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Methodological Limitations in Assessing the Safety of Direct Oral Anticoagulants During Lactation

Bartosz Pomirski
Provincial Polyclinical Hospital in Plock of Marcina Kacprzaka, Medyczna 19, 09–400 Plock, Poland
bartosz.pomirski@gmail.com
https://orcid.org/0009-0004-4868-0073

Anna Wilewska
Provincial Polyclinical Hospital in Plock of Marcina Kacprzaka, Medyczna 19, 09–400 Plock, Poland
wilewskaanna2000@gmail.com
https://orcid.org/0009-0001-5136-4598

Agata Pomirska
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
pomirska.agata@gmail.com
https://orcid.org/0009-0009-5367-7123

Julia Biernikiewicz
Mazowiecki Szpital Brodnowski, Kondratowicza 8, 03-242 Warsaw, Poland
biernikiewiczjulia@gmail.com
https://orcid.org/0009-0004-1192-9365

Konstanty Alabrudziński
The Nicolaus Copernicus Municipal Polyclinical Hospital in Olsztyn, Niepodległości 44, 10-045 Olsztyn, Poland
konstanty.alabrudzinski@gmail.com
https://orcid.org/0009-0008-4729-0937

Milena Biernikiewicz
Wroclaw Medical University, Wybrzeze Ludwika Pasteura 1, 50-367 Wroclaw, Poland
milenabiernikiewicz@gmail.com
https://orcid.org/0009-0006-7288-6965

Agnieszka Borowiec
The Regional Specialist Hospital in Biala Podlaska, Terebelska 57/65, 21-500 Biala Podlaska, Poland
borowiec.agn@gmail.com
https://orcid.org/0000-0002-1428-170X

Aleksandra Dach
Pomeranian Medical University of Szczecin, Rybacka 1, 70-204 Szczecin, Poland,
dach.aleksandra@icloud.com
https://orcid.org/0009-0009-8798-5415

Kinga Borowiec
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
kingaborowiec07@gmail.com
https://orcid.org/0009-0000-5546-9787

Paulina Kwaśniewska
Medical University of Warsaw, Żwirki i Wigury 61, 02-091 Warsaw, Poland
paulinakwasniewska12@gmail.com
https://orcid.org/0009-0009-4677-3387

Corresponding Author
Bartosz Pomirski, E-mail: bartosz.pomirski@gmail.com

Abstract

Introduction. Direct oral anticoagulants (DOACs) offer superior clinical convenience over traditional therapies. However, their use in postpartum women is heavily constrained, routinely forcing a choice between optimal venous thromboembolism (VTE) prophylaxis, and breastfeeding due to a lack of high-certainty safety data.

Objective. This review synthesizes clinical data regarding DOAC excretion into human breast milk, evaluates current pharmacokinetic indices and outlines the methodological limitations hindering definitive clinical guidelines.

Materials and Methods. A comprehensive literature search was conducted in the PubMed database up to June 2026 to evaluate human clinical data concerning maternal DOAC therapy and subsequent infant exposure metrics.

Results. Available evidence indicates distinct profiles among DOACs. Apixaban exhibits significant accumulation in breast milk driven by active BCRP transport, yielding an unacceptable Relative Infant Dose (RID) of up to 21%. Conversely, rivaroxaban and dabigatran demonstrate promising safety margins, with RIDs substantially below the 10% safety threshold. Data regarding edoxaban remain constrained to an isolated case report.

Conclusion. Contemporary literature is severely undermined by methodological vulnerabilities, including small sample sizes, lack of standardized milk fraction sampling (foremilk vs. hindmilk), and non-steady-state sampling parameters. Due to the suspension of breastfeeding during trials, investigators frequently rely on mathematical proxies like the Relative Infant Dose Daily (RIDD). To establish high-certainty guidelines, future protocols must address these flaws, utilize advanced PBPK modelling and implement long-term observational registries to evaluate infant safety.

Keywords: Direct oral anticoagulant(DOAC), Lactation, Breastfeeding, Pharmacokinetics, Venous thromboembolism(VTE)

1. Introduction

Pregnancy and the puerperium are associated with numerous physiological changes in the female body, aimed at sustaining the pregnancy and ensuring neonatal well-being. However, some of these adaptations carry hidden biological costs, such as an increased risk of venous thromboembolism (VTE) [1]. Research indicates that this risk escalates during pregnancy and peaks during the postpartum period, where it can be up to 60-fold higher compared to non-pregnant controls [2]. This profound increase in postpartum risk stems from endothelial damage during delivery, a sharp rise in procoagulant factors, and an acute inflammatory response [3]. Consequently, pulmonary embolism represents the third leading cause of maternal mortality in developed countries, posing a critical challenge for modern healthcare systems [4].

Currently, the prophylaxis and management of VTE rely primarily on anticoagulant therapy [5,6]. Recommended pharmacological options include low-molecular-weight heparin (LMWH), unfractionated heparin (UFH), fondaparinux, danaparoid, vitamin K antagonists (VKAs), and direct oral anticoagulants (DOACs), including apixaban, dabigatran, edoxaban, and rivaroxaban [7]. Unfortunately, the clinical utility of these agents is significantly constrained by patient-specific contraindications. For postpartum women, the primary barrier is breastfeeding. Many clinicians advise against breastfeeding due to concerns that DOACs transfer into breast milk could adversely affect the infant.

However, contemporary research increasingly highlights the importance of lactation. Breastfeeding plays a fundamental role in both the psychological and physical development of the infant, promoting healthy nervous and immune system maturation while fostering the maternal-infant emotional bond [8]. Furthermore, the benefits extend to the mother, including a reduced risk of cardiovascular disease, hypertension, and diabetes, accelerated postpartum recovery, and a protective effect against postpartum depression [8].

These multifaceted benefits have led researchers to re-evaluate anticoagulants that traditionally required the cessation of breastfeeding—particularly those classes whose breast milk transfer and subsequent impact on infant development remain largely uncharacterized. Because these agents lack definitive evidence of neonatal toxicity, questions are increasingly raised regarding the clinical justification for their absolute exclusion during lactation. DOACs represent one such pharmacological group [9].

Currently, their use in lactating women requires the discontinuation of breastfeeding due to a paucity of data regarding their excretion into breast milk and subsequent infant exposure. Consequently, there is a lack of evidence concerning potential adverse effects, which could manifest as an increased risk of hemorrhage typical for this drug class [10,11,12], or developmental and growth impairments specific to this age group [13]. Conversely, compared to traditional anticoagulants, DOACs offer superior clinical convenience. Unlike heparins, fondaparinux, or danaparoid, they do not require subcutaneous injection [14,15]. Moreover, unlike VKAs, they eliminate the need for routine International Normalized Ratio (INR) monitoring, frequent dose adjustments, and strict dietary restrictions [16].

This paper outlines the current methodological limitations that hinder the progress of clinical research on DOACs in lactating women. To establish a framework for this evaluation, the subsequent sections will delineate the principles of lactation pharmacokinetics, review the indices used to predict infant drug toxicity during breastfeeding, and synthesize existing clinical data regarding DOAC use during lactation.

2. Pharmacokinetics in Lactation – Theoretical Framework

Drugs undergo complex processes of transformation and distribution between various body fluids. With the onset of lactation, maternal pharmacokinetics change significantly, primarily due to the excretion of xenobiotics into breast milk. This transfer depends heavily on the physicochemical properties of the drug—such as its degree of ionization, plasma protein binding, molecular weight, and lipophilicity—as well as the properties of the breast milk itself, including its pH and lipid content [17]. The multiplicity of these variables poses a substantial challenge for mathematical modeling of theoretical drug transfer. This is further complicated by the dynamic composition of breast milk, which alters both the concentration of active substances and their subsequent bioavailability to the infant, as absorption is modulated by drug-protein binding within the milk [18].

Crucially, certain agents undergo active transport via specific efflux pumps, rendering estimation models based solely on passive diffusion inaccurate. Apixaban serves as a prime example of this phenomenon [19]. Its relatively high excretion into breast milk compared to other DOACs is driven primarily by active transport mediated by the Breast Cancer Resistance Protein (BCRP) transporter [20].

To standardize the assessment of drug transfer into breast milk and evaluate subsequent infant exposure, the Milk-to-Plasma (M/P) ratio and the Relative Infant Dose (RID) are widely

utilized [21]. These pharmacokinetic indices allow investigators to estimate the weight-adjusted dose received by the infant, thereby quantifying the risk of clinical exposure [22,23]. Generally, an M/P ratio greater than 1.0 indicates a propensity for the drug to accumulate in breast milk, whereas an RID less than 10% is conventionally considered safe and acceptable for compatible breastfeeding [9,24].

However, a fundamental limitation of these parameters in clinical research is their high susceptibility to confounding variables. Each study introduces specific clinical baselines under which the RID and M/P values fluctuate. Beyond the previously mentioned factors, these variables include the infant's weight and chronological age (which dictate metabolic and clearance capacity), as well as the timing of maternal drug administration relative to breastfeeding sessions [17,18]. Consequently, there is a growing consensus among researchers toward utilizing Physiologically Based Pharmacokinetic (PBPK) modeling. PBPK models allow for the dynamic simulation of M/P ratios and RID, providing far greater predictive precision than standard, static clinical sampling [22,25].

3. Review of Available Clinical Data

A comprehensive literature search in the PubMed database up to June 2026 - utilizing the search strings "direct oral anticoagulants" AND (lactation OR "breast feeding" OR "breast milk") and (DOAC OR NOAC OR edoxaban OR apixaban OR rivaroxaban OR dabigatran) AND (lactation OR "breast feeding" OR "breast milk" OR "infant risk") - yielded only a limited number of pharmacokinetic studies focusing on DOACs during lactation. To map the pharmacokinetics of these agents, existing literature relies predominantly on animal models and biological profiling of breast milk collected from postpartum women. In isolated cases, drug concentrations were evaluated in breastfed infants or analyzed using epithelial glandular tissue cultures to evaluate transmembrane permeability [20,22,24]. These preliminary studies have clarified certain safety concerns associated with specific DOACs. The following section synthesizes these clinical findings, intentionally omitting animal data due to profound interspecies pharmacokinetic discrepancies that limit their clinical translation to human lactation.

For apixaban, clinical data demonstrate significant accumulation in breast milk driven by the previously detailed mechanism of active transport, presenting a high risk of exposure for the breastfed infant. The reported RID for apixaban ranged from 12.78% to 21%, with a corresponding M/P ratio of 2.61 to 2.67 [20,22,26,27]. These values indicate that any future

clinical application of apixaban in lactating women will demand extreme caution, rigorous risk-benefit stratification, and secondary prioritization relative to other DOACs that exhibit a more favorable safety profile.

In contrast, clinical evaluations of rivaroxaban demonstrated encouraging parameters, with an RID ranging between 0.82% and 5% and an M/P ratio between 0.27 and 0.45 [12,22,20,27,28,29]. These values fall substantially below the standard 10% safety threshold, rendering rivaroxaban a highly promising candidate for further clinical investigation.

The pharmacokinetic profile of dabigatran is unique among DOACs. This distinct behavior stems not only from its mechanism as a direct factor IIa inhibitor (unlike the factor Xa inhibitors mentioned above) but primarily from its formulation as a prodrug. Dabigatran etexilate must undergo systemic absorption via the gastrointestinal tract before being hydrolyzed into its active form, which contributes to its exceptionally low M/P and RID values [25]. Available clinical data report an M/P ratio between 0.01 and 0.2, while the definitive RID could not be calculated due to undetectable drug concentrations in infant plasma [30,31]. Based on these metrics, dabigatran holds the highest clinical promise for safe administration in breastfeeding mothers.

Data regarding edoxaban remain the most constrained. As the most recently approved agent among the standard DOACs, literature evaluating its safety profile is scarce. The PubMed search identified only a single clinical study investigating edoxaban administration in a postpartum, lactating patient [9,24,32]. Although the investigators did not quantify the M/P ratio or RID, no clinical bleeding tendencies or adverse hemorrhagic events were observed in the infants [32].

4. Methodological Limitations of Existing Literature

The contemporary body of evidence carries severe methodological limitations that significantly undermine the clinical utility of the data and restrict their future application. Consequently, the current evidence remains of low certainty, precluding definitive clinical conclusions regarding the safety of any DOAC class during lactation. To generate higher-quality scientific evidence and accelerate clinical translation, future research designs must systematically address these specific vulnerabilities, which are detailed below.

Small Sample Sizes and Cohorts

The vast majority of published studies are restricted to case reports or very small cohorts consisting of only a few women, often failing to measure direct drug concentrations in the infant's plasma. Consequently, drawing robust statistical conclusions regarding maternal-milk transfer or subsequent neonatal systemic exposure remains challenging. While neonatal clinical trials face substantial ethical hurdles, studies involving lactating women who have already voluntarily elected to discontinue breastfeeding are free from these constraints. A primary obstacle, however, remains the reluctance of women to participate in such trials due to various multifaceted factors. Nonetheless, investigators retain control over several of these variables and can design clinical trials to optimize recruitment. According to a study by Zhao et al., incorporating home-based study visits rather than requiring overnight stays at a research facility is a highly effective strategy to enhance participant enrollment [33]. Other proven methods to increase engagement include target-recruiting patients who may derive future benefits from the research insights, multiparous women following the birth of a subsequent child, as well as providing fair financial compensation [33]. Additionally, women exhibit a significantly higher willingness to enroll when the study is proposed by medical staff who have previously established a high-standard, trusted care relationship with them [33].

Lack of Standardization in Breast Milk Sampling

Most protocols fail to standardize or document the exact type of breast milk sample analyzed - specifically, whether the aliquot represents foremilk, hindmilk, or a completely expressed volume [9]. This omission is critical, as lipid and protein concentrations shift dynamically between foremilk and hindmilk, directly altering the ratio of protein-bound, ionized, and active, free fractions of the drug available for infant absorption. To prevent the accidental ingestion of toxic drug volumes due to variable feeding patterns, future protocols must investigate diverse milk fractions. Additionally, because the biochemical composition of breast milk matures continuously post-delivery, longitudinal sampling across different postpartum intervals is mandatory to ensure that transitional shifts do not precipitate toxic accumulations in the infant [17]. Investigators should systematically report sample volumes, extraction methods (preferably utilizing high-efficiency electric breast pumps), and chronological time elapsed since delivery.

Sampling Outside of Steady-State Pharmacokinetics

To accurately simulate real-world therapeutic exposure, drug quantification in maternal plasma and breast milk must occur only after achieving steady-state pharmacokinetics. Chronic drug administration establishes a steady-state plasma concentration that is significantly higher than that observed following a single or double initial dose. This elevated plasma baseline naturally yields higher drug concentrations in breast milk, compounding infant exposure. Unfortunately, several existing studies sampled breast milk after only a single day of therapy, systematically underestimating the true exposure metrics that occur during long-term maternal treatment [20]. Furthermore, milk samples should be systematically collected at the predicted maternal peak plasma concentration within the dosing interval to establish a reliable upper limit of safety for DOAC exposure.

Cessation of Breastfeeding during Clinical Trials

To eliminate all risk of neonatal exposure, researchers routinely mandate the absolute cessation of breastfeeding for the duration of pharmacokinetic sampling. However, recent pediatric trials evaluating therapeutic doses of each of the previously mentioned DOACs have demonstrated favorable safety profiles with a low incidence of adverse events [34,35,36,37]. These data suggest that future lactation studies carrying a minor risk of low-level infant exposure are ethically justifiable, as the absolute drug dose delivered via breast milk is predicted to be orders of magnitude lower than these proven, safe therapeutic pediatric doses. For example, in a pivotal study by Ayuk et al., the investigators concluded that postpartum maternal dabigatran therapy yielded infant exposure levels approximately 100,000-fold lower than the concentration required to alter neonatal coagulation metrics [30].

Because breastfeeding was suspended in most trials, definitive RID data are missing. Investigators frequently substituted this parameter with the Relative Infant Dose Daily (RIDD), calculated against an assumed standardized daily milk intake [22]. While this mathematical proxy is acceptable for early-stage safety screening, establishing high-certainty data requires protocols that maintain active breastfeeding during maternal therapy. Direct clinical assessment of the infant is essential to map infant-specific metabolic clearance and identify late-stage or long-term clinical outcomes. Future clinical designs should include long-term prospective observational registries to track the physical and cognitive development of infants exposed to low-level DOACs via breast milk, thereby establishing a comprehensive short- and long-term safety profile.

5. Summary

DOACs are increasingly utilized in modern clinical practice due to their superior convenience and predictable profile. However, because they entered a market already saturated with decades-old, well-established anticoagulants, there is a distinct lack of commercial incentives to fund clinical trials for "orphan" patient populations, such as lactating women. While restricting their use due to a lack of safety data is a legally conservative approach, it effectively stigmatizes postpartum patients and forces an unnecessary choice between optimal maternal therapy and breastfeeding. In an era where global healthcare systems increasingly prioritize maternal and infant well-being, resolving these clinical gaps should be a priority. The promising, albeit limited, data presented in this review should encourage investigators to conduct more standardized studies, while this critical analysis serves as a methodological roadmap to improve the quality of future clinical research.

Disclosure

Author Contributions:

Conceptualization: Bartosz Pomirski, Agata Pomirska, Anna Wilewska;

Methodology: Julia Biernikiewicz, Milena Biernikiewicz;

Validation: Agnieszka Borowiec, Julia Biernikiewicz;

Formal Analysis: Konstanty Alabrudziński, Milena Biernikiewicz;

Investigation: Julia Bierniewicz, Paulina Kwaśniewska;

Resources: Aleksandra Dach, Anna Wilewska;

Data Curation: Agnieszka Borowiec, Kinga Borowiec;

Writing-Rough Preparation: Bartosz Pomirski;

Writing-Review and Editing: Bartosz Pomirski, Agata Pomirska;

Visualization: Konstanty Alabrudziński, Paulina Kwaśniewska;

Supervision: Bartosz Pomirski, Agnieszka Borowiec;

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