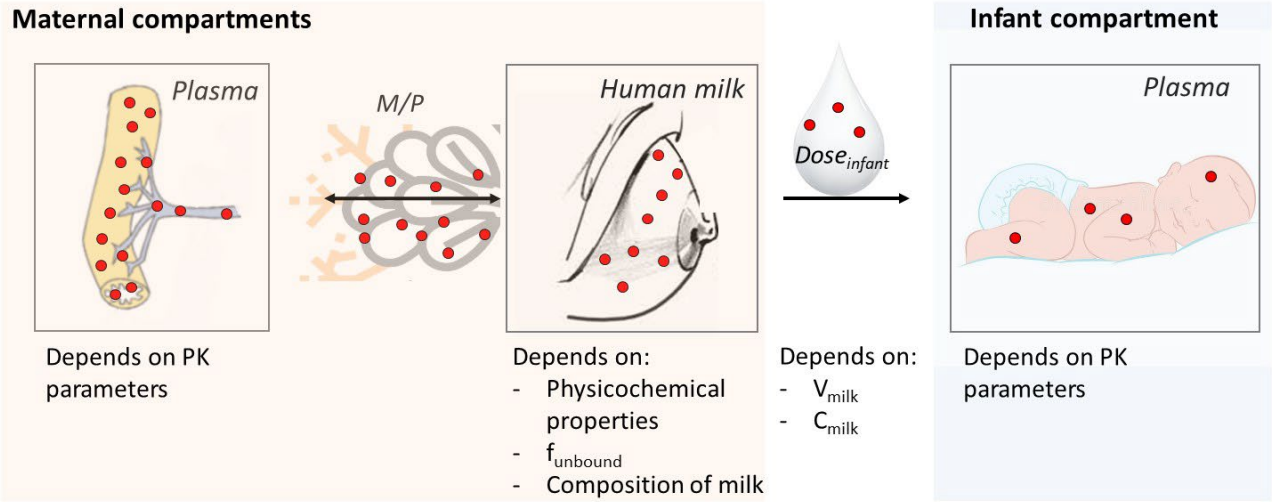

Figure 1. Pharmacokinetic model of the drug transfer from mother to infant.

C_{milk} : drug concentration in human milk ; $Dose_{infant}$: ingested dose by the breastfed infant; $f_{unbound}$: unbound fraction ; M/P: milk-to-plasma ratio; PK: pharmacokinetics ; V_{milk} : volume of human milk ingested. Composition of milk refers to e.g. lipids and ions, and physicochemical properties includes e.g. molecular weight, charge, lipophilicity. Drug is represented by red dots.

<u>*Maternal plasma compartment*</u>

The drug transfer into human milk depends primarily on the maternal plasma concentration that in turn depends on the drug dosage and several PK factors [5].

The bioavailability

The bioavailability refers to the fraction of the administered drug that reaches the systemic circulation in an unchanged form. This parameter primarily depends on the route of administration. Bioavailability is usually incomplete for most routes of administration due to drug absorption and first pass metabolism, with the exception of intravenous administration for which the bioavailability is 100%. The administration route has an impact on the infant exposure to the maternal drug. For example, inhaled bronchodilators used in the treatment of asthma, such as salmeterol or terbutaline, have a low systemic passage in mothers and

therefore are not expected to be excreted in significant amounts in human milk. Hence, their use during breastfeeding is considered acceptable despite the lack of concentration data in human milk [6].

The volume of distribution

Once the drug reaches the systemic circulation, it is distributed in the general circulation (i.e. transport in the body's tissues and organs). The drug distribution depends on the affinity of the drug to both plasma and tissue proteins. High plasma protein binding decreases the ability of the drug to distribute in compartments other than blood. The volume of distribution characterizes the distribution of the drug in the body. A drug with a high volume of distribution leaves the blood compartment to a large extent to be concentrated in one or more tissues resulting in generally low blood levels. A smaller proportion of the maternal dose is therefore available for the transfer into milk, but the drug will be found in traces in milk for a longer time.

The half-life

The elimination half-life is the time required to reduce the drug concentration in the body by half. This parameter makes it possible to estimate the amount of drug remaining in the mother's blood. In general, after four half-lives, more than 90% of the drug is eliminated from the body and complete elimination is expected after seven half-lives. This parameter is very important to estimate the likelihood of drug accumulation in the nursing infant.

The biotransformation of drug in active metabolites

During the elimination phase of the drug, pharmacologically active metabolites may be produced. The potency and the half-lives of these metabolites should be considered when assessing the risk in breastfed infants.

Human milk compartment

The amount of drug available through human milk is low as it reflects on the maternal plasma concentration and not on the maternal dose (i.e. because of the dilution in the maternal body). Furthermore, drug transfer from plasma to human milk is influenced by different drug physicochemical properties and by milk composition [7]. Most drugs are transferred from blood into human milk by passive diffusion following a concentration gradient. Only unbound

(i.e. not bound to plasma proteins) and nonionized molecules (i.e. without any charge) can diffuse through the mammary epithelium to reach the milk storage alveoli. Since the pH of milk is slightly more acidic than that of plasma, weak bases tend to accumulate in milk, in a process commonly called "ion trapping" [8]. Inversely, weak acids are found in lower concentrations in milk when compared to plasma. Moreover, diffusion is facilitated for lipophilic and low molecular weight molecules. On the contrary, drugs with a high molecular weight, like heparins and insulins, are not excreted in high amounts into human milk. For some drugs, the transfer into human milk is facilitated by a transporter, such as the breast cancer resistance protein (BCRP) [9].

Variations in the lipid amount in human milk have an impact on the transfer of some drugs into milk. Indeed, fat-soluble molecules are more concentrated in a milk rich in lipids, like mature milk compared to colostrum. Moreover, with a lipid content that increases during the feed, fat-soluble drugs are more concentrated at the end than at the beginning of the feeding.

The milk-to-plasma ratio (M/P) is a parameter that estimates the propensity of a drug to transfer from the maternal blood to the milk [10]. This parameter is usually defined by calculating the ratio of drug concentrations measured simultaneously in milk and in maternal blood, ideally after reaching the steady state. The M/P is widely used to compare the transfer in the human milk between different drugs. However, it should be noted that this parameter does not reflect the drug exposure in the breastfed infant and remains not very precise as it is often estimated on a limited number of measurements.

Infant plasma compartment

The dose ingested by the infant through breastfeeding depends on the drug concentration in the human milk (C_{milk}) and the milk volume (V_{milk}) ingested by the infant at each feeding time. The daily infant dose can be calculated by summing up the drug intakes over 24 h as follows:

$$Daily\ infant\ dose\ [mg/kg/day] = \sum_{i=1}^{n} {C_{milk}}^{i}[mg/mL] \times {V_{milk}}^{i}\ [mL/kg/day] \qquad \text{(eq.1)}$$

where *i* denotes the feeding time and *n* the number of feeding per day.

In practice, because of rare information on drug concentration in human milk, a single C_{milk} value can be assumed at each feeding and used together with the daily V_{milk} to estimate the daily infant dose. Alternatively, it is possible to use the maternal plasma concentration (C_{plasma}

$_{maternal}$) measured or available in drug monographs at a given time after drug administration and to multiply it by the M/P (if available) and daily V_{milk} (equation 2).

$$Daily\ infant\ dose\ [mg/kg/day] = C_{plasma\ maternal}[mg/mL] \times M/P \times V_{milk}[mL/kg/day]$$

(eq.2)

The maximal concentration (C_{max}) in plasma or milk can be used to assess the "worst case scenario". The V_{milk} ingested by the infant is also another important factor to consider. A value of 150 mL per kilogram per day of infant body weight for an exclusively breastfed healthy infant is often assumed in the PK literature [11]. The importance of this component in the above equation allows to quickly understand that the level of exposure is correlated to the ingested V_{milk} (full breastfeeding > partial breastfeeding > colostrum during the first few days postpartum before milk comes in).

To compare the dose received by the breastfed infant to a dose inducing a pharmacological (adverse)-effect, the relative infant dose (RID) is calculated by reporting the daily infant dose divided by the maternal dose (equation 3). When the drug is used in pediatrics, it is then possible to compare the calculated infant dose with a pediatric dose, which provides not only information on the level of exposure but some reassurance on its safety profile for the nursing infant.

$$RID = \frac{Daily\ infant\ dose\ [mg/kg/day]}{Maternal\ dose\ [mg/kg/day]} \times 100 \qquad \text{(eq.3)}$$

Finally, the PK in the breastfed infant, which is different from that in adults, is a key element to consider in the assessment of the systemic exposure of a drug. The maternal drug is delivered into the infant digestive tract through the human milk. Thus, the oral bioavailability of the drug determines the systemic exposure. Unfortunately, this PK parameter in infants is generally unknown. A common approach when a drug is known to be orally bioavailable, is to assume a 100% bioavailability, so to assess the systemic exposure using a “worst case scenario” approach. For therapeutic classes with a digestive absorption known to be very low (e.g. aminoglycoside class of antibiotics), breastfeeding is often considered as acceptable, even in absence of information on infant systemic exposure. In the event of relevant absorption, the elimination capacity of the infant is a crucial element. Premature babies, newborns and infants less than 2-3 months are at greater risk of drug accumulation due to immature hepatic and renal functions [12,13]. The glomerular filtration and the cytochrome

P450 enzymes activity, which metabolize a large number of drugs, are particularly different in infants compared to adults [14]. Thus, conditions with even slower elimination/metabolism and long half-lives are considered as important risk factors for accumulation and, consequently, for reaching levels of systemic exposure with potential pharmacological effects.

Up-to-date and valid information sources needed to assess risk of a drug in the breastfed infant

As evidence is still scarce on safety of drugs during breastfeeding, risk assessment relies on the little clinical evidence available and on the PK principles described above. RID is the parameter commonly used to estimate the level of exposure to a maternal drug in the breastfed infant. This parameter as well as evidence on the available clinical outcomes of infants exposed to a drug through human milk are only available in specialized sources of information written by experts. These information sources are essential for clinical decision-making. As a matter of fact, for most drugs, the breastfeeding labeling subsection provides overly cautious information that is less useful for making evidence-based clinical decisions than specialized sources of information. Fortunately, several up-to-date resources are available for health care providers, including Hale's medications & mothers' milk [15], Briggs Drugs in Pregnancy and Lactation [16], as well as the National Library of Medicine's database on drugs and lactation, LactMed [6]. They include several information, such as PK data (e.g. M/P, RID), risk classification, possible adverse effects in the breastfed infant and suggestions of therapeutic alternatives. Hale and Briggs are both available in a paper format, as well as in an online version. LactMed is a free and frequently updated online database that is derived from the scientific literature. Moreover, some websites, such as e-lactancia (in English and Spanish) [17], Embryotox (in German) [18] and Le CRAT (in French) [19], are reliable sources directly accessible to parents, which is also important given that internet is frequently consulted when looking for information.

In addition to medical literature, health care providers, and sometimes the general population, can contact the Teratology Information Services (TIS) centers for information and individual risk assessments in the field of the safety of medication use during spermatogenesis, pregnancy and breastfeeding. These centers of expertise provide free information and advice, and they can prospectively collect high quality data on reported cases of exposure and their outcome. These data are pooled at a network level (e.g. European

Network of Teratology Information Services – ENTIS [20]) to improve knowledge on drug safety during breastfeeding.

These specialized information sources also help in integrating the other elements that need to be considered during risk assessment, such as the health of the infant, the drug toxicity profile and the presence or absence of adverse events reported in the breastfed infant.

Finally, there is a great hope that the ConcePTION project will help generate new evidence on drug excretion in human milk in the next decades. ConcePTION is a project funded by the Innovative Medicines Initiative, a private-public partnership with the goal to design and build a lasting ecosystem of data collections, methods, people and infrastructures, that allow generation and dissemination of evidence on medicine safety in pregnancy and lactation [21].

Key practical principles for risk assessment

The decision to use a drug during breastfeeding should be **based on a favorable benefit-risk analysis for the mother and the infant**. In addition to the potential risk of a drug for the breastfed infant, several important factors such as the benefits associated with breastfeeding, the risks of untreated maternal disease and the maternal willingness to breastfeed are important elements to consider. If some drugs can cause a potential risk for the breastfed infant, abruptly discontinuing a needed treatment can also lead to an exacerbation of the maternal disease, which itself poses a risk for the breastfed infant (e.g. epilepsy related seizure during infant care).

The benefit-risk assessment needs to be **based on up-to-date evidence and PK reasoning** to prevent unnecessary interruption of breastfeeding or a delay of a required treatment. Only specialized sources of information should be considered when making therapeutic decisions.

The **risk associated with drugs is not the same throughout the breastfeeding period**. The level of drug exposure in the breastfed infant evolves as the infant grows and develops. Indeed, the volume of milk intake changes over time from a few milliliters in the first days of life leading to non significant exposure (e.g. analgesic in the postpartum while breastfeeding is acceptable whatever the drug is) to more than one liter of milk for an older fully breastfed infant. Maturation in transporters, metabolic enzymes and renal function are all factors that may vary considerably with the growth and development of the infant and that can have an important impact on the drug exposure in the infant [13,22,23].

The level of **exposure to a drug in the breastfed infant is correlated with the level of systemic exposure in the mother**. The dose and route of administration are important factors to consider when assessing the risk for a nursing infant. The topical route of administration (e.g. application to the skin, ocular, nasal or auricular instillations, inhalation, topical treatment targeting the intestine) results in a lower exposure than oral or intravenous administration. Single or occasional drug intake leads to lower exposure compared to chronic treatment.

In most cases, **in utero exposure to a treatment is much higher than exposure through human milk except in case of accumulation in the breastfed infant**. Thus, when a mother has been taking a chronic treatment throughout pregnancy, it is the additional risk linked to an often lower exposure through human milk that needs to be assessed for the breastfeeding period. Identifying situations with potential for drug accumulation in the breastfed infant is decisive in this case.

Health care providers should assume that mothers will be concerned about drug effects for their breastfed infant. Thus, risk communication is a key to ensure medication adherence and prevent unnecessary interruption of breastfeeding. The information provided should state what is known about the risks for the nursing infant, the benefit of breastfeeding and the risks of not treating the maternal disease. Moreover, it is important to inform women why the package insert provides an over cautious statement on the use of her treatment in breastfeeding.

Strategies to minimize the drug exposure in breastfed infant

Some precautions can be taken to minimize the exposure in breastfed infants in case a potential concern is described for the assessed treatment or when it enables to finally convince a patient that is not fully reassured even though clinically not justified. According to the half-life of the drug and the frequency of the drug intake, several exposure limitation strategies can be considered (Figure 2):

a) When requiring a **single dose or occasional intake of a drug**, mothers may be advised to continue to stimulate milk production by expressing and discarding their milk, and to resume breastfeeding after 4 half-lives of the drug required to eliminate 94% of the drug. If possible, the mother can prepare by storing her milk before taking the drug. For example, breastfeeding discontinuation during the 24 hours following a

methotrexate administration is recommended as precaution due to its toxicity profile [24]. Of note, giving a bottle to a fully nursing infant can jeopardize breastfeeding by nipple confusion.

b) When the mothers require **multiple doses of a drug with a short half-life** (e.g. 1-3 hours), the infant exposure can be reduced by taking the drug immediately after a feeding around the time of drug intake.

c) When the mothers require **multiple doses of a drug with a long half-life**, clinical monitoring of the expected adverse reactions during the first 4 weeks of breastfeeding or time after start of treatment is possible.

d) When the mother is taking a **chronic treatment that she already had during pregnancy**, it is important to communicate that in utero exposure to a treatment is much higher than exposure through human milk when there is no accumulation in the breastfed infant. Identifying situations with potential for drug accumulation in the breastfed infant is the decisive point in this case.

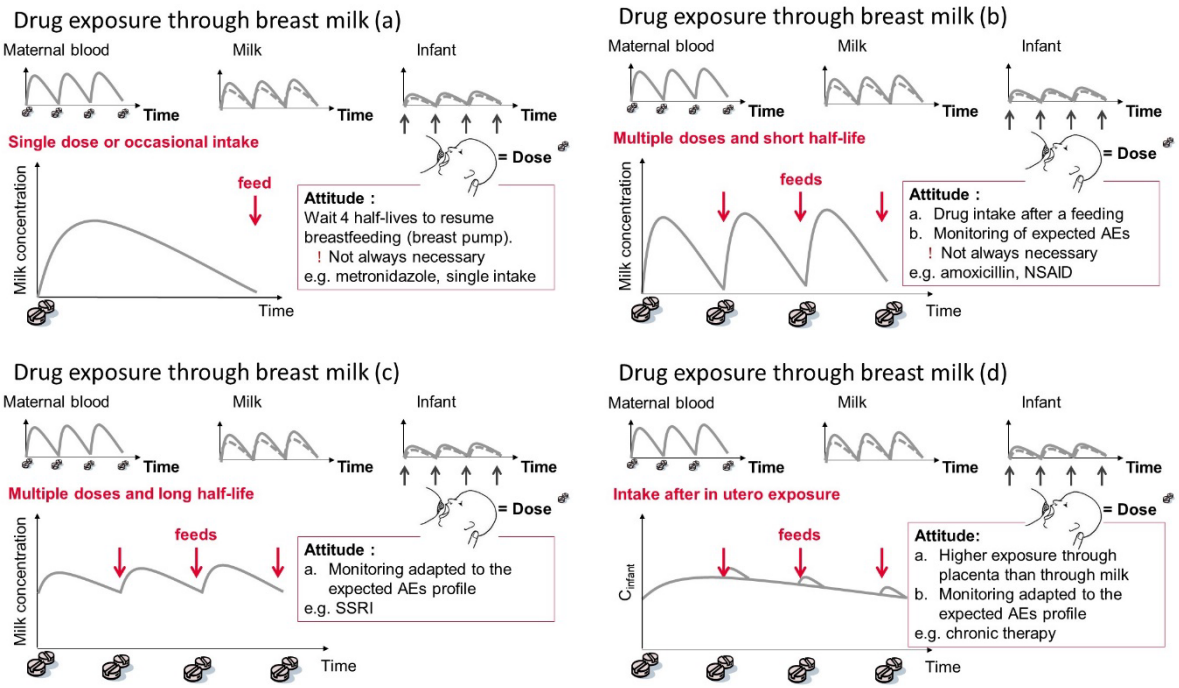

Figure 2. Strategies to mitigate and communicate the risk to patients.

AEs : adverse effects ; C_{infant} : plasma infant concentration ; NSAID : non-steroidal anti-inflammatory drug ; SSRI : selective serotonin reuptake inhibitor

Finally, to increase safety information of drugs for breastfed infants, it is essential to report observed adverse events, or the cases in which no adverse events occurred, to the regional pharmacovigilance centers.

The Figure 3 presents an algorithm that summarizes the principles described above for shared decision-making with women requiring a medication and willing to breastfeed.

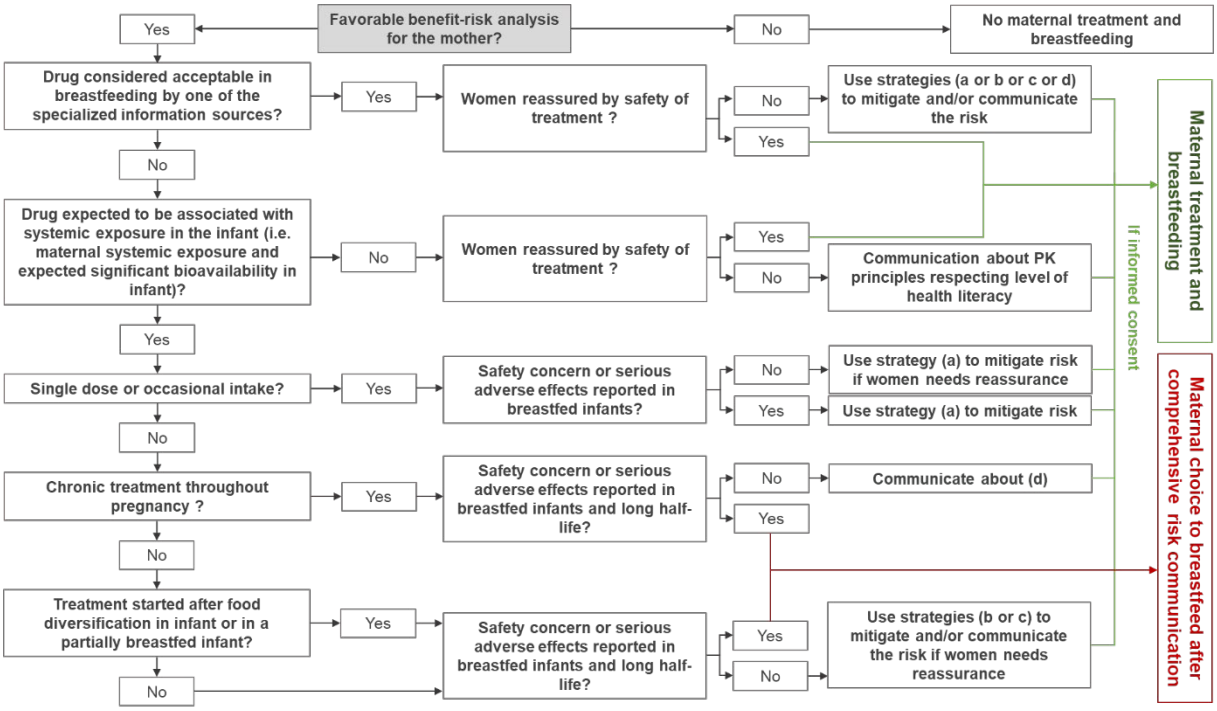

Figure 3. Algorithm for shared decision-making with women requiring a drug and willing to breastfeed.

Conclusion

Maternal drug intake does only rarely require interruption of breastfeeding. According to the available information so far, most drugs are transferred in human milk in minimal levels for the breastfed child. However, drug accumulation in the breastfed infant can lead to situations at risk. The benefit-risk assessment should be made using evidence-based information sources while considering several elements including what is known about the risks for the nursing infant, the consequences of untreated maternal disease and the benefits of breastfeeding. The PK in both the mother and the infant is an essential component when assessing drug exposure of the breastfed infant, especially when little clinical information is available. When a mother still expresses concerns, decision support algorithms may facilitate communication and some strategies can be offered to minimize the exposure in the breastfed infant even

when clinically not justified. The exploration of the drug transfer in human milk for a wide range of drugs is underway through several approaches (i.e. in vitro, in vivo, physiologically based pharmacokinetic modeling and population pharmacokinetic modeling) in the framework of the European consortium ConcePTION, in order to provide more precise answers.

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Disclosure of interests

The authors declare that they have no competing interest.

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