Prioritization Report of Therapeutic Research Gaps and Needs in Pregnant, Postpartum, and Lactating Women

August 2026

Maternal and Pediatrics Precision in Therapeutics (MPRINT) Hub

This work has been supported and/or funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) grant P30HD106451.

Contents

Introduction

The Maternal and Pediatrics Precision in Therapeutics (MPRINT) Hub, funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), announces the Prioritization Report of Therapeutic Research Gaps and Needs in Pregnant, Postpartum, and Lactating (PPL) Women. This report reflects the observations and recommendations of expert working groups coordinated through the MPRINT Hub and serves as a resource for interested parties who participate in maternal and lactation drug development, therapeutics research, and clinical care. The report is also intended to guide future research in critical scientific and clinical areas that have been historically understudied in pregnant, postpartum, and lactating populations. The report should not be interpreted as National Institutes of Health (NIH) clinical recommendations or formal NIH research priorities.

Prioritization Background

The development of this report emanates from recommendations developed by the Congressionally-mandated Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), which was formed in 2016 via the 21st Century Cures Act. PRGLAC released its 2018 Report to Congress, which included 15 recommendations that focus on improving the inclusion of pregnant women and lactating women in clinical research to advance research on safe and effective therapies for pregnant women and lactating women. PRGLAC also published an Implementation Plan in 2020 to guide implementation of the PRGLAC recommendations. The charter for PRGLAC expired in 2021. While the Prioritization effort is an extension of the PRGLAC recommendations and Implementation Plan, it is independent of the PRGLAC charter. The two recommendations that establish the need for this report are recommendation 8, "Develop separate programs to study therapeutic products used off-patent in pregnant women and lactating women using the NIH BPCA as a model" and recommendation 9, "Develop programs to drive discovery and development of therapeutics and new therapeutic products for conditions specific to pregnant women and lactating women," including, subparts 8B, "Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women"; and 9A, "Create separate prioritization processes for pregnant women and lactating women". Recommendation 8B specifically recommended considering NIH's Best Pharmaceuticals for Children Act (BPCA) program as a model for developing a prioritization process. However, unlike the BPCA program, the current effort to prioritize therapeutic research needs for pregnant, postpartum, and lactating women did not have legislative authority or associated funding. Consequently, the NICHD and other NIH components have focused on leveraging existing programs for the study of existing medications using existing approaches to advance recommendation 8B. Additional information on the implementation progress of PRGLAC recommendations is available in the 2024 Report of the PRGLAC Implementation Working Group of the National Advisory Child Health and Human Development (NACHHD) Council.

In response to the 2020 PRGLAC implementation plan, NICHD and the NIH Office of Research on Women's Health (ORWH) published a 2023 Request for Information (RFI) inviting nominations for drug, vaccine, and dietary supplement research needs to be considered in the development of a priority list of therapeutic research needs for pregnant, postpartum, and lactating women. Information collected through this RFI helped assess the landscape of needs, engage key stakeholders, incorporate new data sources and analytical approaches, consider integrating new processes, and discuss who would use a list of therapeutics priorities. A total of 136 nominations across 24 therapeutic areas were received during the public comment period.

Based on these nominations, NICHD convened an inaugural stakeholder meeting in July 2024 to begin discussions on prioritization of preventive and therapeutic product research needs for use in women who are pregnant, postpartum, and lactating. Stakeholders included NIH extramural program staff, academic researchers, clinicians, and representatives from scientific professional organizations and patient advocacy organizations who registered to attend this open to the public meeting. With logistical and data science support from the MPRINT Hub, working groups were launched in summer 2025 to continue discussions from the July 2024 meeting and finalize recommendations for research gaps and research needs in other therapeutic areas not addressed previously. Working group participants also registered to participate in the discussions, which were open and non-competitive exercises that would provide publicly available knowledge that could be used by multiple stakeholders. All meetings began with a statement that NIH sought input to identify research gaps and needs and that participants were not being asked to set NIH priorities. To ensure transparency, working group participants were asked to disclose any affiliation or activity that may present a conflict of interest to the therapeutic area topic under discussion when speaking at each working group meeting. Across the prioritization discussions from 2024 - 2026, working group leads and participants were tasked with reviewing the nominations and identifying knowledge gaps and research needs for the nominated therapeutics and any other therapeutics that were deemed appropriate to consider. Working group participants had multiple opportunities to provide input on the final research needs and recommendations reflected in the 2025-2026 discussions and contained in Section 1.

Introduction to the report

The sections that follow contain the Prioritization Report of Therapeutic Research Gaps and Needs for Pregnant, Postpartum, and Lactating Women, beginning with the 2025-2026 Working Group Discussions by therapeutic area. Most of these discussions were a continuation from 2024, although three working groups, Environmental, Sleep, and Obesity, arose after 2024 based on common therapeutic nominations. Section Two summarizes therapeutic areas only discussed at the July 2024 meeting. Section Three includes therapeutic areas where nominations have not been discussed at the July 2024 meeting or in Working Groups due to constraints with time and staffing.

This report is designed to identify research gaps, indicate research needs, and provide a prioritization framework for addressing evolving research priorities. As many of the

therapeutic areas have different research landscapes, many working groups discussed wide-ranging research gaps and needs. Some broad examples include:

- Instances where there is insufficient pharmacokinetic (PK) data about Drug X during pregnancy which would be necessary to design a large, controlled clinical trial. Therefore, obtaining PK data is a priority research need for Drug X and could be achieved via opportunistic studies.
- There is a significant amount of PK data on Drug Y during pregnancy and real-world evidence (RWE) suggests positive outcomes for mothers and newborns at higher doses with no safety signal. In this case, a pivotal randomized controlled trial (RCT) is a priority research need to assess the efficacy of Drug Y.

Of note, this report was not designed to provide a priority list of therapeutics to research, nor did it extend to prioritizing the development of new drugs for conditions that do not currently have any treatment options.

Special considerations

While this report is intended to serve as a resource for researchers and clinicians and guide research in scientific areas where pregnant and lactating women have been historically understudied, the identified research gaps and needs in this report should not be interpreted to be interchangeable between each population. Indeed, pregnancy and lactation have unique physiological challenges, health implications (i.e., for the perinatal woman, fetus, and breastfed infant), and distinct research needs, which are particularly pronounced in lactation. The 2024 PRGLAC Implementation Working Group of Council Report noted that implementation progress of PRGLAC recommendations for lactating populations exhibited insufficient gains, observing that "different trial designs are needed for pregnancy therapeutic studies and lactation therapeutic studies." Working groups attempted to define topic-specific distinctions for pregnancy and lactation in the identified research gaps and needs, where appropriate. However, because of the general dearth of research specific to lactation across all working groups there were many common questions that should be considered for lactation research in any therapeutic area. These included study designs that address physiological questions such as 'what is the drug effect on milk composition?'; 'what is the amount of drug in breastmilk?'; and in the cases where the drug is transferred to the milk supply 'what is the effect of the drug on the infant consuming the milk?' Additionally, there were important comments on the current resources available to accurately assess lactation retrospectively; this discussion emphasized the need for additional infrastructure to capture necessary information. While each of the sections in this report provides lactation-specific recommendations, those presented here as special considerations are meant to also be included as general recommendations.

This report represents discussions that occurred across August 2025-January 2026 which were largely a continuation of discussions that took place in July of 2024. It is probable that additional information, changes to guidelines, or new emerging topics were not considered

during the creation of this report. However, the frameworks provided here should remain helpful in addressing research needs, even if the context shifts.

Lastly, the identified research gaps and needs contained within this report should not be interpreted as NIH clinical recommendations or formal NIH research priorities. Readers should be aware of the limitations in current research methodologies when designing studies that are responsive to the research gaps and needs.

Section 1: Therapeutic Areas Discussed in Working Groups Between July 2025 and January 2026

1. Cardiovascular and Hypertensive Disorders

Cardiovascular Disorders in PPL Populations

Background

The working group reviewed four nominated therapeutics: statins for the treatment of hypercholesterolemia and the prevention of atherosclerotic cardiovascular disease (ASCVD); and nadolol, propranolol, and sotalol for the treatment of maternal and fetal arrhythmias. Two additional therapeutics — flecainide for arrhythmia in pregnancy and rivaroxaban for venous thromboembolism — were discussed at the July 2024 Inaugural Stakeholder Meeting; recommendations for those agents are available in the 2024 meeting summary (Appendix 1). The group also discussed emerging cardiovascular agents — including sodium-glucose co-transporter-2 (SGLT2) inhibitors, neprilysin inhibitor and angiotensin receptor blocker (ARB) sacubitril/valsartan, and glucagon-like peptide 1 (GLP-1) receptor agonists— for which use in women of reproductive age is growing in the context of a limited evidence base. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors were additionally flagged as an emerging priority.

A research landscape analysis indicating the number of pharmacokinetic (PK), clinical trial (CT), and pharmacoepidemiological (PE) publications identified is provided (Appendix 2), and a brief summary of the salient findings is described in Table 1.1.

Table 1.1 Cardiovascular Priorities

Therapeutic Area	Nominations	Research Landscape Summary
Hypercholesterolemia and ASCVD Prevention	Statins	Multiple human pregnancy exposure cohorts and animal studies do not support teratogenicity[1-8]. The FDA removed the strongest pregnancy contraindication in 2021, though statins remain broadly discontinued at pregnancy recognition. NICHD-sponsored pravastatin trials showed similar frequency of serious adverse events and similar neonatal outcomes versus placebo, with lower rates of preeclampsia in the treated group[9, 10]. Outside of pregnancy, statins are standard of care for ASCVD prevention and are widely prescribed to women of reproductive age; pregnancy increases LDL-C synthesis and familial hypercholesterolemia affects approximately 1 in 200–1 in 300 individuals. Lactation data are limited across the class[11, 12]; pravastatin and rosuvastatin each have at least one lactation PK study documenting drug-in-milk levels. Despite this, breastfeeding is broadly discouraged during statin use or statins are held during breastfeeding. Concern has been raised about potential statin effects on breast milk lipid composition and downstream infant cholesterol synthesis — a question driven largely by theoretical extrapolation from statin mechanism rather than observed harm in breastfeeding infants, and one that remains unresolved. Long-term follow up of school-age children born to mothers who received pravastatin during pregnancy (as part of the NICHD trials) showed similar neuromotor, cognitive, and behavioral outcomes compared to children born to mothers who received placebo[13].
Heart Failure (HF)/ Cardiometabolic Risk	SGLT2 Inhibitors	Use is increasing in non-pregnant women of reproductive age for the treatment of HF; however, SGLT2 inhibitors are not recommended in pregnant women with HF or cardiomyopathy because of the potential risk for fetal harm[14, 15]. A case report documents empagliflozin use in pregnancy resulting in healthy offspring[16], but systematic pregnancy outcome data are absent. European guidelines advise avoidance during pregnancy. No lactation data exist across the class for milk transfer, infant renal exposure, milk production, or composition effects.
Heart Failure	Neprilysin inhibitor/ ARB Sacubitril/Valsartan	Neprilysin inhibitor/ ARBs are used in treatment of HF in non-pregnant population. There are limited data on the sacubitril/valsartan treatment for peripartum cardiomyopathy as well as its transfer to human milk. A single lactation study measuring drug-in-milk levels exists[17], with valsartan below detectable levels in milk. This study has not been sufficient to update clinical practice guidelines — illustrating

		how limited lactation data, even when present, may not meet the evidentiary threshold applied by guideline committees independently of regulatory status.
Cardiometabolic / CVD Prevention	GLP-1 Receptor Agonists	The FDA approved the use of GLP-1 agonist in obese subjects to prevent CVD risk. However, the use of GLP-1 agonists during pregnancy and lactation is generally not recommended due to limited clinical data on their safety and efficacy and potential risks to the infant[18-22]. Preliminary lactation data exist[23] but have not been incorporated into cardiovascular or obstetric guidelines. Pregnancy and lactation safety data are insufficient to guide clinical decision-making.
ASCVD Prevention	PCSK9 Inhibitors	No lactation or pregnancy safety data exist. Use in women with familial hypercholesterolemia or established ASCVD of reproductive age is increasing, and clinical decision-making occurs without any evidence base to support risk-benefit counseling.
Maternal or Fetal Tachyarrhythmias	Nadolol	Used clinically for maternal and fetal arrhythmias; considered relatively safe in pregnancy, with low risk of neonatal bradycardia and hypoglycemia[24]. Animal data show embryotoxicity at high doses in rabbits but not rats or hamsters; fetal growth restriction has been raised as a concern. Nadolol is excreted into breast milk; the FDA label notes consideration for nursing discontinuation based on neonatal effects. Lactation PK data are sparse with no systematic characterization of infant dose via breastfeeding.
	Propranolol	First-line beta-blocker for many maternal arrhythmias. Generally considered safe in pregnancy with low risk of neonatal bradycardia and hypoglycemia[24]. One PBPK modeling study exists[25]. Propranolol is excreted in human breast milk; at least one lactation PK study documents drug-in-milk concentrations. The FDA label advises caution when administered to a nursing woman. Existing lactation data have not been consistently incorporated into clinical counseling frameworks.
	Sotalol	Used for specific maternal and fetal arrhythmias; associated with QT prolongation and higher maternal adverse event rates. Nearly complete transplacental transfer documented. Lactation data exist and substantiate current FDA labeling: high breast milk concentrations have been measured (plasma: milk ratio approximately 1:5.4[26], and PBPK modeling projects infant plasma concentrations in the therapeutic range[27]. The FDA recommendation against breastfeeding is evidence-supported. Sotalol is infrequently used in clinical practice given its adverse event profile and the availability of alternatives; research prioritization should reflect this limited real-world use.

The working group identified the following research gaps and prioritized research needs across the PPL population. Pregnancy and lactation represent physiologically distinct states with distinct PK profiles, risk-benefit considerations, and study design requirements; both are addressed below.

Research Gaps

Statins

1. Lack of pregnancy-specific PK/PD data across the statin class (except for pravastatin); appropriate dosing in pregnancy is uncertain despite long clinical use outside pregnancy.
2. Limited long-term outcome data for children exposed to statins in utero, reducing the ability to complete comprehensive risk-benefit assessments for pregnant women who require ongoing therapy.
3. Insufficient data on efficacy of statins for ASCVD prevention during pregnancy; evidence for high-risk populations (familial hypercholesterolemia, prior ASCVD) is based on extrapolation from non-pregnant populations.
4. Limited evidence on effects of statin discontinuation or switching during pregnancy — the predominant clinical approach — including maternal cardiovascular outcomes.
5. Lactation data are limited across the statin class; where drug-in-milk levels have been measured (pravastatin, rosuvastatin), these data have not been consistently incorporated into clinical practice assessing individualized risk versus benefit.
6. Observational data on statin use in pregnancy and lactation are limited by low prescribing under current labeling, creating a circular evidence problem: restrictions reduce prescribing, which limits data generation, which sustains restrictions.

SGLT2 Inhibitors

1. No systematic pregnancy outcome data exist; one case report[16] documents empagliflozin use in pregnancy with healthy offspring, but there is insufficient evidence to support clinical guidance.
2. No lactation data exist across the class. For drugs whose milk transfer is entirely unstudied, active transport cannot be excluded. Infant exposure, maternal plasma level adequacy, and effects on milk production and composition are all unknown.
3. Real-world prescribing patterns and rates of inadvertent early pregnancy or postpartum exposure are uncharacterized as clinical use increases.

Sacubitril/Valsartan

1. Lack of specific data on the efficacy and safety of sacubitril/valsartan treatment for postpartum HF.

2. A single lactation study including 5 women documents valsartan below detection in milk and negligible sacubitril transfer (relative infant dose, RID < 0.25%)[17]. The study has not been sufficient to update clinical practice guidelines.
3. Effects on milk composition and production are uncharacterized for sacubitril/valsartan.
4. No infant outcome data exist for breastfed infants of mothers receiving sacubitril/valsartan.

GLP-1 Receptor Agonists

1. There are limited data on the efficacy and safety of GLP-1 receptor agonists during pregnancy that are insufficient for clinical guidance.
2. Lack of human pregnancy- and lactation-specific PK/PD data.
3. Lactation data exist on drug transfer into milk, and the FDA has updated drug labeling accordingly. However, without data on milk composition, guidelines have had difficulty formulating recommendations.

PCSK9 Inhibitors

1. No pregnancy or lactation data exist, limiting clinical decision-making for women with familial hypercholesterolemia or established ASCVD who wish to continue therapy through pregnancy or lactation.
2. For lactation specifically, active transport cannot be excluded in the complete absence of milk transfer data, making infant exposure and maternal therapeutic coverage both unknown.
3. No counseling framework exists for these high-risk populations.

Nadolol

1. Pregnancy PK data are limited; fetal growth restriction has been raised as a concern requiring further evaluation.
2. Inconsistent documentation of dose and duration in RWD limits pharmacoepidemiological analyses.
3. Limited lactation PK data; drug-in-milk levels are not systematically characterized and infant dose via breastfeeding is unknown.
4. Sparse breastfeeding safety data and no systematic characterization of infant outcomes following breastfeeding exposure.

Propranolol

1. While generally considered safe in pregnancy, PK in large studies as well as comparative data across arrhythmia indications in pregnant populations are limited.
2. Lactation PK data exist documenting drug-in-milk levels but have not been consistently incorporated into clinical counseling frameworks.

3. Limited data on infant outcomes following breastfeeding exposure; longer-term outcomes are uncharacterized.

Sotalol

1. Sotalol is infrequently used in pregnancy and during lactation given its adverse event profile and availability of alternatives; research prioritization should reflect its limited real-world utilization.
2. For the subset of patients who do require sotalol, the clinical decision between breastfeeding continuation and drug discontinuation has not been prospectively studied as a comparative question, despite the availability of supporting lactation data.
3. Awaiting Prospective Randomized Clinical Trial of Fetal Atrial Flutter & Supraventricular Tachycardia Therapy (FAST RCT) results before finalizing comparative effectiveness data for fetal arrhythmia management.

Cross-Cutting (Cardiovascular)

The working group identified several fundamental problems that cut across all cardiovascular therapeutics:

1. Existing research and clinical guidance fail to distinguish three separate lactation questions that require different study designs, different biospecimens, and different expertise to answer. Conflating them produces incomplete and often misleading guidance.
    - **Question 1 — What is happening with the milk from treated and untreated mothers?** This encompasses two distinct sub-questions: what does the underlying maternal condition do to milk composition and production independent of any treatment; and what does drug treatment do to milk composition and production, independent of transfer into milk. Both are almost never studied. For statins, the concern about effects on breast milk lipid composition and downstream infant cholesterol synthesis sits here — it is a question about what the drug does to the milk, not what the milk does to the infant. This question remains unresolved even where transfer data are reassuring, and in its unresolved state it sustains precautionary restrictions that transfer data alone cannot dispel. The milk composition question is not unique to statins; it is relevant for any drug class that could plausibly alter milk lipid content, protein, immune factors, or production volume.
    - **Question 2 — What is happening to the baby receiving the milk?** This covers both the dose the breastfeeding infant actually receives and the clinical effects on that infant — recognizing these require different study designs to answer and should not be treated as a single endpoint.
    - **Question 3 — What amount is actually being excreted in breast milk?** This is simultaneously an infant exposure question and a maternal pharmacology question. For any drug whose milk transfer is unstudied, active transport — rather

than passive diffusion — is a possibility: milk concentrations could exceed plasma concentrations, infant exposure could be substantially higher than predicted, and maternal plasma levels could be lower than intended. This risk cannot be ruled out without direct measurement and applies as a default uncertainty across all drugs in this report for which transfer data are absent. Additionally, significant drug excretion into milk by active transport may result in subtherapeutic maternal plasma concentrations, undertreatment of the underlying condition, and worse maternal outcomes. This maternal pharmacology dimension of milk excretion is almost entirely absent from the lactation research literature and from current research priorities.

2. Beyond the three lactation questions, the working group identified a broader translational problem: in many areas data are absent; in others, data exist but are not being applied in clinical practice. Fear of liability, regulatory uncertainty, and unresolved questions about milk composition effects — even where they reflect theoretical extrapolation rather than observed harm — lead to precautionary restrictions applied more conservatively during lactation than during pregnancy, and more conservatively than the available evidence base warrants. As a contemporary illustration of this pattern, published subsequent to the working group meetings: the 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia[28] imposes more restrictive recommendations for statin use during lactation than during pregnancy due to theoretical risk, despite a narrower biological risk profile in the postpartum period than during pregnancy. As a consequence, the further research required to change practice is challenging to conduct using interventional or observational designs.
3. Breastfeeding status is not reliably or standardly documented in non-obstetric postpartum settings, including cardiology encounters — a solvable infrastructure gap that limits RWE generation for all of these agents.

Prioritized Research Needs

Statins

1. Pregnancy-specific PK/PD and clinical safety studies to characterize dosing requirements and maternal-fetal transfer, including in high-risk populations (familial hypercholesterolemia, prior ASCVD).
2. Comparative effectiveness studies of statin continuation versus discontinuation during pregnancy in high-risk populations, with maternal cardiovascular outcomes as primary endpoints.
3. Studies stratified by ASCVD risk and familial hypercholesterolemia status to clarify how the maternal benefit–fetal risk balance varies across disease-severity groups.
4. Long-term child follow-up studies with larger sample size to assess dose-response effects on developmental and cardiovascular outcomes following in utero or breastfeeding exposure.

5. Lactation studies structured around all three clinical questions: (1) effects of maternal statin treatment and underlying hypercholesterolemia on milk lipid composition and production; (2) drug-in-milk concentrations and estimated infant dose; and (3) clinical outcomes in breastfed infants. These require separate study designs and should not be collapsed into a single endpoint.
6. Where PBPK modeling is employed, paired collection of observed drug-in-milk concentrations to validate models against observed measurements.
7. Active engagement with guideline-developing organizations on the evidentiary standard required to incorporate existing lactation data into recommendations, and whether current standards are calibrated appropriately to the constraints of lactation research.
8. Use of registries and RWD to capture management patterns and inform prospective trial design.
9. Development of ethical and regulatory frameworks to support inclusion of lactating women in cardiovascular trials.

SGLT2 Inhibitors

1. Enhance pregnancy outcome surveillance given increasing inadvertent early pregnancy exposure. Real-world PE studies will help to characterize prescribing patterns and exposure rates.
2. Initial PK/PD studies in pregnancy to identify safe and effective dosage.
3. Lactation PK studies characterizing drug-in-milk levels and infant exposure, ideally with simultaneous assessment of maternal plasma levels for therapeutic adequacy, as a priority given increasing postpartum prescribing.
4. Studies characterizing effects on milk production and composition.

Sacubitril/Valsartan, GLP-1 Receptor Agonists, PCSK9 Inhibitors

1. Integration of all three drug classes into cardiovascular registries with standardized pregnancy and lactation documentation.
2. For agents with existing data: involvement of experts in pregnancy/lactation pharmacology in guideline development groups to discuss what additional evidence is needed to translate existing findings into recommendations, before commissioning new studies.
3. Initial pregnancy and lactation PK studies for PCSK9 inhibitors in women with familial hypercholesterolemia or established ASCVD, including assessment of active transport potential and maternal therapeutic coverage.

Nadolol

1. PK studies in lactating women with matched maternal plasma, milk, and infant plasma sampling to characterize infant dose and assess maternal plasma levels for adequacy of therapeutic coverage.

2. Breastfeeding safety studies characterizing infant outcomes following exposure.
3. Registry-based outcome studies to capture real-world postpartum and lactation use patterns and fetal growth data in pregnancy.

Propranolol

1. Expanded PK studies in lactating women with matched milk and infant plasma sampling, with assessment of maternal plasma concentrations for therapeutic adequacy.
2. Breastfeeding outcome studies with standardized measures across institutions.
3. Active integration of existing lactation PK data into clinical counseling frameworks.

Sotalol

1. Given limited clinical use, primary near-term priority is to await FAST RCT results before finalizing sotalol-specific research prioritization.
2. For the subset of patients requiring sotalol, prospective evaluation of breastfeeding continuation versus drug discontinuation as clinical alternatives, rather than treating discontinuation as the default in the absence of comparative data.

Hypertensive Disorders, Postpartum Hypertension, and Pulmonary Arterial Hypertension in PPL Women

Background

The working group reviewed therapeutics across two clinical contexts: angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) for postpartum hypertension, and phosphodiesterase-5 (PDE5) inhibitors (tadalafil, sildenafil) for pulmonary arterial hypertension (PAH).

Postpartum hypertension is a distinct and underrecognized clinical problem: elevated blood pressure persists after hypertensive pregnancy disorders in 40–50% of women; hypertensive pregnancy disorders are a leading cause of maternal mortality between 7 days and 1 year after delivery; and elevated blood pressure can occur postpartum without antecedent hypertension in pregnancy. ACE inhibitors and ARBs are contraindicated in pregnancy due to fetal renal toxicity and are therefore primarily relevant in the postpartum and lactation context. The three lactation questions identified in the cardiovascular section apply to all therapeutics reviewed here; Question 3 — regarding the possibility of active transport and its implications for both infant exposure and maternal therapeutic coverage — is particularly salient for drugs in this section whose milk transfer is wholly unstudied.

A research landscape analysis was provided (Appendix 2), and a brief summary of the salient findings is described in Table 1.2.

Table 1.2 Hypertensive disorders and related cardiovascular priorities

Therapeutic Area	Nominations	Research Landscape Summary
Postpartum Hypertension	ACE Inhibitors (captopril, enalapril, lisinopril, perindopril, ramipril)	Captopril and enalapril are effective for postpartum hypertension including in severe postpartum preeclampsia[29-32], and are considered safe in lactation based on low infant exposure[33, 34]. One study documented minimal lisinopril milk transfer[35]. A prospective observational study on perindopril directly quantified drug-in-milk and infant plasma[36]; while one infant had undetectable plasma concentrations, two of three infants had levels equivalent to adult therapeutic peak plasma concentrations — a finding that requires further investigation. There is no lactation or postpartum hypertension data on ramipril and caution is advised. ACE inhibitors are contraindicated in pregnancy due to fetal renal toxicity.
	ARBs (valsartan, losartan, candesartan)	ARBs are contraindicated in pregnancy. In the postpartum period, losartan has been used in clinical trials for postpartum hypertension with blood pressure reduction comparable to standard agents[37, 38]. Recent lactation data are emerging: candesartan ingestion by the breastfeeding infant was 0.09% of maternal dose with undetectable infant plasma levels[39]; valsartan levels in breast milk were below detection when sacubitril/valsartan was administered[40]. Despite these data, ARBs as a class carry a recommendation to avoid during lactation in most guidelines — illustrating how available evidence can fail to reach the threshold required for guideline incorporation.
Pulmonary Arterial Hypertension (PAH)	PDE5 Inhibitors (tadalafil, sildenafil)	PDE5 inhibitors are commonly used in pregnant and lactating women with severe PAH, where untreated disease risk outweighs drug risk. In pregnancy, limited tadalafil case series data have not identified drug-associated risks; animal studies showed no adverse developmental effects[41]. Sildenafil has no human pregnancy safety data; animal studies show no adverse effects at standard doses[42]. In lactation: tadalafil has no human milk data (rat data show milk concentrations approximately 2.4-times plasma); sildenafil and its active metabolite have been detected in human milk in limited number of studies[43, 44], though effects on breastfed infants and milk production remain uncharacterized.

Research Gaps

ACE Inhibitors

1. Lactation data exist for select agents (captopril and enalapril considered safe in lactation with low infant exposure; lisinopril with minimal transfer in one study) but are limited in sample size and have not been systematically incorporated into clinical guidance across the class.
2. The perindopril finding[36]— in which two of three infants had plasma concentrations equivalent to adult therapeutic peak levels — has not been followed up and represents a safety signal requiring clarification before perindopril can be recommended for routine postpartum use in lactating women.
3. Ramipril has no postpartum or lactation data despite clinical use.
4. Effects on milk production and milk composition (Question 1) are uncharacterized across the class.
5. Whether maternal plasma concentrations remain therapeutic in the context of drug excretion into milk has not been studied for any ACE inhibitors (Question 3).

Angiotensin Receptor Blockers

1. ARBs are contraindicated in pregnancy; postpartum and lactation data represent the relevant clinical evidence base for this class.
2. Lactation data exist for candesartan (infant ingestion 0.09% of maternal dose, undetectable infant plasma[39]) and valsartan (below detection in milk when administered as sacubitril/valsartan[40]), yet ARBs as a class carry a recommendation against use in lactation in most current guidelines — consider using "individualized risk versus benefit evaluation" over a blanket recommendation against use.
3. No systematic infant outcome data exist for breastfed infants of mothers receiving ARBs.
4. Whether drug excretion into milk affects maternal therapeutic plasma levels has not been studied (Question 3).
5. Absence of standardized transition protocols for antihypertensive management across the peripartum and postpartum period accounting for breastfeeding status.

PDE5 Inhibitors

1. In pregnancy, evidence is limited to case series for tadalafil and is absent for sildenafil; both are used clinically in pregnant women with severe PAH where the risk of untreated disease outweighs drug risk, without adequate data to individualize counseling.
2. Tadalafil has no human milk data; rat data showing milk concentrations approximately 2.4-times plasma raise the possibility of active transport, making the risk profile for breastfed infant exposure unknown.

3. Sildenafil and its active metabolite have been detected in human milk in limited studies[43, 44], but effects on breastfed infants and on milk production are uncharacterized.
4. Effects of PDE5 inhibition on milk composition and production (Question 1) are uncharacterized.
5. No risk-stratified counseling framework exists for lactating women with PAH requiring PDE5 inhibitor therapy.

Cross-Cutting (Hypertension Related Therapeutics)

1. There are two gaps contributing to suboptimal care for PPL patients: in some areas data are absent; in others, data exist but are not being applied in practice. Both gaps contribute to suboptimal care for PPL patients.
2. Question 3 — the possibility of active transport and its dual implications for infant exposure and maternal therapeutic adequacy — applies with particular force in this section, where most drug classes have no lactation transfer data at all. The tadalafil rat data showing milk concentrations above plasma levels provides a concrete example of why passive diffusion cannot be assumed as a default.
3. Breastfeeding status is not reliably documented in postpartum cardiology and hypertension settings — a solvable infrastructure gap that limits RWE generation for all of these agents.
4. For several agents, guidance is more restrictive during lactation than during pregnancy despite a narrower biological risk profile postpartum underscoring an immediate need for evidence generation.

Prioritized Research Needs

ACE Inhibitors

1. PK studies for agents with no lactation data (ramipril), with matched maternal plasma, milk, and infant plasma sampling, including assessment of maternal plasma levels for therapeutic adequacy.
2. Studies characterizing effects on milk production and milk composition (Question 1) as distinct endpoints from drug transfer.
3. Systematic engagement with guideline-developing organizations on what additional evidence is needed to incorporate existing captopril and enalapril lactation data into recommendations.
4. Harmonized documentation of breastfeeding status across cardiology, maternal-fetal medicine, and primary care.

Angiotensin Receptor Blockers

1. Direct engagement with guideline-developing organizations on what additional evidence is needed to translate existing candesartan and valsartan lactation data

into clinical recommendations, before commissioning new studies that may face the same translational barrier.

2. Registry-based data capture of postpartum hypertension treatment patterns and breastfeeding outcomes.
3. Standardized peripartum antihypertensive transition protocols that account for breastfeeding status.

PDE5 Inhibitors

1. Targeted lactation PK studies for tadalafil in human milk and infant plasma, with assessment of maternal plasma concentrations, given rat data indicating above-plasma milk concentrations and the possibility of active transport.
2. Characterization of sildenafil infant exposure and outcomes in breastfeeding women receiving it for PAH.
3. Observational case series and registry-based follow-up to characterize clinical outcomes in pregnant and lactating women with PAH, recognizing RCTs are not feasible in this high-risk population.
4. Risk-stratified counseling frameworks for lactating women with PAH pending comprehensive data.

Overarching Research Framework for Cardiovascular and Hypertension Therapeutics in PPL Populations

The working group recognizes the opportunity in organizing future research in these areas around the following principles:

1. **Distinguish pregnancy, postpartum, and lactation as separate research contexts.** These are physiologically distinct states with different PK profiles, different risk-benefit considerations, and different study design requirements. Distinguishing them may produce separate guidance that will serve adequately all of these populations.
2. **Organize lactation research around all three clinical questions explicitly.** Study designs, biospecimen collection, and outcome measures should be specified for each question separately. Question 1 (what is happening with the milk, treated and untreated) requires milk composition and production endpoints alongside or independent of transfer measurements. Question 2 (what is happening to the baby) requires both dose estimation and clinical outcome assessment. Question 3 (what dose is being excreted) requires simultaneous maternal plasma level assessment to evaluate therapeutic adequacy alongside infant exposure.
3. **Apply active transport as a default uncertainty for all drugs without milk transfer data.** As passive diffusion cannot be assumed in the absence of direct measurement, active transport, with the potential for above-plasma milk concentrations, higher-than-expected infant exposure, and subtherapeutic

maternal plasma levels must be acknowledged as an alternative possibility requiring targeted study.

4. **Pair PBPK modeling with observed concentration data.** Validated PBPK models against observed drug-in-milk and maternal plasma concentrations could be valuable alternative models/tools in informing prescribing guidance or labeling.
5. **Standardize documentation of breastfeeding status across all non-obstetric postpartum clinical settings.** This is a solvable infrastructure problem that immediately expands the utility of existing registries and RWD across all cardiovascular therapeutics.
6. **Address the evidentiary threshold problem before commissioning new studies.** Guideline-developing organizations should be involved in discussions on establishing standards/pathways for the lactating evidence achievable for this population. Generating more data will not be sufficient if the infrastructure for recognizing and translating that data into clinical guidance is not also addressed.

There is broad consensus across the working group that the care of pregnant, postpartum, and lactating patients with cardiovascular and hypertensive disease is suboptimal. The absence of data in many areas and the underutilization of existing data in others are all meaningful contributors. The goal of the research priorities in this report is to close both gaps: generating new evidence where it is absent and ensuring that evidence already generated reaches clinical practice.

2. Environmental

The environmental working group reviewed two therapeutics: chemical and mineral sunscreens. A research landscape analysis was provided (Appendix 2), and a summary of the salient findings is presented in Table 2.1.

Table 2.1 Environmental Priorities

Therapeutic area	Nominations	Research Landscape analysis summary
Sun exposure/ Skin cancer	Chemical sunscreens*	1. ~53 pregnancy PK and PE publications;~22 fetal PK and PE publications exist for oxybenzone 2. Isolated clinical trial for PABA during pregnancy[45] 3. Almost no studies for other chemical sunscreens in any of the populations
	Mineral† sunscreens	1. Less than 5 PK or PE publications for zinc oxide and titanium dioxide during pregnancy; 1 PE in fetus 2. No other population specific publications 3. Only one CT in case of lactating individuals for zinc oxide[46]

*Chemical sunscreens include avobenzone, octocrylene, octyl methoxycinnamate, oxybenzone, para-aminobenzoic acid (PABA)

†Mineral sunscreens include zinc oxide and titanium dioxide

The group also reviewed additional information from pertinent literature (Table 2.2).

Table 2.2 Summary of Evidence in Sunscreen[47]

Chemical	FDA 2019 proposed classification as safe and effective	Absorbed through the skin	Hormone disruption*	Skin allergy or other concerns*
Oxybenzone	No	Yes[a]	Strong	Some
Octinoxate (Octyl methoxycinnamate)	No	Yes[a]	Strong	Some
Homosalate	No	Yes[a]	Some	Some
Octisalate	No	Yes[a]	No/weak	No/weak
Octocrylene	No	Yes[a]	No/weak	Some
Avobenzone	No	Yes[a]	Some	Some
Titanium dioxide	Yes	No/weak	No/weak	Inhalation concerns
Zinc oxide	Yes	No/weak	No/weak	Inhalation concerns

* Strong, some, or no/weak denote the level of evidence available

[a] Skin absorption evaluation based on findings from Matta et al.[48]

Matta et. al. demonstrated systemic absorption of the active ingredients from topical application of the sunscreen in healthy participants, with levels higher than the threshold set by FDA for waiving future safety studies related to the sunscreen (Table 2.3)[48].

Table 2.3 Maximum Plasma Concentrations for Sunscreen Active Ingredients[48]

Ingredient Name	Lotion	Aerosol Spray	Nonaerosal Spray	Pump Spray
Avobenzone	7.1 (73.9)	3.5 (70.9)	3.5 (73.0)	3.3 (47.8)
Oxybenzone	258.1 (53.0)	180.1 (57.3)	NA	NA
Octocrylene	7.8 (87.1)	6.6 (78.1)	6.6 (103.9)	NA
Homosalate	NA	23.1 (68.0)	17.9 (61.7)	13.9 (70.2)
Octisalate	NA	5.1 (81.6)	5.8 (77.4)	4.6 (97.6)
Octinoxate	NA	NA	7.9 (86.5)	5.2 (68.2)

Geometric mean (ng/mL) (coefficient **of variation, %)**; NA, not analyzed

Questions for Consideration

The working group considered the following questions:

1. Are the drugs represented in the RFI nominations representative of the topic area and align with use (standard of care?) If not, what is needed to assess missing sunscreens (therapeutics)?
2. What are the long-term effects of use of chemical sunscreens in the prenatal, antenatal, and lactation phase?
3. What are the impacts on pregnancy and the developing fetus for those who actively use chemical sunscreen while pregnant?
4. How much do the active chemicals in sunscreens enter breast milk and what side effects could the exposure cause for the breastfed baby?
5. What is the impact of chemical sunscreens on the skin microbiome?
6. Is there a need for prospective pregnancy cohorts comparing the use of chemical-based sunscreens against mineral-based sunscreens, physical barriers (e.g. hats), and no protective measures used?
7. What kinds of tissues and biomarkers are optimal to address the impact of chemical sunscreen in PPL populations – fetal/newborn tissues (placental tissues, amniotic fluid, cord blood, newborn blood spots); parental tissues (blood, urine, human milk).

Research Gaps

1. Targeted review of European Union regulatory actions that restricted certain sunscreen ingredients to inform U.S. research prioritization - restricting certain ultraviolet filters like oxybenzone (benzophenone-3) which is now limited/banned in

some uses due to safety concerns, and proposing bans for others, such as octocrylene for similar reasons.
2. Landscape analyses of country-specific guidance where sunscreen use is prevalent (e.g., Australia) for PPL population-relevant recommendations.
3. Study design comparators: need evidence comparing users vs. non-users; concern that messaging may bias exposure, complicating causal inference.
4. Physiologic trade-offs: Sunscreen may impact vitamin D synthesis; weigh potential endocrine and metabolic effects in pregnancy and lactation.
5. Heat and exposure context: high temperature is a risk factor for birth defects; capture use-context (e.g., frequency and duration, geographical location, occupation/leisure) when assessing sunscreen benefits/risks.
6. Product complexity: assess inactive ingredients, label accuracy, and variability across products; potential for low-concentration constituents (e.g., the example of formaldehyde in hair products but not listed among ingredients) to contribute to risk.
7. Ethics/outreach: considering known concerns such as endocrine disruption, should PPL populations be counseled on or encouraged to adopt alternative sun protection strategies instead of relying on chemical sunscreens?

Prioritized Research Needs

1. Prevalence of use in PPL populations (overall and by age, geography, or product type; consider day creams with sun protection factor (SPF) vs. dedicated sunscreens).
2. Exposure kinetics and transfer: in-utero, placental transfer, and breast milk levels for key active ingredients.
3. Comparative safety/effectiveness: chemical vs. mineral sunscreens (including duration of use), users vs. non-users; building of a prospective cohort was raised but not prioritized as a standalone effort versus being combined with the study of other medications. Alternatively, the use of existing cohorts and surveillance databases was proposed.
4. Mechanistic or toxicology endpoints relevant to PPL populations: impact of endocrine disruption on fetal development or hormone-sensitive tissues (e.g., mammary gland); oxidative stress, inflammation, and immune regulation markers that may mediate disease risk.
5. Mixtures/combined exposures: consider combinatorial exposure and interaction effects across multiple skin-applied products.
6. Evaluation of daily creams with SPF may warrant inclusion of boundaries or definitions since many people obtain sunscreen exposure via non-sunscreen products.
7. Promote research to address long-term data regarding mothers who use chemical sunscreens on outcomes in their offsprings – pregnancy cohort is needed

3. Hematology

The working group reviewed three therapeutics: direct oral anticoagulants (DOACs) for deep vein thrombosis and pulmonary embolism indications; intravenous (IV) iron formulations for treatment of iron deficiency, with and without anemia; and hydroxyurea as a disease-modifying therapy for sickle cell anemia (SCA). A research landscape analysis was provided (Appendix 2), and the working group further reviewed a select set of relevant clinical trials[49-51]. A brief summary of the salient findings is described in Table 3.1.

Direct Oral Anticoagulants (DOAC)

Background on DOACs

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT) and pulmonary embolism. Direct oral anticoagulants are indicated for both DVT and pulmonary embolism. The risk of VTE increases with pregnancy and occurs in 1-2 out of 1,000 pregnancies. Some pregnant women are at even higher risk if they have additional inherited or acquired risk factors as well as older age and comorbid conditions. VTE is a leading etiology of preventable maternal morbidity and mortality. It should be noted that more than 70% of pregnancy-associated VTE events occur in the postpartum period. Current guidelines recommend anticoagulation for a minimum of 6 weeks postpartum, with a total treatment duration of at least 3 months. Because approximately 85% of mothers initiate breastfeeding, these treatment timelines substantially overlap, making the compatibility of anticoagulant therapy with breastfeeding a critical clinical consideration.

Active transport of medications into human milk—including apixaban—poses dual clinical concerns. In addition to potential exposure risk for the breastfed infant, enhanced drug elimination via milk may reduce maternal plasma concentrations, increasing the risk of subtherapeutic anticoagulation. Physiologically based pharmacokinetic (PBPK) models should therefore evaluate drug transfer into milk, infant tolerance to drug exposure, and maternal PK response to altered plasma levels.

Nominated agents: DOACs: decrease thrombin generation to prevent thrombus formation (apixaban, edoxaban, betrixaban, rivaroxaban, dabigatran)

Commonly used agents: Low molecular weight heparin (LMWH) enoxaparin (subcutaneous), unfractionated heparin (UFH) (subcutaneous or intravenous).

Currently there have been a few studies done on DOACs, mostly concentrating on lactating women. Table 3.2, Table 3.3, and Table 3.4 show a literature review for rivaroxaban, apixaban, and dabigatran respectively. Table 3.5 shows a literature review for pediatric DOAC models. Table 3.6 shows two references for apixaban use during pregnancy. The take-home message from Butler comparing apixaban and rivaroxaban safety for breastfeeding women was that apixaban would not be a suitable agent for breastfeeding women during the postnatal period, while rivaroxaban shows significant promise due to low infant exposure and warrants further investigation[52].

Table 3.1 Hematology Priorities

Nominations	Therapeutic area	Research Landscape analysis	Prioritized Research Area
Direct oral anticoagulants	Venous thromboembolism, proximal DVT and pulmonary embolism	• DOAC use in pregnant/lactating women has very limited clinical data. • The current standard of care is LMWH; warfarin and UFH have limitations. • DOACs may offer advantages (oral, no monitoring). • Existing data scattered across literature; additional data may exist in FDA clinical pharmacology reviews.	1. Conduct observational studies using EHR/administrative databases to characterize maternal use patterns. 2. Conduct mixed-methods studies of patient and provider preferences. Collect and analyze observational data for patients not lactating. 3. Evaluate DOACs for postpartum thromboprophylaxis. 4. Conduct PK studies of drug passage into breast milk; include maternal + infant plasma sampling. 5. Build PBPK models using existing datasets and MPRINT modeling capacity. 6. Utilize infrastructure: MFMU, NRN, PTN, UCSD's Mommy's Milk Biorepository[a].
Intravenous (IV) iron formulations for treatment of iron deficiency anemia (IDA) and iron deficiency without anemia (IDWA) in pregnancy	Iron deficiency anemia	• IDA and IDWA are common in pregnancy and are associated with increased maternal and fetal morbidity and mortality. • Current treatments include oral iron, IV iron, and red blood cell transfusion. • Multiple ongoing trials (e.g., EDIVA[49], IVIDA2[51], REVAMP-TT[53]) are generating data, but	1. Develop and adopt standardized diagnostic criteria and treatment algorithms for iron deficiency/IDA/IDWA in pregnancy. a. Design studies that assess maternal and fetal/infant/toddler outcomes (e.g., neurodevelopment, MRI/EEG; follow-up of toddlers exposed to IV iron as in IVIDA2[51]). b. Conduct comparative studies of IV vs oral iron and standard vs threshold-based dosing strategies.

		diagnostic criteria and treatment guidelines remain inconsistent.	2. Use systems pharmacology models (iron disposition) to optimize dosing. 3. Leverage multidisciplinary networks and registries (e.g., MFMU, IVIDA2[51], ASH) to coordinate long-term follow-up and malformation surveillance. 4. Explicitly include quality-of-life and functional outcomes, such as postpartum mood and lactation success, as key endpoints.
Hydroxyurea as a disease-modifying therapy for SCA (with transfusion and supportive care as comparators)	Sickle cell anemia Pregnant Women	• Hydroxyurea is a standard disease-modifying therapy for SCA in adults, but the label recommends against use in pregnancy. • Pregnancy in women with SCA is high-risk, with maternal morbidity and mortality 5–10× higher than in women without SCA. • Existing data on hydroxyurea in pregnant women are limited and mostly retrospective, uncontrolled, or anecdotal (registries, look-back studies, self-report). • In clinical practice, alternatives beyond hydroxyurea are largely blood transfusions and supportive care.	1. Develop a play book for how to do ethical research on pregnant women. 2. Look at observational data in pregnancy to understand hydroxyurea use in pregnancy (i.e. women who have used the drug before they found out they are pregnant and women who restart use of the drug in the 3rd trimester). 3. Use existing retrospective data and PK/PD modeling to inform feasibility, expected exposure (maternal–placental–fetal), and FDA engagement for future trials. 4. Implement mixed-methods studies to capture patient and provider perspectives and support shared decision-making across disciplines (hematology, MFM, etc.). 5. Pursue translational research, including non-human primate models sampling maternal–fetal–placental compartments across gestation to identify safer windows for treatment[b]. 6. Plan dissemination and implementation trials to evaluate real-world uptake and best

			strategies for implementing evidence-based recommendations as data emerge.
Hydroxyurea as a disease-modifying therapy for SCA (with transfusion and supportive care as comparators)	Sickle cell anemia Lactating Women	• Hydroxyurea is a standard disease-modifying therapy for SCA in adults, but the label recommends against use for lactating women. • Existing data on hydroxyurea in lactating women are limited and mostly retrospective, uncontrolled, or anecdotal (registries, look-back studies, self-report). • In clinical practice, alternatives beyond hydroxyurea are largely blood transfusions and supportive care.	1. Implement mixed-methods studies to capture patient and provider perspectives and support shared decision-making across disciplines (hematology, MFM, etc.). Does taking Hydroxyurea impact a women's decision to breast feed? What implications does this have for long term health of the mother and baby? 2. Pursue translational research, including non-human primate models sampling to identify safer windows for treatment[b]. 3. Plan dissemination and implementation trials to evaluate real-world uptake and best strategies for implementing evidence-based recommendations as data emerge.

DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; UFH, unfractionated heparin, EHR, electronic health records; PK, pharmacokinetic; PBPK, physiologically based pharmacokinetc; MPRINT, Maternal Pediatric PRecision In Therapeutics; MFMU, Maternal Fetal Medicine Units; NRN, Neonatal Research Network; PTN, Pediatric Trials Network; UCSD, University of California, San Diego; IV, intravenous; IDA, iron deficiency anemia; IDWA, iron deficiency without anemia; EDIVA, Efficacy and Demonstration of IntraVenous Iron for Anaemia in pregnancy; IVIDA2, Intravenous Versus Oral Iron for Treating Iron-Deficiency Anemia in Pregnancy; REVAMP-TT, Randomized controlled trial of the Effect of intraVenous iron on Anaemia in Malawian Pregnant women in their third trimester; MRI, magnetic resonance imaging; EEG, electroencephalogram; ASH, American Society of Hematology; PD, pharmacodynamic; MFM, maternal fetal medicine; FDA, Food and Drug Administration; SCA, sickle cell anemia,

[a] Although not federally funded, the InfantRisk Center (IRC) contributed 25% of the rivaroxaban cases and 75% of the available human milk concentration data. The IRC biorepository further provides a critical infrastructure asset that can be leveraged. Northwestern University also has a milk biorepository. See Reference [54] for additional information on milk banks.

[b] SCDPAIN U24 (Sickle Cell Disease Pain Analgesia & Integrative Network) is a NIH-funded Research Network that has some sickle cell in pregnancy research including in rodent models.

Table 3.2 Research Landscape Data: Lactation references for rivaroxaban

Reference	Data Type	Exposure	n	PK/Adverse Outcomes
Wiesen (2016)[55]	Case Report PK	15 mg every 12 hours Milk + maternal plasma collected @ 1 month	1	M:P = 0.4 RID = 1.3%; Tmax = 3 h
Saito (2019)[56]	Case Report PK + AEs	15 mg every 24 hours Milk collected @ 3 months	1	RID = 1.79% No infant AEs detected
Muysson (2020)[57]	Case Series PK	15 mg every 12 hours Milk collected @ 3 months 20 mg every 24 hours Milk collected @ 6 months	2	RID = 5%; Tmax = 1 h RID = 4%; Tmax = 2 h
Zhao (2020)[58]	Clinical Trial PK	20 mg single dose Milk + maternal plasma @ 8 months	2	M:P ratio = 0.27 RID = 1.63%
Yamashita (2024)[59]	Case Series PK + AEs	25 mg every 24 hours Milk + maternal/infant plasma collected @ <1 week	2	RID = 0.82%, 0.82%, 1.27% Tmax = 2-4 h $[Riv]_{infant}$ not detected @ 2 h No infant AE concerns

M:P, milk to maternal plasma ratio; RID, relative infant dose; Tmax, maximum concentration; h, hours; AE, adverse event; $[Riv]_{infant}$ infant concentration of rivaroxaban

Table 3.3: Research Landscape Data: Lactation References for Apixaban

Reference	Data Type	Exposure	n	PK
Wang (2011)[60]	Animal data (rats)	5 mg/kg	N/A	Cmax and AUC much higher in milk than in maternal plasma
Zhao (2020)[58]	Case Study (CT) PK	5 mg every 12 h x 2 doses	1	M:P ratio = 2.61 RID = 12.78% Tmax = 3-4 h
Muysson (2021)[57]	Case Series PK	5 mg every 12 h x 2 doses	3	Tmax = 1-2 h RID = 18% (range 14–21%) No M:P ratio

Cmax, maximum plasma concentration; AUC, area under the concentration-time curve; M:P, milk to maternal plasma ratio; RID, relative infant dose; Tmax, maximum concentration; h, hours

Table 3.4 Research Landscape Data: Lactation references for Dabigatran

Reference	Data Type	Exposure	n	PK/Adverse Outcomes
Ayuk (2020)[61]	Clinical Trial PK	220 mg	2	M:P ratio 0.2 and 0.01 Tmax = 5-7 hours

M:P, milk to maternal plasma ratio; Tmax, maximum concentration

Table 3.5 Research Landscape Data: Pediatric DOAC Models (0-18 years)

Reference	DOAC	Model Type	Notes
Willmann (2014)[62]	Rivaroxaban	PBPK	Scaled from adult data
Kubitza (2018)[63]	Rivaroxaban	PBPK/PD	PT, aPTT, anti-Factor Xa activity
Willmann (2018)[64]; Willmann (2018)[65]	Rivaroxaban	PopPK PopPK + PBPK	PopPK only > 6 mo.
Xu (2021)[66]	Apixaban	PBPK	No pediatric data for validation
Merali (2023)[67]	Apixaban	PopPK/PD	Birth to 27 days, n = 1; 28 days to <9 months, n = 11
Ajavon-Hartmann (2025) [68]	Apixaban	PopPK/PD	Updated model w/ additional data
Maas (2018)[69]	Dabigatran	Exposure Response	Aged < 2 months exhibited slight upward shift in ecarin clotting time and aPTT relative to adults
Roshammer (2021)[70]	Dabigatran	PopPK	Based on 5 pediatric studies
Zou (2025)[71]	Edoxaban	PopPK/PD	Exposure similar to adults receiving 60 mg every 24h

PBPK, physiologically based pharmacokinetics; PD, pharmacodynamic; PopPK, population pharmacokinetics; PT, prothrombin time; aPTT, activated partial thromboplastin time; h, hours

Table 3.6 Studies looking at safety when apixaban was given during pregnancy

Species	Author	Type	Exposure	Dose	n	Timeframe	Summary
Human	Komori (2020)[72]	Case Study	Apixaban	10 mg	1	1st-3rd Trimester	Baby had no external congenital anomalies, intracranial hemorrhage, or bleeding tendency
Human	Nekoogh adam (2023)[73]	Case Study	Apixaban	10 mg twice daily	1	1st Trimester	Elective abortion

Current drug label guidance for pregnancy for DOACs

Females with reproductive potential requiring anticoagulation should discuss pregnancy planning with their physician. Current warnings state that DOACs should be used with caution during pregnancy; drugs should be used in pregnancy only if the potential benefit justifies the potential risk to mother and fetus. It should also be noted that DOACs can be

used both for the prevention of DVT and treatment of them. Different treatment regimens apply. When making recommendations for these drugs in pregnant and lactating women the indication (prevention or treatment) should be taken into account.

The working group considered the following questions:

1. What is the excretion profile of direct anticoagulants in breast milk?
2. What are the concentrations of direct anticoagulants in breast milk over time, and how do they correlate with maternal plasma levels and breastfeed infant plasma levels?
3. Is there an increased risk of bleeding events or other adverse outcomes in infants exposed to direct anticoagulants through breast milk?

Research Gaps for DVT and Pulmonary Embolism

- Lack of PK data in pregnancy/lactation, particularly milk levels, milk-to-plasma ratio (M:P), relative infant dose (RID).
- No infant safety data or infant plasma quantification. Unknown optimal dosing (therapeutic vs prophylactic), especially personalized dosing (BMI, comorbidities, lactation status).
- Insufficient data on real-world prescribing patterns. Limited understanding of patient preferences for oral vs injectable therapy.
- Insufficient data for prophylaxis vs treatment of VTE.

Prioritized Research Needs DVT and Pulmonary Embolism

1. Conduct observational studies using EHR/administrative databases to characterize maternal use patterns.
2. Conduct mixed-methods studies of patient and provider preferences. Collect and analyze observational data for patients not lactating.
3. Evaluate DOACs for postpartum thromboprophylaxis.
4. Conduct PK studies of drug passage into breast milk; include maternal + infant plasma sampling.
5. Build PBPK models using existing datasets and MPRINT modeling capacity.
6. Utilize NICHD infrastructure: MFMU, NRN, PTN, UCSD's Mommy's Milk Biorepository.

Intravenous Iron

Background for IV Iron

Iron deficiency with anemia (IDA) affects ~12% of pregnancies in North America. IDA is associated with increased maternal and fetal morbidity and mortality. For the mother this includes thyroid dysfunction, placental abruption, c-section, postpartum hemorrhage, and postpartum depression. Fetal, newborn, and childhood outcomes include prematurity, low birth weight, impaired cognition, behavioral issues, and iron deficiency.

Another area to consider is the compatibility of pharmaceutical preservatives with breastfeeding, as these excipients can influence clinical recommendations independently of the active drug. For example, the presence of benzyl alcohol in sodium ferric gluconate complex has driven recommendations against its use during breastfeeding based on neonatal contraindications to *direct* benzyl alcohol administration, despite limited evidence regarding exposure via human milk.

Table 3.7 below shows IV iron formulations, standard dosing, and current monitoring recommendations.

Table 3.7 IV Iron Formulations and Standard Dosing and Monitoring Recommendations[74]

Formulation	Dose (mg)	Doses to replace deficit[a]	Need for test dose prior to infusion	Need for observation after infusion
Ferric carboxymaltose	750	1-2	Yes	No
Ferric derisomaltose	1000	1	No	Up to 30 min
Feruoxytol	510	1-2	No	No
Iron sucrose	200-300	4-5	No	No
Low molecular weight (LMW) iron dextran	1000	1	Yes	Up to 1 h

[a] Estimated number of doses needed to replace a total body iron deficit of at least 1000 mg. Total body iron deficit = body weight (kg) x (target hemoglobin [g/dL] – actual hemoglobin [g/dL]) x 2.45

Questions for Consideration for IV Iron

The working group considered the following questions:

1. What is the optimal personalized dose and timing of IV iron therapy before delivery to optimize hemoglobin and reduce adverse maternal and newborn outcomes?
2. Regarding supplementation: is an oral supplement non inferior to dietary sources of iron?

Research Gaps in IV Iron

- Overall, there is inconsistent definitions of iron deficiency (i.e., different ferritin cutoffs). See reference for the first clinical consensus guidelines on treatment of IDA[53].
- Limited data on first-trimester IV iron use.
- Sparse evidence on treating iron deficiency without anemia (IDWA) with IV iron[52].
- Poorly characterized relationship between maternal iron stores, treatment of IDA/IDWA, and fetal/infant iron transfer.
- Lack of standardized diagnostic thresholds and harmonized treatment protocols.
- Quality-of-life outcomes (postpartum mood disorders, lactation success) are rarely captured despite being clinically important.

Prioritized Research Needs for IV Iron

1. Develop and adopt standardized diagnostic criteria and treatment algorithms for iron deficiency/IDA/IDWA in pregnancy.
    a. Design studies that assess maternal and fetal/infant/toddler outcomes (e.g., neurodevelopment, MRI/EEG; follow-up of toddlers exposed to IV iron as in IVIDA2[51]).
    b. Conduct comparative studies of IV vs oral iron and standard vs threshold-based dosing strategies.
2. Use systems pharmacology models (iron disposition) to optimize dosing.
3. Leverage multidisciplinary networks and registries (e.g., MFMU, IVIDA2[51], ASH) to coordinate long-term follow-up and malformation surveillance.
4. Explicitly include quality-of-life and functional outcomes, such as postpartum mood and lactation success, as key endpoints.

Hydroxyurea

Background for Hydroxyurea

Sickle cell disease (SCD) affects 100,000 people in the United States and is associated with significant morbidity and shortened lifespan. For this document SCD refers to the full genetic range of the disease while Sickle Cell Anemia (SCA) is defined as sickle SS disease and Sickle beta-thalassemia (SβThal) disease. Pregnancy is high risk for women with SCD, with maternal morbidity and mortality rates being 5 to 10 times higher compared to pregnant women without SCD (~15%). Higher rates of hypertension, infection, venous thromboembolism, preeclampsia, UTIs and fetal/neonatal complications are also associated with pregnancies in women with SCD.

In 1998, the U.S. FDA approved hydroxyurea for the treatment of SCD in adults. It has been shown to improve quality of life and reduce vaso-occlusive episodes (pain & acute chest syndrome), hospital admissions, anemia, and need for transfusion.

Current drug label guidance for pregnancy and hydroxyurea use

- Pregnancy testing: prior to initiating hydroxyurea
- Contraception: during treatment and for at least 6 months after
- Pregnancy management: avoid becoming pregnant while being treated with hydroxyurea
- Lactation: Hydroxyurea is excreted in human milk. Because of the potential for serious adverse reactions in a breastfed infant from hydroxyurea, including carcinogenicity, discontinue breastfeeding during treatment with hydroxyurea.

Questions for Consideration for Hydroxyurea

The working group considered the following questions:

1. Limited data on safety in pregnancy, is it safe for women to take hydroxyurea during pregnancy? A risk/benefit analysis is needed for use of hydroxyurea during pregnancy.
2. Is it safe for women to take hydroxyurea while breastfeeding? Translating evidence into practice based on research [a 75]. A risk/benefit analysis is needed for use of hydroxyurea in lactating women.

Research Gaps in Hydroxyurea

- Lack of prospective studies designed to collect detailed pregnancy/lactation and hydroxyurea exposure data (timing, dose, duration).
- Lack of PK/PD data in pregnant women to inform dosing and timing.
- No robust long-term follow-up data to document maternal and offspring risks/benefits during pregnancy and lactation.
- Difficulty separating drug effects vs underlying SCA on adverse maternal and fetal/neonatal outcomes in observational data.
- Limited data on lactation safety and infant exposure.
- Regulatory/ethical barriers ("medical-legal block" from black box warning) make institutional review board (IRB) approval for prospective studies challenging, even when patients are willing.

Prioritized Research Needs for Hydroxyurea for Pregnant Women

1. Develop a play book for how to do ethical research on pregnant women.
2. Look at observational data in pregnancy and retrospective data to understand hydroxyurea use in pregnancy (i.e. women who have used the drug before they found out they are pregnant and women who restart use of the drug in the 3rd trimester.
3. Use existing retrospective data and PK/PD modeling (including MPRINT capabilities) to inform feasibility, expected exposure (maternal–placental–fetal), and FDA engagement for future trials.
4. Implement mixed-methods studies to capture patient and provider perspectives and support shared decision-making across disciplines (hematology, MFM, etc.).
5. Pursue translational research, including non-human primate models sampling maternal–fetal–placental compartments across gestation to identify safer windows for treatment.

[a] "Lactation is contraindicated for women with sickle cell anemia receiving hydroxyurea therapy, despite sparse pharmacokinetics data. In 16 women who were lactating volunteers, we documented hydroxyurea transferred into breastmilk with a relative infant dosage of 3.4%, which is below the recommended 5%-10% safety threshold. Breastfeeding should be permitted for women taking daily oral hydroxyurea."

6. Plan dissemination and implementation trials to evaluate real-world uptake and best practice strategies for implementing evidence-based recommendations as data emerge.

Prioritized Research Needs for Hydroxyurea for Lactating Women

1. Implement mixed-methods studies to capture patient and provider perspectives and support shared decision-making across disciplines (hematology, MFM, etc.). Does taking hydroxyurea impact a women's decision to breast feed? What implications does this have for long-term health of the mother and baby?
2. Pursue translational research, including non-human primate models sampling to identify safer windows for treatment.
3. Plan dissemination and implementation trials to evaluate real-world uptake and best strategies for implementing evidence-based recommendations as data emerge.

4. Infectious Disease

Background

Women undergo several physiologic changes during pregnancy that affect drug absorption, distribution, metabolism, and excretion. These changes reverse during the early postpartum period and can impact drug dosage. Infections during pregnancy and lactation are common, and infectious diseases in pregnant women can cause substantial maternal and fetal morbidity and mortality. According to the Inaugural Stakeholder Meeting (July 2024, Appendix 1), 63% of pregnant women experience at least one infectious episode during pregnancy. Because pregnant women have often been excluded from clinical trials of many antimicrobials, only limited data are available to guide their appropriate use during pregnancy, the early postpartum period, and lactation. Significant knowledge gaps exist on antimicrobials, including preclinical and clinical safety, PK, their penetration into breastmilk and infant exposure to such drugs via breastfeeding.

During the July 2024 meeting, HIV, hepatitis C virus (HCV), and syphilis were discussed as part of the discussion regarding infectious disease. The following recommendations were made during that discussion:

- Prioritization in the infectious disease category should be guided by population frequency, impact on pregnancy/lactation, impact on the fetus/infant, and feasibility.
- The three conditions discussed (HIV, HCV, and syphilis) were all high-priority examples with drugs at different stages in their pregnancy/lactation pathway.
- Other drugs submitted are also high priority, particularly the multiple tuberculosis (TB) drugs submitted, which will need quite a bit of time to fully consider.

Disease-specific background

Malaria

Pregnant women less effectively clear malaria infections. In addition, malaria parasites sequester and replicate in the placenta. Pregnant women are three times more likely to develop severe disease than non-pregnant women who acquire malaria in the same geographic area. Malaria infection during pregnancy can lead to miscarriage, premature delivery, low birth weight, congenital infection, and/or perinatal death. Malaria remains a significant cause of morbidity and mortality in pregnancy globally.

The first-line recommendation therapy for uncomplicated cases with *P. falciparum* (the most prevalent causative agent world-wide) malaria is a 7-day course of quinine and clindamycin. For uncomplicated malaria caused by *P. malariae*, *P. ovale*, chloroquine-sensitive *P. vivax*, or chloroquine-sensitive *P. falciparum* infection, the recommendation is treatment with chloroquine or hydroxychloroquine. For chloroquine-resistant *P. vivax* infections, treatment options include artemether-lumefantrine, quinine plus clindamycin, or mefloquine. Doxycycline or tetracycline are generally not indicated for use in pregnancy but can be used in combination with quinine if other treatment options are

not available or are not tolerated. Atovaquone-proguanil is not currently indicated for use in pregnant women because of the paucity of data on its safety during pregnancy and lactation. There are no data on the presence of atovaquone in human milk. Proguanil is excreted into human milk in small quantities. There are no data on the effects of atovaquone and proguanil on the breastfed infant or the effects on milk production. However, for pregnant and lactating women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil may be used if other treatment options are not available or are not being tolerated[76].

MRSA infections

Methicillin-resistant *S. aureus (MRSA)* infections are important causes of community- and healthcare-associated infections in pregnant and postpartum women, particularly skin and soft tissue infections, mastitis, surgical site infections following cesarean delivery, and invasive disease. They can be difficult to treat and are associated with serious morbidities and neonatal transmission vertically during delivery or horizontally via contact with infectious maternal secretions postpartum, with subsequent impact on the neonate. Transmission to the neonate can lead to skin infections, sepsis, or pneumonia, particularly in preterm or neonatal intensive care unit (NICU)-admitted infants. Current treatment recommendations include IV vancomycin, and IV linezolid. If there are no other options, IV daptomycin is advocated for severe infections, despite limited data on its use during pregnancy and lactation. Limited published data report that daptomycin is present in human milk at infant doses of 0.1% of the maternal dose. There is no information on the effects of daptomycin on the breastfed infant or the effects of daptomycin on milk production.

Mycoplasma genitalium

The burden of *M. genitalium* during pregnancy ranges from 0.9% to 13.5% globally[77]. However, estimates are limited as routine surveillance, access to testing, and treatment is variable in many settings. It has been associated with adverse pregnancy outcomes including preterm birth, spontaneous abortion, and low birth weight, though causality remains incompletely established. Vertical transmission is possible but not well characterized, and neonatal disease is rarely reported. Treatment in pregnancy is challenging due to antimicrobial resistance and limited safety data. Currently, *M. genitalium* treatments include doxycycline and moxifloxacin, neither of which are currently recommended in pregnancy and lactation. Azithromycin is a treatment option in PPL populations, but prevalence of azithromycin-resistant strains of *M. genitalium* is as high as 60%. There has been interest in evaluating metronidazole for *M. genitalium* infection during pregnancy, but very limited information exists for this application.

Tuberculosis (TB)

Tuberculosis remains a leading cause of infectious mortality globally, with significant impact on pregnant and postpartum women in high-burden settings and among those with HIV, with an estimated 337,100 cases annually[78]. Active TB in pregnancy, especially if untreated, is associated with increased risks of maternal morbidity and mortality, and

adverse pregnancy and birth outcomes. For drug-susceptible TB, standard therapy generally includes isoniazid, rifampin, and ethambutol, with pyrazinamide used in many international guidelines; pyridoxine supplementation is recommended with isoniazid. Pregnancy is not a contraindication to TB preventive treatment, but regimen choice should be individualized because of limited safety data for some of the newer preventive therapy drug regimens during pregnancy and lactation. Six- or nine-month daily regimen of isoniazid (6H or 9H), with 25–50 mg/day pyridoxine (vitamin B6) supplementation, remains the most frequently used preventive option in pregnancy, but requires monitoring for hepatotoxicity. Other preventive regimens used in pregnancy that have more limited safety and PK data in pregnancy and lactation include: Four-month daily regimen of rifampin (4R), Three-month daily regimen of isoniazid and rifampin (3HR), or three-month weekly isoniazid and rifapentine (3HP). For multidrug/rifampin-resistant TB (MDR/RR-TB) an all-oral MDR/RR-TB regimen is recommended whenever possible. This may include drugs such as bedaquiline, linezolid, fluoroquinolones, clofazimine, cycloserine, or delamanid. Limited data in pregnancy warrant caution, balancing maternal and fetal benefit and risk, expert consultation, and close monitoring. A fluoroquinolone-based preventive regimen is conditionally recommended for eligible pregnant MDR/RR-TB contacts, with expert consultation and close clinical monitoring.

Syphilis

Maternal syphilis rates in the United States increased by 696% from 2015 to 2024 and congenital syphilis rates increased 405% during the same timeframe[79]. The majority of congenital syphilis cases are related to a lack of adequate diagnosis and treatment during pregnancy. The stage of syphilis is clinically important because it informs the treatment regimen and the risk of vertical transmission. Currently, penicillin G benzathine is the only approved treatment in pregnancy and a single intramuscular 2.4-million-unit dose is appropriate for patients with primary, secondary, or early latent disease and for post-exposure prophylaxis after sexual contact with a partner with known or suspected syphilis. Some clinicians also administer a second dose for patients with primary, secondary, or early latent disease. In patients with late latent and tertiary syphilis, three doses of penicillin G benzathine administered intramuscularly at weekly intervals is recommended[80].

Hepatitis C Virus (HCV)

In 2022, the CDC reported 67,400 estimated acute HCV infections in the U.S. Perinatal transmission occurs in 5-7% of pregnancies with active HCV. For pregnant women that screen positive for HCV during pregnancy, obstetric guidelines have not generally recommended treatment of HCV infection during pregnancy due to more limited data on direct acting antiviral (DAA) drugs. Some guidelines and recent publications recommend shared decision-making regarding treatment of HCV in pregnancy, acknowledging the benefits and efficacy of treatment versus the limited available data on anti-HCV DAA drugs during pregnancy and lactation[81].

Respiratory Syncytial Virus (RSV)

RSV is one of the leading causes of lower respiratory infections in infants. Severe cases can lead to an increase in associated morbidities and mortality, with newborns to 6 months old having the highest risk[82]. Currently there are no antiviral treatments for severe RSV disease. The American College of Obstetricians and Gynecologists recommends a single dose of Pfizer's bivalent RSVpreF vaccine (Abrysvo) using seasonal administration, to prevent RSV lower respiratory tract infection in infants for eligible pregnant patients meeting the following criteria[83]:

- are between 32 0/7 and 36 6/7 weeks of gestation,
- do not have a planned delivery within 2 weeks,
- did not receive the maternal RSV vaccine during a previous pregnancy, and
- are not planning to have their infant receive a monoclonal antibody

There are two approved long-acting monoclonal antibodies for the prevention of severe RSV disease in infants from birth to 7 months of age. One dose of nirsevimab[84] or clesrovimab is now recommended for all infants younger than 8 months, born during, or entering, their first RSV season, if their mothers did not receive the maternal RSVpreF vaccine or infants were born 14 days or earlier after maternal vaccination.

Infectious Disease Priorities:

The working group reviewed nominations across viral, bacterial, and parasitic infections. A research landscape analysis was provided (Appendix 2), and a summary of salient findings is described in Table 4.1.

Table 4.1 Infectious Disease Priorities

Therapeutic area	Nominations	Research Landscape analysis	Research gaps	Research needs/priorities
Malaria	atovaquone proguanil	1. Preclinical studies in rats and rabbits showed no embryo-fetal toxicity for atovaquone and proguanil at estimated human exposures. 2. Limited human PK/PD data exists from small studies, suggesting an approximately 2-fold decrease in AUC and Cmax[85] 3. Atovaquone is found in rat milk but there are no data in human milk; proguanil is excreted into human milk in small quantities, but infant effects are unknown	1. Lactation data (e.g. breast milk transfer, infant dose) 2. Safety & PK: Limited safety and PK data in pregnancy. 3. Data quality: Unclear if RWD in endemic regions is sufficient to answer questions.	1. Prioritize high-quality RWE collection/ analysis in malaria-endemic regions. 2. PK Studies: Conduct PK studies to bridge efficacy data from non-pregnant populations. 3. Lactation: Critical gap; use preclinical animal models to screen transfer; opportunistically collect and analyze milk samples.
MRSA infections	daptomycin	1. Clinical context: IV treatment for severe infections; difficult to tease drug impact from underlying condition. Very low usage reported in lactation (only ~ 2 calls to InfantRisk in an 11 month period). 2. No adverse developmental outcomes at supratherapeutic	1. Lactation: only two case reports exist regarding daptomycin in lactation. 2. PK Data: Limited PK data in pregnancy.	1. RWE: Focus on electronic health record (EHR) in high-resource settings to capture IV treatment outcomes. 2. Modeling: Use PBPK/PD modeling and simulation. 3. Leverage Biobanking: Landscape analysis of existing biobanked samples for retrospective PK.

		doses during animal organogenesis. 3. Published case reports do not suggest safety concerns with pregnancy use; 4. Minimal excretion into human breast milk. 5. Limited or no data on adverse pregnancy/birth outcomes, transplacental transfer, or long-term/rare teratogenicity surveillance		
Mycoplasma genitalium	metronidazole	1. Nominated for maternal *M. genitalium*, an infection associated with elevated preterm birth risk. 2. Current recommended therapies (doxycycline/ moxifloxacin) carry significant pregnancy warnings, and azithromycin resistance is ~60% in the U.S. 3. Robust data in pregnancy exist for metronidazole for various infectious indications. It is not a primary alternative focus for *M. genitalium*.	1. Lack of data on metronidazole as a safe, effective alternative to tetracyclines or macrolides in pregnancy for *M. genitalium* treatment. 2. Screening vs. Symptoms: Distinguishing treatment needs for symptomatic vs. asymptomatic cases is critical.	1.Shift Focus: Prioritize research on minocycline, lefamulin, and pristinamycin. 2. Non-Pregnant Data: Establish effectiveness of alternatives outside of pregnancy first.

Tuberculosis and **Multi-drug resistant tuberculosis**	bedaquiline delamanid linezolid moxifloxacin pretomanid	1. Antimicrobial treatment of TB is required to prevent significant maternal/fetal morbidity and mortality 2. Preclinical animal data reveal toxicity at maternally toxic doses for delamanid and pretomanid (rat only), embryo-fetal toxicity without malformations at clinical exposures for linezolid, and decreased fetal body weights and delayed skeletal development, but no teratogenicity for moxifloxacin; conversely, bedaquiline at supratherapeutic doses or pretomanid at human equivalent doses show no adverse embryofetal effects. 3. Animal and/or human data suggest that breast milk excretion occurs across all agents: delamanid and pretomanid levels (in rats) generally exceed maternal plasma concentrations, bedaquiline accumulates in breast milk posing theoretical risks, linezolid transfers 6% to 9% of therapeutic doses, and moxifloxacin may cause significant infant exposure.	1. Lactation: Critical gap; some TB drugs (e.g., bedaquiline) are lipophilic and likely concentrate in breast milk. 2. Human Toxicity: Limited human surveillance data to define toxicity profile (miscarriage, congenital disorders). 3. Regimen Risk: Difficulty assessing overlapping risks in combination regimens. 4. Adherence: Absence of lactation data creates counseling uncertainty that may drive non-adherence — particularly high-stakes given MDR-TB resistance implications.	1. Surveillance: High priority. Implement surveillance in high-burden countries including leveraging existing large prospective TB cohorts i.e. RePORT/leDEA or local public health or health record data sources to capture outcomes. 2. Lactation Studies: High priority for bedaquiline. 3. Deprioritize Animal Studies for Approved Drugs: For approved drugs already in clinical use, deprioritize new animal DART studies in favor of human surveillance and human-based preclinical models, while noting that animal DART studies remain necessary for new therapeutic agents. 4. Lactation studies should include maternal drug level monitoring alongside infant exposure estimation.

		4. Limited clinical safety and PK data exists for delamanid and pretomanid; linezolid and moxifloxacin reviews show no definitive associations with major birth defects; in utero bedaquiline exposure may independently predicts lower birth weight but better postnatal development.		
Skin and soft tissue infection	omadacycline	1. Tetracycline antibacterial used to treat adult bacterial pneumonia and skin infections. 2. Animal studies report fetal loss, reduced fetal weight, and congenital malformations at high doses. 3. Use during tooth development may cause permanent tooth discoloration and inhibit bone growth	Lack of pediatric bone safety data to "de-risk" use in pregnancy.	Deprioritized due to safety barriers and low clinical demand.
Extended Spectrum beta-lactamases (ESBL) + Urinary Tract Infection	tebipenem	Potential first oral carbapenem outpatient treatment for resistant pyelonephritis (ESBL), avoiding hospitalization.	Targeted indication (ESBL + cUTI) is a small population making prospective trials hard.	High priority (conditional). Advocate for inclusion of pregnant women in Phase 3 trials for resubmission. Prioritize PBPK modeling.

Syphilis	cefixime	1. Cefixime is highly protein-bound; unclear if it crosses placenta sufficiently to treat the fetus. 2. Alternatives: penicillin G benzathine is the only approved treatment in pregnancy; shortages drive urgency for alternatives.	1. Fetal Efficacy: Lack of data on whether cefixime crosses the placenta to cure the fetal infection (congenital syphilis prevention). 2. Alternative Dosing: Question regarding dosing regimens for penicillin G benzathine (1 vs 3 shots).	1. PK/PD Studies: Confirm placental transfer and fetal exposure for cefixime. 2. Broaden Scope: Prioritize research on ceftriaxone (congenital syphilis prevention) and doxycycline (improve data on safety to enable increased use).
Hepatitis C Virus	sofosbuvir/ velpatasvir glecaprevir/ pibrentasvir	1. Clinical Shift: glecaprevir/ pibrentasvir is increasingly preferred clinically due to shorter-course (8 weeks) and pangenotypic efficacy. 2. Postpartum loss-to-follow-up is high; pregnancy is a key window for cure.	1. Pregnancy PK: Lack of PBPK modeling and specific pregnancy PK data for glecaprevir and pibrentasvir. 2. Lactation: Data is extremely limited.	1. Glecaprevir/ pibrentasvir Focus: Prioritize safety/efficacy data. 2. Endpoints: Validate "HCV viral load at delivery" as surrogate for preventing transmission.
RSV in infant	RSV vaccine	1. Status: Robust post-marketing safety studies (Pfizer) are enrolling. 2. Need: Maternal vaccination is a critical layer of infant protection	1. Safety Signal: Preterm birth signal (~1% difference) needs clarification. 2. Revaccination: Gap in knowing if boosters are needed for subsequent pregnancies.	1. Clarify Safety: Update preterm birth rate data. 2. Revaccination: Determine necessity of boosters for subsequent pregnancies.

PK, pharmacokinetic; PD, pharmacodynamic; AUC, area under the concentration-time curve; Cmax, maximum plasma concentration, IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; RWD, real-world data; RWE, real-world evidence; EHR, electronic health records; PBPK, physiologically based PK; TB, tuberculosis; DART, developmental and reproductive toxicology; ESBL, extended-spectrum beta lactamase; cUTI, complicated urinary tract infection; HCV, hepatitis C virus; RSV, respiratory syncytial virus

Summary of Infectious Disease Working Group Discussions

The Infectious Disease Working Group convened across multiple sessions in late 2025 and early 2026 to refine prioritization. The following key themes and consensus points emerged:

1. **Are the nominated drugs representative of the topic area and do they align with the standard of care?**
    a. Regimen vs. Single Agent (TB): The group agreed that research and prioritization for TB must not be limited to individual agents but also focus on studying new agents in the context of approved regimens (drug combinations) that are used clinically.
    b. Clinical Reality vs. Guidelines (Hepatitis C): Clinicians noted that "practice is going to exceed data". While sofosbuvir/velpatasvir was nominated, providers are already shifting toward glecaprevir/pibrentasvir due to its shorter treatment course (8 weeks vs. 12) and pan-genotypic utility, despite it having less pregnancy-specific data. Research prioritization must pivot to match this clinical reality.
    c. Expanding Syphilis Options: Focusing solely on cefixime was deemed too narrow. The group emphasized the urgent need to prioritize alternatives like penicillin G benzathine (optimizing dosing strategies) and doxycycline (establishing safety) to address drug shortages and penicillin allergies.
    d. Missing Conditions: Mastitis was identified as a valid clinical need missing from the original nominations, with a specific gap in distinguishing inflammatory from bacterial mastitis to guide antibiotic use. Furthermore, current treatment guidelines for bacterial mastitis are not evidence-based; data on causative organisms, their prevalence, and resistance patterns are insufficient to drive rational antibiotic selection.
2. **What considerations are most important for determining topic and therapeutic prioritization?**
    a. "Minimum Gaps" Strategy: For drugs like atovaquone/proguanil, the group proposed identifying the "minimum gaps" (e.g., confirmatory RWE) necessary to enable guideline updates, rather than demanding a full suite of new prospective trials.
    b. Risk-Benefit in High-Stakes Disease: For Multidrug-Resistant TB (MDR-TB), the benefit of treatment clearly outweighs the risk, as the alternative is untreated, severe disease. Therefore, the group consensus was to deprioritize further animal DART studies for approved drugs, as the decision to treat is already made clinically. Resources should instead focus on human surveillance and human-based new approach methodologies (NAMs). The group noted that animal DART studies still remain necessary and relevant for the evaluation of new therapeutic agents.
    c. Demand as a Filter: The group recommended using RWD (e.g., InfantRisk Center call volume) as a filter. For example, omadacycline was deprioritized partly due to low interest from clinicians in the context of bone/tooth development safety concerns, whereas daptomycin showed demand compared to malaria drugs.
    d. Potential "Game Changers": Tebipenem was prioritized because it offers a paradigm shift – allowing outpatient oral treatment for resistant pyelonephritis

(extended-spectrum beta-lactamase) instead of hospitalization for IV carbapenems.

3. **What types of studies are needed for this topic area?**
    a. Surveillance vs. Clinical Trials: For TB and malaria, the group discussed the need for both clinical trials and surveillance. Phase I/II trials, or the inclusion of pregnant and lactating women in Phase III/IV trials, are needed to establish dosing and initial safety. Meanwhile, large-scale surveillance studies in high-burden countries were identified as the top priority to define human toxicity and pregnancy outcomes, and smaller differences in risk that require sample sizes too large for clinical trials.
    b. PK Bridging: PK studies were emphasized as a feasible, high-yield priority to "bridge" efficacy data from non-pregnant populations, particularly for drugs where efficacy is established but dosing in pregnancy or lactation is unknown.
    c. Defining Efficacy: The group distinguished between maternal cure and prevention of vertical transmission.
    d. For Syphilis, a drug must cross the placenta to treat the fetus; thus, efficacy is defined by both maternal cure and congenital syphilis prevention.
    e. For HCV, "viral load at delivery" was proposed as a surrogate endpoint for preventing transmission, even if the maternal cure regimen is not fully completed by birth.
4. **What types of research infrastructure are needed to address the primary questions?**
    a. Global Collaboration: U.S. data alone are insufficient for conditions like malaria and TB. Leveraging international networks such as RePORT (TB) and leDEA (HIV/TB) is essential to achieve sufficient pharmacosurveillance.
    b. Universal Protocols: To effectively pool data across different international sites and funding sources (NIH, Pharma, non-governmental organizations), the development of "universal protocols" for surveillance as recommended.
    c. Biobanking: A landscape analysis of existing biobanked samples (serum/milk) and strategies to leverage national and international biobanks was recommended to enable retrospective PK analyses without new recruitment.

5. **How should safety signals and animal data be interpreted?**
    a. Interpretation of Animal Data: A framework is needed to interpret Developmental and Reproductive Toxicology (DART) studies (which include embryofetal development, fertility, early embryonic development, and pre- and postnatal development studies). While DART studies help anticipate potential effects, they do not definitively define safety in humans. The group noted that for life-saving TB drugs, animal findings should not preclude consideration for use or study in humans. A weight-of-evidence approach that considers the risk/benefit ratio, similar to global regulatory recommendations for drugs like efavirenz despite initial neural tube defect concerns, is necessary.
    b. New Approach Methodologies (NAMs): NAMs were identified as complementary tools to traditional surveillance. For instance, an existing neural tube defect model based on inducible pluripotent stem cells can rapidly evaluate risks, alternative

etiologies, and pathogenesis within weeks. This combinatorial approach using NAMs offers a way to optimize pharmacovigilance, which is otherwise typically prolonged and requires large datasets to confirm or deny safety signals.

c. Preterm Birth Signal (RSV): The group highlighted the need for updated U.S. data to clarify the preterm birth safety signal (~1% difference) seen in RSV vaccine trials to improve clinician and patient confidence.

5. Mental Health

Background

Although there is little data to establish whether medications for mental health disorders are safe during pregnancy, untreated mental illness may pose risks for both the pregnant woman and the fetus. The decision of whether a pregnant woman should start or continue mental health medication during pregnancy is made on a case-by-case basis, taking into account the severity of the symptoms, their ability to take care of themselves and their pregnancy, including whether or not they are able to go to obstetric appointments and follow the doctor's recommendations. The American College of Obstetricians and Gynecologists (ACOG) advises against discontinuing ongoing mental health medications solely because of pregnancy or breastfeeding. All psychotropic medications cross the placenta, but overall, the data on these drugs have not been conclusive as to potential harm to the infant, except with specific agents.

This working group began discussion of some of the nominations for mental health at the July 2024 meeting (Appendix 2). The previous discussion covered selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SNRIs); bupropion; amphetamines; atomoxetine; guanfacine; benzodiazepines; hydroxyzine; buspirone; and gabapentin. The nominated agents include both specific drugs and large drug classes and fall into three therapeutic areas: 1) treatment of mood disorders, 2) treatment of anxiety disorders, and 3) treatment of attention-deficit/hyperactivity disorder (ADHD). Within each area, the amount and quality of data available for use in pregnancy and lactation are highly variable.

The recommendations from the July 2024 meeting include:

- In a clinical context, understanding patients and their mental health challenges during the perinatal period is important for developing optimal safe and effective use of pharmacotherapy options.
- Align with the standard of care.
- More medication registries; the lamotrigine registry in particular helped to establish the drug's safety for use in pregnancy.
- Case-control series, tracking the course of patients on medication throughout pregnancy (or portions of pregnancy) compared with patients who declined medication.
- More PK studies, tracking changes in medication concentrations across pregnancy. There is a particular research gap with regard to mood stabilizers, other than the well-established contraindication for the use of valproate during pregnancy.
- Benefits and risks of combination treatments (e.g., medication and psychotherapy).
- Consider diversity.
- Clinical research should not increase risk to participants; this should be taken into consideration in the timing of medications, timing of nursing, and tapering of medications.
- Follow neonatal health over time.

- Always consider benefit-to-risk ratio, including the risk of untreated mental illness for mothers and their babies.
- Mood stabilizers and atypical antipsychotics should be considered for serious study. Many of the latter now have FDA indications for use as adjuncts in depression and bipolar disorder, and such drug combinations were not included in the nomination list.

Additional context on lactation for July 2024 nominations

While almost all psychotropic drugs enter breast milk, there are few large-scale studies documenting exposure of the nursing infant to the medication and any related adverse effects. In many cases, drug concentration in breast milk has been assessed in early-stage PK testing, with implications for actual clinical use suggested but often not proven. For example, initial trials of two neurosteroid GABA-A receptor modulators approved by the FDA in recent years for the treatment of postpartum depression – intravenous brexanolone and oral zuranolone – reassuringly found low weight-adjusted infant exposure (<1% of maternal dose); post-marketing studies in non-research settings are awaited. Practical efforts at minimizing drug exposure to nursing infants, for example by aligning feeding schedules with dosing times, successfully tested for the SSRI sertraline decades ago, have not achieved widespread replication.

Recent progress in studying psychotropic drugs in lactating patients comes from the establishment of specialized registries, such as the InfantRisk Center's Human Milk Biorepository at Texas Tech University Health Sciences Center. Women in the community at medication steady-state are invited to provide frozen breast milk samples collected at fixed time points over a 24-hour period, along with self-reported health information about themselves and their baby. In a report from the Center published in early 2026, 10 women taking atomoxetine for ADHD reported no adverse effects in their breastfed infants, who had a relative infant dose RID of 0.19%, noted to be well below the accepted 5% safety threshold for psychoactive medications[86]. This low risk was felt to support the use of atomoxetine as an appropriate medication choice for the treatment of ADHD in lactating women.

Landscape Analysis

The working group continued the discussion of mental health nominations that were not previously covered and expanded the prior discussion for some of the previously reviewed therapeutics. The agents discussed are detailed in Table 5.1 .

Table 5.1 Examples of Mental Health Medications, illustrating limited data in pregnancy and lactation

Therapeutic area	Nomination	Research Landscape analysis	Research gaps	Research needs/priorities
Bipolar disorder	cariprazine	Cariprazine is an atypical antipsychotic approved for manic and mixed episodes of bipolar I disorder. Very limited pregnancy and lactation data; most evidence derives from nonpregnant adult populations. Clinical use in pregnancy appears uncommon and often avoided due to lack of safety data and polypharmacy associated with its use as an adjunct.	Absence of human pregnancy data on congenital anomalies, obstetric complications, and neonatal outcomes. No PK data across pregnancy or lactation. Lack of comparative data versus other antipsychotics used for bipolar mania. Limited understanding of maternal relapse risk if therapy is withheld.	Pregnancy registries and large observational studies to assess fetal and neonatal safety. PK studies across pregnancy and postpartum. Comparative effectiveness and safety studies against established bipolar treatments or no treatment. Drug-specific pregnancy safety data rather than class-level extrapolation.
Major depressive disorder (MDD)	brexpiprazole cariprazine	Used as adjunctive therapy for MDD in nonpregnant adults. No meaningful pregnancy or lactation data; SSRIs remain first-line in perinatal care.	Lack of safety and efficacy data for adjunctive antipsychotic use in perinatal MDD. No data on infant exposure through breastfeeding.	Evaluation of whether adjunctive antipsychotics provide benefit over optimized antidepressant therapy in pregnancy. Lactation exposure and infant safety studies.
Anxiety (off-label); Neuropathic pain	gabapentin	Gabapentin is sometimes used off-label for mood symptoms, anxiety, and sleep disturbances. Frequently prescribed during pregnancy	Limited drug-specific, long-term data on neurodevelopmental outcomes.	Indication-specific analyses separating psychiatric from pain-related use. Mechanistic and PK studies to inform dosing and timing.

		for pain syndromes and comorbid conditions. Existing pregnancy data are sparse and largely observational, often confounded by comorbid conditions and polypharmacy.	Poor characterization of dose–response and timing of exposure. Unclear contribution of gabapentin versus underlying maternal illness.	Long-term child neurodevelopment follow-up.
Schizophrenia and other psychotic disorders	aripiprazole	Aripiprazole is widely used for psychotic disorders and has a distinct pharmacologic profile compared with other antipsychotics. Often perceived as having a more favorable metabolic profile, but pregnancy-specific evidence is limited. Available data are largely observational and class-based rather than drug-specific.	Lack of robust data on pregnancy outcomes and neonatal adaptation. Limited lactation safety data and infant exposure estimates. Unclear comparative safety relative to other atypical antipsychotics.	Drug-specific pregnancy registries and pharmacoepidemiologic studies. PK studies across pregnancy and postpartum. Comparative effectiveness and safety analyses versus other atypical antipsychotics.
	clozapine	Clozapine is one of the most effective antipsychotics for treatment-resistant psychosis and may be clinically indispensable for some pregnant individuals. Available evidence does not strongly support an increased risk of congenital malformations but suggests	Limited safety data for breastfed infants, including risks of agranulocytosis, seizures, and neurodevelopmental effects. Small sample sizes and lack of well-controlled comparative studies.	Focused observational studies and registries for pregnant and lactating individuals requiring clozapine. Systematic evaluation of infant outcomes and hematologic monitoring strategies.

		higher rates of miscarriage and gestational diabetes. Clozapine crosses the placenta and accumulates in breast milk, raising concerns for infant exposure. Existing data largely derived from case reports, case series, and small observational studies.	Absence of standardized guidance for infant monitoring when clozapine is continued.	Comparative studies assessing continuation of clozapine versus switching to alternative antipsychotics during pregnancy.
	olanzapine	Olanzapine is a commonly prescribed atypical antipsychotic and is used during pregnancy when clinically indicated. Known metabolic side effects (weight gain, insulin resistance) raise concerns for gestational diabetes and pregnancy complications. Limited but growing observational data exist; long-acting injectable formulations raise additional safety considerations.	Incomplete data on dose-specific and trimester-specific risks. Limited information on long-acting injectable olanzapine during pregnancy and lactation. Sparse lactation and infant exposure data.	Comparative safety studies focused on metabolic and obstetric outcomes. Evaluation of long-acting injectable formulations in pregnancy. Infant follow-up studies, including growth and neurodevelopment.
	brexpiprazole cariprazine	Brexpiprazole and cariprazine are atypical antipsychotics approved for schizophrenia and increasingly used in nonpregnant adults.	No data on risk of congenital anomalies, pregnancy complications, or neonatal outcomes. No PK data across pregnancy or lactation.	Pregnancy registries and large observational studies to characterize maternal, fetal, and neonatal outcomes. PK studies to evaluate placental transfer and

		Clinical use during pregnancy appears limited, largely due to absence of safety data and its frequent use as adjunctive therapy rather than monotherapy. No dedicated human pregnancy or lactation studies were identified.	Lack of information on infant exposure via breast milk.	changes in maternal drug levels across pregnancy. Lactation studies to assess infant exposure and short-term safety.
attention-deficit hyperactivity disorder (ADHD)	dextroamphet-amine	Stimulants are widely prescribed outside pregnancy; pregnancy data are limited and often confounded. Use during pregnancy is controversial and highly individualized.	Insufficient data on neurodevelopmental outcomes and dose–timing effects. Limited guidance on continuation versus discontinuation during pregnancy.	Longitudinal child outcome studies. Comparative studies versus nonpharmacologic management strategies.
anxiety	hydroxyzine	Commonly used for anxiety and sleep; often perceived as low risk. Evidence base in pregnancy is limited and largely historical.	Lack of modern pregnancy and lactation outcome data. Limited data on neonatal sedation or adaptation effects.	Systematic evaluation of short-term and repeated exposure in pregnancy. Comparison with nonpharmacologic sleep interventions.

PK, pharmacokinetic; MDD, major depressive disorder; ADHD, attention-deficit hyperactivity disorder

Antidepressants (SSRIs/SNRIs)

Selective serotonin reuptake inhibitors (SSRIs) and related agents are first-line treatments for depression and anxiety and are among the most commonly used psychotropic medications during pregnancy. Use of these agents has increased substantially over the past decade, reflecting both high prevalence of perinatal depression and expanded indications.

Knowledge Gaps

- Most studies evaluate drug classes rather than individual medications, limiting the ability to identify differential safety profiles.
- Limited PK and PD data across pregnancy stages and lactation.
- Incomplete understanding of neonatal adaptation syndrome, including mechanisms, severity spectrum, and long-term significance.
- Sparse data on dose adjustments across pregnancy and the impact of tapering strategies on risk of maternal relapse and withdrawal symptoms in mother and neonate.

Evidence Review

- Recent studies suggest a dose-dependent association between late-pregnancy SSRI exposure and delayed neonatal adaptation, with increased NICU admissions.
- Neuroimaging studies describe potential structural brain differences, and a recent meta-analysis found an increased risk of preterm birth, postnatal adaptation syndrome, and persistent pulmonary hypertension of the newborn in children prenatally exposed to SSRIs; however, clinical relevance remains unclear, and findings may reflect underlying maternal illness severity.
- Umbrella reviews and meta analyses indicate that many reported associations are weak or not statistically significant, emphasizing the need for cautious interpretation.
- While SSRIs and SNRIs are not classified as teratogens, some studies suggest a slightly increased risk for cardiac malformations - most notably associated with paroxetine - when SSRIs are used in the first trimester.

Clinical Considerations

- Untreated maternal depression carries significant risks to both the mother, including psychiatric emergencies and postpartum relapse, and poor outcomes for the neonate
- Benefit–risk assessment must explicitly compare medication exposure versus no treatment, rather than assuming medication avoidance is safer.
- Non-pharmacologic therapies (e.g., cognitive behavioral therapy, exercise, light therapy, transcranial magnetic stimulation (TMS)) may be appropriate for mild symptoms but are often insufficient for moderate to severe illness; initiating treatment with a non-pharmacologic intervention may prevent or delay the need to introduce antidepressant medication in some cases. Optimizing dietary intake, with

an emphasis on whole foods and a reduction in ultraprocessed foods and added sugar, is recommended as part of any treatment plan during the peripartum period.

Antipsychotic Medications

Antipsychotics are essential for managing severe mental illnesses such as schizophrenia and, in some cases, bipolar disorder. Their use during pregnancy is often unavoidable, yet safety data—particularly for newer agents and long-acting formulations—remain limited.

Cariprazine

- Beyond schizophrenia, cariprazine is increasingly used as an adjunctive treatment in mood disorders but lacks robust pregnancy and lactation data.
- Clinical practice patterns suggest limited use during pregnancy, yet inadvertent exposure may occur.
- Key research needs are to determine risks of congenital anomalies, pregnancy complications, and neonatal effects.

Clozapine

- Clozapine is one of the most effective treatments for refractory schizophrenia but is underutilized due to safety concerns.
- Evidence suggests higher rates of miscarriage and gestational diabetes compared with other antipsychotics or no medication.
- Clozapine crosses the placenta and accumulates in breast milk, raising concerns about infant exposure and the need for monitoring.
- Safety data for breastfed infants are particularly limited.

Long-Acting Injectable Antipsychotics (LAIs)

LAIs may improve adherence in patients with severe illness.

- Very limited data exist on maternal exposure, fetal transfer, and infant exposure during pregnancy and lactation.
- Olanzapine LAI presents additional safety considerations due to post-injection monitoring requirements.

First-generation antipsychotics (neuroleptics), e.g., fluphenazine, haloperidol

Research Landscape Analysis

- Typical antipsychotics have long-standing clinical experience and are sometimes used during pregnancy.
- Most evidence is older and predates contemporary obstetric and neonatal care.
- Data are primarily observational and often pooled across drugs.

Research Gaps

- Limited modern data on pregnancy, neonatal, and long-term child outcomes.

- Lack of drug-specific analyses within this class.
- Sparse lactation safety data.

Research Needs / Priorities:

- Updated observational studies using contemporary datasets.
- Drug-specific analyses rather than pooled class estimates.
- Long-term follow-up of exposed children.

Second-generation (atypical) antipsychotics, e.g., paliperidone, risperidone

Research Landscape Analysis

- Paliperidone and risperidone are commonly prescribed atypical antipsychotics.
- Pregnancy data exist but are limited and often analyzed at the class level.
- Long-acting injectable formulations are increasingly used but poorly studied in pregnancy.

Research Gaps

- Limited drug-specific data on fetal, neonatal, and lactation outcomes.
- Insufficient evidence on long-acting injectable formulations.
- Lack of comparative studies versus other atypical antipsychotics.

Research Needs / Priorities

- Drug-specific pregnancy and lactation safety studies.
- Evaluation of long-acting injectable exposure during pregnancy.
- Comparative studies to inform individualized benefit–risk assessment.

Prioritized Research Needs and Recommendations

- Mental health treatment during pregnancy requires individualized benefit–risk assessment, explicitly accounting for risks of untreated illness. Patient assessment may differ in women already taking mental health medication at the onset of pregnancy versus those initially medication-free. To achieve optimal personalized approaches to pharmacotherapy of mental disorders during the peripartum period, the following studies are needed:
    - Case-control series, tracking the course of patients on medication throughout pregnancy (or through specific portions of pregnancy) compared with patients with similar mental health disorder/symptoms who declined meds
    - Studies of necessary dose adjustments during and after pregnancy, with emphasis on minimizing withdrawal symptoms in mother and neonate

    - Studies that prioritize lactation findings, prospectively evaluating psychotropic medication concentrations in breast milk and related drug exposure and effects on the nursing infant as named study aims.
    - Studies of non-pharmacologic interventions that could replace medications or permit lowering of dose (combined treatments), if appropriate
    - Any study type should consider mediators and moderators of clinical response, including patient characteristics (e.g., age, ethnicity, history of previous pregnancies, family history of mental disorders) and clinical research should not increase risk to participants
- Drug-specific data are urgently needed; reliance on class-level evidence obscures meaningful differences between medications, in terms of both effectiveness and safety.
- SSRIs and antipsychotics remain high-priority research areas due to widespread use and persistent evidence gaps. Medications for sleep are also understudied.
- Registries, PK studies, and large-scale observational and longitudinal data are essential to advance the evidence base. These must include consideration of both the mother and the fetus.
- Polypharmacy, mechanistic insights, paternal exposures, and long-term child outcomes are underexplored but critical areas for future research.
- In research as in clinical practice, the needs and preferences of the patient and her family, and principles of informed consent remain paramount.

6. Obesity

This working group considered two nominations: Glucagon-like peptide 1 (GLP-1) receptor agonists and metformin. A research landscape analysis was provided (Appendix 2). A summary of the salient findings are described in Table 6.1.

Table 6.1 Obesity Priorities

Nomination	Research landscape analysis
GLP-1 agonists (liraglutide, semaglutide, etc.)	1. GLP-1 receptor agonists have extremely limited published studies (<10) across all study types in PPL populations. 2. Liraglutide had the most, with 7 PE studies in the pregnant population.
Metformin	1. Substantial literature exists for metformin, with 173 PK, 636 PE, and 448 CT studies, noted in the pregnant population. 2. Besides the pregnant population, studies with information on fetal health are more common (54 PK, 134 PE, and 91 CT), followed by postpartum studies (15 PK, 37 PE, and 27 CT), and lastly lactation studies (4 PK, 8 PE, and 4 CT).

GLP-1, glucagon-like peptide 1; PPL, pregnant, postpartum, lactating; PE, pharmacoepidemiology; PK, pharmacokinetic; CT, clinical trial

Questions for Consideration

The working group considered the following questions:

1. How is obesity defined in PPL populations?
2. What conditions are GPL-1 receptor agonists and metformin (drug nominations) used to treat in PPL populations?
3. What are potential adverse effects of stopping when pregnancy is identified? What are the adverse effects of using these medications?
4. Are the drugs represented in the RFI nominations representative of the topic area and align with standard of care? If not, what is needed to assess missing therapeutics?
5. What are the long-term effects of prenatal, antenatal, and lactation exposure to GLP-1 medications?
6. What are the impacts on pregnancy and the developing fetus for those who inadvertently become pregnant while using GLP-1s?
7. How much do these medications enter breast milk and what side effects could the exposure cause for the breastfed baby?
8. Since the drug crosses the placenta, what is the potential long-term impact on the fetus?

The discussion produced the following recommendations:

Filling Research Gaps

1. There is no established standard of care for GLP-1 receptor agonists (e.g., liraglutide semaglutide, tirzepatide) in PPL populations; use tends to be patient-driven or guided by individual risk–benefit discussions (*the semaglutide (Ozempic) FDA label states that it should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus*).
2. Insufficient biological plausibility research on fetal impact of GLP-1s.
3. When abruptly discontinued after a positive pregnancy test, the weight gain and potential hyperglycemias might be an effect to consider.
4. Effect on milk volume, micronutrients, fatty acid composition, human milk oligosaccharides, trace minerals, etc. from reduced calorie intake under GLP-1 therapy, particularly in pregnancy and lactation, is unknown. Contributing factors may be potential food deserts, malnutrition, or metabolic/bariatric surgeries.
5. Comorbidities such as hypertension and hyperlipidemia should be addressed in evaluating therapeutic priorities, as they substantially influence pregnancy outcomes and may confound observed drug effects.
6. Patient behavior information and medication access information may not be fully available. Patients may sometimes obtain GLP-1 prescriptions through outside compounding vendors, complicating accurate exposure assessment. Transition of care throughout the process from preconception, pregnancy, postpartum, and back to the primary care physician could also affect adherence or compliance with drugs.
7. Exposure assessment is also challenging, considering that some of these GLP-1s come from compounding pharmacies and other online providers where other things may get added intentionally or unintentionally. Additional factors complicating assessment include the use of other supplements and nutraceuticals to counteract the negative effects of these drugs.
8. Administrative claims data have very limited information available on lactation/breastfeeding status; however electronic health records in some health care systems may capture this information. Additionally, use of GLP-1 drugs may not be accurately captured by EHR or claims data unless it is prescribed by their physician or other regular health care provider when it is documented in their EHR along with the prescription.
9. Standardizing outcomes and data definitions across systems is essential, referencing the United States Core Data for Interoperability (USCDI) Plus maternal-health data standards as a framework for consistent EHR variable capture.
10. Long-term follow-up studies among offspring exposed to metformin or GLP-1s are lacking.
11. Newer GLP-1–based agents, such as tirzepatide (dual GLP-1/ glucose-dependent insulinotropic polypeptide (GIP) agonist) and oral semaglutide (with permeation enhancer), introduce additional complexity due to formulation differences that may alter absorption and interactions.

Prioritized Research Needs

1. Develop reports that summarize current evidence and will support prioritization of a research needs framework.
2. Determine the prevalence of GLP-1 use across pregnancy, postpartum, and lactation, including preconception exposure given that many pregnancies are mistimed or unplanned.
    a. Postpartum and lactation periods are unique risk windows where motivations for weight loss and return to pre-pregnancy weight may drive unsupervised GLP-1 use, warranting special prioritization in research planning.
    b. Some patients with severe type 2 diabetes reportedly continue GLP-1 therapy during pregnancy due to perceived benefit–risk trade-offs; this group should be specifically studied as a clinically distinct subgroup.
3. Capture real-world diversity, including race, ethnicity, comorbid conditions, socioeconomic status, health insurance availability and type, and health-system access to understand risk profiles and support equitable prioritization.
4. Understand risks associated with abrupt discontinuation of GLP-1s during pregnancy.
5. Leverage existing consortia like Environmental influences on Child Health Outcomes (ECHO) or Implementation of Preeclampsia Screening and Prevention (IMPRESS)[87], as well as potential engagement with the FDA's Sentinel Initiative for utilization tracking and safety signal detection.
6. Design and conduct studies using large-scale RWD to capture drug exposure across pre-conception or pregnancy stages as well as breastfeeding and to evaluate longitudinal outcomes.
7. Develop or expand biorepositories, particularly for human milk, to study pharmacokinetic and compositional effects of GLP-1 exposure during lactation.
8. Design survey-linked cohort studies to capture patient motivations, reasons for continuation/discontinuation, and perceptions of side effects (that are rarely recorded in structured data) among reproductive age, pre-conception, and pregnant populations.
9. Continual assessment/reassessment of the GLP-1's, including the newer GLP-1's, evidence landscape to understand health impact on PPL populations.
10. Exploratory studies to assess potential gut-microbiome and/or environmental interactions that could influence therapeutic effects of GLP-1 RA.

7. Preterm Birth

Background

A preterm delivery, also known as premature birth, occurs when a baby is born before 37 weeks of pregnancy. It is considered a syndrome with multiple pathogeneses. Preterm deliveries can be categorized into different subcategories based on gestational age, including:

- Extremely preterm: < 28 weeks
- Very preterm: 28 to <32 weeks
- Moderate to late preterm: 32 to < 34 weeks
- Late preterm: 34 to <37 weeks

Preterm delivery is the leading cause of neonatal morbidity and mortality and the most common reason for antenatal hospitalization. It accounts for 25-50% of cases of long-term neurologic impairment, cerebral palsy, breathing problems, feeding difficulties, and/or impaired vision or hearing. Current practice for preterm labor involves the use of tocolytic drugs to delay labor and allow for the administration of corticosteroids and magnesium sulfate and transport to a tertiary facility. Common medications to treat preterm labor include nifedipine and indomethacin; terbutaline can be used in acute settings, and magnesium is now used only for neuroprotection for 12 hours. These medications have limited effectiveness in preventing preterm birth and there is a lack of consensus on the optimal tocolytic drug to use, leading to variability in practice. There is a need for more research and evidence-based guidelines to guide the use of these drugs effectively and safely. Despite decades of clinical use of tocolytics, no therapy has meaningfully reduced the overall rate of preterm birth.

The RFI nominations for the preterm birth therapeutic area included hydroxyzine; aspirin; statins; azithromycin; novel synthetic progestin; progesterone; choline/ phosphatidylcholine; and prenatal multivitamin/mineral supplements (over-the-counter (OTC) and prescribed). These were discussed at the July 2024 Inaugural Stakeholders meeting (Appendix 1). Those early RFI nominations were not aligned with current clinical realities, therefore the group expanded the scope, and additional therapeutic agents were considered. The additional nominations are presented here.

The MPRINT Hub performed additional analyses for the below listed drugs (Appendix 2). The drugs were placed into three categories: those used for the prevention of preterm birth, currently used for the management of preterm birth, and emerging therapeutics. The high-level discussion points are included in Table 7.1 - Table 7.3.

Table 7.1 Preterm Birth Priorities – Prevention

Nominations	Research Landscape analysis	Research gaps	Research needs/priorities
Progesterone **17-hydroxy-progesterone acetate**	Identified as the highest-priority agents; currently the most studied, yet dosing and efficacy data remain debated	1. PK/PD Deficit: Significant lack of PK and PD data across all gestational stages and lactation for prevention agents. 2. Dosing ambiguity: Even for widely used agents like vaginal progesterone, current dosing is likely inadequate and not based on proper PK studies. 3. Regulatory Barriers: Historically, the lack of clear regulatory pathways and standardized definitions for 'safety' and 'efficacy' in pregnancy trials has contributed to regulatory complexity and hesitancy in study design and implementation. However, the Committee recognizes the recent release of draft guidance from the U.S. Food and Drug Administration on the inclusion of pregnant and breastfeeding women in clinical trials[88], which represents an important step toward greater regulatory clarity and consistency. 4. Lactation Data: Lactation-specific studies are almost non-existent for these agents.	1. Foundational PK/PD: Conduct foundational PK/PD studies to optimize dosing and administration before launching further large clinical trials. 2. Confirmatory Trials: Design well-structured confirmatory studies for 17-OHPC which is considered the 'closest to patient' therapeutic available. 3. Biomarker Development: Develop precision medicine approaches to identify patient phenotypes responsive to specific therapies. 4. Pre-pregnancy Interventions: Explore pre-pregnancy interventions as they may be easier to study and approve.
Aspirin	Large trials comparing doses are currently underway (e.g., MFMU Network)		
Statins	Emerging as a 'close second' priority due to promising early data, though large trials are currently on hold by the FDA.		
Omega-3 docosahexaenoic acid **Icosapent** **Eicosapentaenoic acid** **L-arginine** **Selenium**	Nominated supplements generally lack a compelling evidence base or clear mechanism of action		

PK, pharmacokinetic; PD, pharmacodynamic; MFMU, Maternal Fetal Medicine Units; FDA, Food and Drug Administration; 17-OHPC, 17-alpha-hydroxyprogesterone caproate

Table 7.2 Preterm Birth Priorities – Management

Nominations	Research Landscape analysis	Research gaps	Research needs/priorities
Nifedipine	1. Current Efficacy: Existing tocolytics (nifedipine, indomethacin) have minimal impact on overall preterm birth rates and are primarily used to 'buy time' for steroid administration. 2. Entrenched Practice: Agents like Nifedipine and Indomethacin are 'entrenched' in clinical practice despite a lack of rigorous evidence supporting their efficacy.	1. Lack of Biomarkers: No biomarkers currently exist to guide therapy or stratify patients (e.g., distinguishing calcium-driven vs. inflammation-driven labor). 2. Standardization: Lack of harmonized definitions for safety and efficacy hinders trial comparability. 3. Trial Challenges: Historically, conducting placebo-controlled trials for new agents (like oxytocin receptor antagonists) has been difficult due to regulatory requirements and ethical concerns. However, the Committee acknowledges the FDA's recent draft guidelines on including pregnant and lactating populations in clinical trials[88], which represents an important step toward facilitating these necessary studies.	1. Comparative Effectiveness: Conduct comparative effectiveness studies (e.g., nifedipine vs. indomethacin) to refine the use of currently available agents without needing a placebo arm. 2. PK Studies: Prioritize PK studies for standard-of-care drugs (nifedipine, indomethacin) to understand metabolism at different gestations. 3. Precision Medicine: Incorporate panels of biomarkers (e.g., inflammatory cytokines) into ongoing studies to enable machine learning and targeted therapy.
Indomethacin			
Retosiban	Previously showed promise and a good safety profile. The Phase 3 trials were halted primarily due to feasibility challenges driven by the FDA's requirement for a placebo arm, rather than safety or efficacy failures; considered a candidate for revisiting.		
Nicardipine **Atosiban** **Celecoxib** **Isosorbide dinitrate**			

Glyceryl trinitrate **Dexlansoprazole** **Esomeprazole** **Illaprazole** **Lansoprazole** **Omeprazole** **Pantoprazole** **Rabeprazole** **Nicorandil** **Rofecoxib** **Ketorolac**			

Table 7.3 Preterm Birth Priorities - Emerging Therapeutics

Nominations	Research Landscape analysis	Research gaps	Research needs/priorities
Anti-TLR4 antibody **Lipid A mimetic CXR-526** **Naloxone** **Naltrexone** **Rilonacept** **Kineret** **Canakinumab** **Tocilizumab** **Satralizumab** **Sarilumab** **BN83470** **FX125L** **5z-7-oxozeaenol** **Tiophene2-carboxamide 1** **N-acetyl cysteine** **Sulfasalazine** **Rytvela** **MR-16** **HSJ633**	1. Inflammatory Pathway: Inflammation identified as the critical 'converging pathway' for multiple preterm birth phenotypes, offering a target for broad therapeutic impact. 2. Repurposing Potential: Significant opportunity exists to repurpose immunomodulators and biologics currently used in rheumatology and immunology.	1. Mechanism-Based Gaps: Lack of therapies that specifically target the underlying biological mechanisms of preterm labor, such as chronic infection or uteroplacental insufficiency. 2. Targeted Delivery: Currently, there is a lack of available drugs or molecules in development that target the myometrium, thereby improving efficacy and reducing fetal adverse effects.	1. Inflammation Targeting: Prioritize research into anti-inflammatory agents and monoclonal antibodies targeting specific cytokines. 2. Organ-targeted therapy: Develop 'organ personalized' delivery methods to target the myometrium specifically. 3. Preclinical Candidates: Explore PGF2-alpha antagonists as potential candidates based on preclinical data.

Summary of Preterm Birth Working Group Discussions

The group considered the following questions:

1. What are the current strengths and limitations of available tocolytic therapies?

The group discussed the significant limitations of current tocolytics and the evidence supporting their use including:

- current tocolytics have limited impact on preterm birth rates
- concerns about the overuse of tocolytics without clear indications, emphasizing the need for research on patient selection and stratification to inform practice guidelines.
- lack of biomarkers to guide therapy and the multifactorial nature of preterm labor. Consider incorporating inflammatory cytokine profiling into future studies.
- drugs are titrated to a clinical response (i.e., cessation of contractions), and this already serves as a PD response, complicating the rationale for formal PK/PD studies.

2. Which agents show the most promise for improving maternal and neonatal outcomes?

- The "lowest hanging fruit" would be to refine the use of currently available agents, nifedipine and indomethacin, by comparing them against each other and against a placebo.
- From a preclinical standpoint, PGF2-alpha antagonist is a potential candidate to explore further.
- A recommendation for revisiting ritosiban, an oxytocin receptor antagonist was presented as it showed promise and had a good safety profile before its Phase 3 trial was pulled.
- A proposal for focusing on the inflammatory pathway, highlighting emerging data on anti-inflammatory agents and monoclonal antibodies that target specific cytokines.

3. How should we prioritize therapies for further study—based on biological plausibility, safety, or feasibility of large trials?

The group discussed a prioritization matrix to guide therapeutic selection based on:

- Biological plausibility
- Safety profile
- Feasibility of large trials
- Equity/access
- Alignment with guidelines

4. What trial designs would best evaluate efficacy and safety in pregnancy, given regulatory, ethical and PK/PD considerations?

- Comparative Effectiveness Trials: would be a practical approach that could avoid the need for a placebo arm.

- Placebo-Arm Challenges: studies requiring a placebo arm are difficult to conduct in preterm birth,

Innovative trial designs are needed in pregnancy and should be considered including RWE approaches.

5. How can PK/PD studies, biomarkers, or precision medicine approaches be incorporated?

- Biomarkers: identify an agreed-upon panel of biomarkers (e.g., inflammatory cytokines) that could be incorporated into any ongoing study. This would build a dataset that could be fed into machine learning models to find patterns that are not currently apparent.
- Precision Medicine: the inflammatory pathway provides an opportunity for a precision medicine approach where biomarkers could be used to target therapies to patients most likely to respond.
- Targeted Delivery: developing drugs that specifically target the myometrium without crossing the placenta, an approach of "organ personalized" medicine that would improve efficacy and reduce fetal adverse effects.
- PK: Multiple members stressed the need for better PK data including studies to understand how pregnant patients at different gestations metabolize nifedipine and indomethacin.

6. What role do underlying mechanisms play in guiding therapeutic development?

- The inflammatory pathway appears to play an important role as it is where "all the phenotypes begin to converge," making it a powerful therapeutic target for a wide range of patients who experience preterm birth for different initial reasons.
- There is a current lack of mechanism-based treatment, noting that clinicians do not know if a patient's labor is driven by a calcium pathway (for which nifedipine would be logical) versus an inflammatory one (for which indomethacin would be better).

7. Are there opportunities for repurposing drugs currently used in other fields?

- Any repurposed drug would require dedicated pharmacologic studies for use in pregnancy.
- Potential for using novel immunomodulators and monoclonal antibodies from fields like rheumatology and immunology for use in obstetrics.

Research Landscape Analysis Summary

The working group noted that while progesterone remains the most studied agent for prevention, data for other therapeutics is sparse. For the management of preterm labor, clinicians rely on ‘entrenched’ agents like nifedipine and indomethacin, which have been used for decades despite minimal impact on the inflammatory pathway, with potential for repurposing immunomodulators (e.g., IL-1R and IL-6R antagonists) from other fields.

Overarching Research Gaps

- Standardization Needs: There is a lack of harmonized definitions for safety and efficacy in pregnancy-related studies. Improved protocols are needed to enhance trial comparability and outcomes.
- PK and Precision Medicine: PK studies tailored to pregnancy physiology are essential. A precision medicine approach should be adopted to optimize treatment strategies.
- Mechanistic Focus: Research should target mechanisms of preterm birth such as chronic infection, inflammation, and uteroplacental insufficiency.
- Development of common biomarkers to aid precision medicine.
- Development of targeted therapy to the mother to decrease possible side effects to the fetus.

Prioritized Research Needs

1. PK/PD: critical need for PK/PD studies for both new and existing agents (including vaginal progesterone and nifedipine) to optimize dosing and safety across gestation and lactation.

2. Comparative Effectiveness: for management, the group prioritized comparative effectiveness trials of current standards (e.g., nifedipine vs. indomethacin) over placebo-controlled trials. Revisit high-promise agents (e.g., retosiban, statins).

3. Precision Medicine & Biomarkers: future research must move toward precision medicine by validating biomarker panels (e.g., cytokines) to stratify patients and target therapies to specific mechanisms (e.g., inflammation vs. calcium pathway).

4. Regulatory Alignment: establishing standardized definitions for ‘safety’ and ‘efficacy’ in pregnancy is essential to overcome regulatory hurdles that stall drug development.

Framework for future prioritization decisions

Matrix for Preterm Labor Therapies

Therapy Candidate	Biological Plausibility	Safety in Pregnancy	Feasibility of Large Trials	Novelty / Repurposing Potential
Nifedipine (Calcium channel blocker)	High	High	Medium	Low novelty
Atosiban (Oxytocin receptor antagonist)	High	Concerns from European Union data	Medium	Medium
Indomethacin (Nonsteroidal antiinflammatory)	Strong	Medium	Medium	Low novelty
Magnesium sulfate	Medium/ Moderate	High	Medium	Low
Nitric oxide donors (e.g., nitroglycerin)	Medium/ Moderate	Medium	Medium	Medium
Proton-pump inhibitors (repurposing)	Weak	High	Medium	High
Novel immunomodulators (e.g., TNF-α blockade)	Strong	Unknown, likely safe based on limited data	Low due to costs	High

Matrix for Prevention of Preterm Labor

Therapy Candidate	Biological Plausibility	Safety in Pregnancy	Feasibility of Large Trials	Novelty / Repurposing Potential
Progestogens	High	High	Medium	Low
Statins	Medium	Awaiting data, certain statins likely safe	Low	High
Aspirin	High	Medium	Medium for dosing	Low
Omega-3 docosahexaenoic acid (DHA)	Medium	High	Low	Low
Eicosapentaenoic acid (EPA)	Medium	High	Low	Low
Selenium	Low	High	Medium	medium
L-arginine	Low	High	medium	high

8. Sleep/Circadian disorders

Background/Rationale:

Women experience an array of sleep problems across peri and post-partum including sleep disorders (e.g., insomnia, restless legs syndrome, sleep apnea) and other indices of sleep deficiency, such as insufficient sleep duration, poor sleep quality, irregular timing of sleep/wake schedules and excessive daytime sleepiness. Poor sleep has been linked to an increased risk for adverse pregnancy outcomes and emerging evidence points to potential effects of maternal sleep on fetal development and neonatal health. Sleep problems may increase the risk for gestational hypertensive disorders, gestational diabetes, post-partum depression, cesarean delivery, and NICU admissions. Pharmacological agents widely used in the general population to treat sleep disorders and offer relief from sleep deficiency are also used by pregnant, post-partum and lactating (PPL) women. FDA approved medications may be prescribed on- or off-label to address poor sleep, and OTC products are widely available for self-medicating. The decision to use prescription and/or OTC products to address sleep problems includes consideration of the potential benefits vs. risks to maternal and fetal health. Pregnancy-specific physiology that may impact PK/PD, and potentially efficacy, also need to be considered. The PRGLAC Sleep Working Group evaluated (a) current knowledge gaps and urgent research needs/opportunities regarding the use of sleep medications by PPL women, (b) existing publications on the efficacy and safety of sleep-related medications on maternal and fetal health, and (c) strategies to move a research agenda forward to close identified gaps in sleep medication use in PPL women.

Landscape analysis

Table 8.1 depicts the medications (prescription and OTC) and respective sleep/circadian conditions included in the publication landscape analysis. The working group expanded the list of medications that appeared in the initial nomination list since it was determined that the scope of therapeutics available for sleep/circadian conditions was much broader. For example, insomnia medications span a range of drug classes, including benzodiazepines, non-benzodiazepine hypnotics (Z-drugs), dual orexin antagonists, tricyclic antidepressants, antihistamines, and melatonin agonists among others. Some medications used for indications such as depression, anxiety, and nocturia may have secondary effects on sleep but are not necessarily used with sleep/circadian rhythm as the primary target outcome – these medications were not comprehensively represented in the landscape analysis (Appendix 2).

In summary, the landscape results show that few PK, pharmacoepidemiological (PE) or clinical trial (CT) studies are available for medications used for primary sleep/circadian indications in PPL women. Therefore, these studies may not reflect the dosing, timing and/or duration of use comparable to when medications are used for specific sleep/circadian conditions. The majority of manuscripts involving 'sleep drugs' focus on frequent co-morbid conditions (e.g., depression, anxiety), but not primarily on sleep/circadian disorders or complications. These findings point to important unanswered

questions about how accurately medication data can be generalized from PPL to non-PPL women and from one primary indication to another.

Therefore, a major research gap identified is an apparent lack of information on the efficacy and safety of medications used specifically for sleep/circadian indications in the PPL population. Similar questions relate to whether the dose, duration, and administration of sleep/circadian medications need to be specific to the PPL population vs. the general population, and whether dosing requirements may change across pregnancy, postpartum, and lactation (e.g., trimester) to ensure optimal efficacy and safety. Systematic data is lacking on what prescription and OTC products PPL women are most commonly using in the real world (e.g., outside of medical care). Additional gaps pertain to lack of information on patient-centered factors that influence the decision to use or not use medications and the need for decision support tools to assist women and healthcare providers make informed and evidence-based decisions. The Working Group determined that a strategic approach is needed to address the near and long-term research needs and priorities for the use of sleep/circadian medications in PPL women, described below.

Table 8.1 Sleep/Circadian Disorders and Medications

Therapeutic area*	**Nominations***
Insomnia	FDA-approved Dual orexin receptor antagonists - **suvorexant, lemborexant, daridorexant** **Benzodiazepines – temazepam, lorazepam, flurazepam, estazolam, triazolam, quazepam** **Z drugs – zolpidem, eszopiclone, zaleplon** Tricyclic - doxepin Antihistamines - diphenhydramine, doxylamine MT1/MT2 receptor agonist: ramelteon
	Off label Tri/tetracyclic antidepressants -**trazodone**, amitriptyline, mirtazapine Antipsychotics - quetiapine, olanzapine **Benzodiazepine - clonazepam, oxazepam** **Buspirone** **Gabapentin** Barbiturates - amobarbital, phenobarbital, pentobarbital, secobarbital Dimenhydrinate **Hydroxyzine** Over the counter **Melatonin**
Narcolepsy	FDA-approved Amphetamine/Dextroamphetamine Armodafinil Modafinil Sodium Oxybate Solriamfetol Calcium, magnesium, potassium, and sodium oxybates Methylphenidate

	Dextroamphetamine H3 receptor antagonist – pitolisant
	Off label SNRI - desvenlafaxine Lisdexamfetamine Ephedrine
Idiopathic Hypersomnolence	FDA-approved Calcium, magnesium, potassium, and sodium oxybates
	Off label Modafinil Armodafinil H3 receptor antagonist – pitolisant Solriamfetol Methylphenidate Amphetamine Dexedrine
Restless leg syndrome	FDA-approved Dopamine agonists - pramipexole, ropinirole, rotigotine Gabapentin enacarbil
	Off label Gabapentin Pregabalin Carbidopa, levodopa Clonazepam, temazepam, oxazepam Baclofen Iron supplements
Bruxism	Off label Clonazepam Buspirone Botulinum toxin Opioids - hydrocodone, codeine, tramadol, oxycodone, methadone, extended-release morphine sulphate
Obstructive/central sleep apnea	FDA-approved Tirzepatide
	Off label Acetazolamide Dronabinol Theophylline
Non-24-hour sleep-wake cycle	FDA-approved Tasimelteon)
REM sleep behavior disorder	FDA-approved Pramipexole Rivastigmine Clonazepam
Sleepwalking	Off label Estazolam Clonazepam

	Trazodone Gabapentin

*Bold text denotes indications and nominations from the original Request for Information.

Research Gaps

1. *Real-world medication use* for sleep/circadian disorders is not well characterized in PPL populations, including off-label and OTC agents

- Need for systematic data on prescribed or OTC medications for sleep and circadian disorders in PPL populations, including FDA-approved drugs, off-label prescription agents (e.g., trazodone and sedating antidepressants), and OTC products (e.g., melatonin and antihistamines)
- Need for data on use patterns of sleep/circadian medication, including primary indications for medication use (sleep vs. comorbid conditions), timing of use across gestation (i.e., trimester) and postpartum (i.e., peripartum through lactation), duration of use, and patterns of tapering or discontinuation

2. Insufficient evidence base regarding *dosing requirements* of sleep/circadian medications *and PK* across pregnancy, postpartum, and lactation

- Need for clarity on what is known and unknown about dosing of specific sleep/circadian medications across trimesters and postpartum to optimize efficacy and safety profiles
- Need to prioritize drugs and classes where PK data are most urgently needed in pregnancy, postpartum, and lactation to inform practical dosing guidance

3. Lack of *safety information* on medications used specifically for sleep/circadian indications during pregnancy, postpartum, and lactation in mothers, fetuses, and children.

- Need for short- and long-term safety data for mothers, fetuses and children resulting from sleep/circadian medication use during gestation through lactation
- Need for safety data related to drug transfer into breast milk, effects on lactogenesis and milk volume, and maternal ability to safely care for the infant at night

4. Paucity of *qualitative patient-centered, decision-support evidence* on medication use during pregnancy, postpartum, and lactation

- Need for qualitative and patient-centered evidence on how PPL women perceive sleep/circadian medications, weigh risks and benefits, and make decisions to use/not use, including drivers of mistrust and misinformation
- Need for decision aids and communication tools that translate what is known about sleep/circadian medications into practical support for shared decision-making between patients and clinicians

5. Lack of data on *practice patterns by health care providers*

- Need for information about potential differences between recommendations and prescriptions provided by sleep specialists and obstetricians to PPL women

- Need for detailed mapping of the practice differences and how prevalent they are to inform implementation and education work

6. Limitations of *RWD* in pregnancy, postpartum, and lactation

- RWD sources often lack indication, under-capture OTC use, and cannot reliably distinguish primary sleep treatment from other uses, which constrains how precisely drug–outcome relationships can be inferred.
- Need for methods to capture real-world OTC medication use, duration of exposure, and patient-determined indication to better understand sleep/circadian therapeutics

Prioritized Research Needs

1. Review and synthesize existing data

- Undertake a comprehensive evidence review or meta-analysis of safety, efficacy, and dosing of sleep and circadian medications in pregnancy, postpartum, and lactation
- Encourage joint sponsorship by sleep and obstetric societies, with opportunities for junior investigators, to produce a shared reference for the field

2. Leverage existing descriptive and epidemiologic studies to identify real world use patterns

- Use EHR, claims, and/or other databases, repositories or cohort studies to describe which sleep/circadian medications are used, when they are started and stopped, how long they are continued, and which populations receive them.
- Use these data to prioritize specific drugs for in-depth safety review, efficacy, and/or comparative effectiveness studies.

3. Generate high-priority safety studies using RWD

- Conduct observational safety studies (cross-sectional and/or prospective) focused on commonly used sleep/circadian medications (FDA-approved, off-label or OTC agents) for systematic evaluation of maternal, fetal, neonatal and longer-term child outcomes, including neurodevelopment and sleep.
- Include efficacy and safety outcomes in the same studies, acknowledging that in general, safety studies predominate the literature.
- Note: low frequency use may be reflective of lack of data and reluctance to use medications without sufficient evidence. As such, potential sleep agents with low prescription frequency may still be relevant and warrant evaluation.

4. Evaluate dosing and PK during pregnancy, postpartum, and lactation

- Prioritize sleep/circadian agents for PK and related studies to define trimester-specific and postpartum changes in exposure and drug transfer into breast milk using doses, timing and duration typically used for sleep/circadian indications.

- Translate these findings into practical dose adjustment guidance that balances maternal benefit with fetal and infant safety.

5. Create postpartum and lactation-focused studies

- Design studies that explicitly address postpartum sleep physiology, medication effects on nighttime caregiving, and the trade-offs between symptom control and infant care.
- Examine effects on lactogenesis and milk production for commonly used agents and integrate these outcomes into future guidance.

6. Design pragmatic comparative effectiveness studies combining safety and efficacy

- Design pragmatic comparative studies that compare commonly used agents with each other and, where relevant, with non-drug interventions, without relying on placebo arms that are unlikely to be acceptable.
- Include both clinical safety outcomes and patient-centered sleep and function outcomes to inform real-world decision-making.

7. Conduct qualitative and patient-centered decision-support research

- Conduct qualitative and mixed-methods studies with PPL women to understand beliefs, risk perceptions, and reasons for accepting or declining medications.
- Use these insights to create decision aids and communication tools that support shared decision-making and address mistrust and misinformation.

8. Develop PPL-specific common data elements for sleep

- Build a set of sleep and circadian common data elements (CDE) for pregnancy and postpartum, aligned with NICHD CDE work and developed through a structured consensus process.
- Recommend core questionnaires, objective measures, and biospecimens so that future studies collect harmonized data that can be pooled and compared.

9. Leverage existing cohorts and biorepositories before building new ones

- Mine existing pregnancy and mother–child cohorts that already contain some sleep or medication data and biospecimens to address focused questions.
- Use insights from these analyses to inform the design of new, more targeted longitudinal cohorts.

10. Develop new longitudinal pregnancy–child cohorts as a long-term goal

- Plan cohorts that enroll participants before or during pregnancy. Systematically collect sleep, medication and biospecimen data. Collect data on breastfeeding duration and extent. Follow offspring into childhood and adolescence for relevant developmental and health trajectory indices.
- Ensure that these cohorts are designed to close the most important gaps identified from RWE and safety work.

11. Conduct surveys of clinicians (health providers) and patients as part of the RWE ecosystem

- Implement surveys of obstetric providers, sleep specialists, and other clinicians (e.g., family medicine, primary care) to capture practice patterns, perceived risks, and barriers to prescribing or referring.
- Pair these with patient surveys to align research priorities with patient concerns and to identify barriers to study participation.

12. Engage a multi-stakeholder collaborative structure to sustain the agenda

- Encourage coordinated efforts led by federal agencies, academia, and foundations, with strong involvement from professional societies, patient groups, and where appropriate, industry.

Section 2: Therapeutic Areas Only Discussed at July 2024 Meeting

The therapeutic areas covered in this section were only presented at the July 2024 meeting. The meeting spanned two days, and each therapeutic area was discussed for approximately 30 minutes. Of note, the discussion on these topic areas was not as comprehensive as those discussed with the working groups. A high-level summary of research gaps and needs is provided below. A final Meeting Summary from the July 2024 "Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating (PPL) Persons" is available (Appendix 1).

1. Low Milk Supply

Research gaps

- Lack of information on most galactagogues, many of the clinical studies that have been conducted lack stringency, and it is difficult to define clinical outcomes

Research needs

- Identify the supplements mothers are using including those that other countries have shown to be effective.
- Need to understand questions about the contents of human milk, the variability of milk composition among individuals, the biological function of individual milk components, and standardized methods for quantifying an infant's milk intake volume. These metrics could then be utilized to assess a supplement or therapeutic agent's effect on lactation.
- Explore feasibility of identifying components of herbal supplements that are effective for lactation, realizing it may be difficult to tease out dynamics of multiple active constituents.
- Understand the role of psychosocial elements and other maternal factors that influence human milk composition and production.

2. Nutritional

Research gaps

- Which nutrients should be considered for optimal health outcomes in pregnancy and infancy and what are the potential effects of contamination in dietary supplements.

Research needs

- Understand how a person's diet informs which micronutrients they need and how much they should consume.

- Evaluate iodine in lactation as well as in the prenatal context, as iodine levels in breastmilk are affected by the mother's diet
- Examine prenatal vitamins holistically to study the best forms, absorption rates, and actual needs
- Consider role of precision health/medicine for research needs in this area (e.g., Nutrition for Precision Health study, powered by the *All of Us* Research Program, is currently still enrolling and is a model to capture deep phenotyping of the pregnant woman, the lactating woman, and the infant)
- Clear messaging to public on this topic is needed

3. Hyperemesis/Vomiting

Research gaps

- Limited research is available on medicinal therapies for nausea and vomiting in pregnancy.
- Although supplement products may be widely used for these purposes, few studies have been reported on their composition, safety, or efficacy.

4. Substance Abuse/Exposure

Research gaps

- Few studies address how substance use disorders (SUDs) and their medicinal therapies affect lactation and breastmilk.
- Basic mechanistic studies of substance use in pregnancy are limited, and relatively few studies of any type exist to inform understanding of possible therapeutic approaches in pregnant people who used several commonly abused illicit drugs

Research needs

Additional studies are required prior to forming a consensus on prioritization

- Studies targeted at delineating changes in the PK of SUD therapeutics during pregnancy and in the postpartum period
- Studies targeted at the transfer of addictive substances as well as therapeutic agents through the placenta and into breast milk
- Influence of polysubstance use on maternal and fetal outcomes
- Establishing normative and SUD-related brain changes during pregnancy and postpartum
- Identification of specific windows of vulnerability and biological factors that increase vulnerability during pregnancy and in the postpartum period
- Elucidating mechanisms underlying individual differences in vulnerability
- Influence of comorbidities such as postpartum depression, sleep disturbances, etc.

Consideration of non-pharmaceutical interventions:

- Circumvent polydrug use and exposure as well as drug-drug interactions
- Cognitive behavioral and digital behavioral therapies
- Neuromodulation (e.g., TMS, focused ultrasound and low intensity focused ultrasound, phrenic nerve stimulation, etc.)

5. General Anesthesia

Research gap

For general anesthetics, there was a question of whether the advice to pump and dump breastmilk is backed up by actual evidence of transfer or harm to the baby.

- Data from MPRINT studies on general anesthetics showed more studies conducted during pregnancy than in the postpartum period, with almost none during lactation

Section 3: Therapeutic Areas Not Discussed during 2025-2026 Working Groups or July 2024 Meeting

Drug nominations submitted in response to the RFI across some therapeutic areas were not discussed at the July 2024 meeting or during the 2025-2026 Working Groups due to staffing constraints. The therapeutic areas represented in this category included:

1. Asthma
2. Autoimmune conditions
3. Endocrinological conditions
4. Gynecological conditions
5. Neurological conditions
6. Orthopedics
7. Pain
8. Radiology
9. Select nominations for Substance Abuse
10. Select nominations for Substance Exposure

While drug nominations from the above therapeutic areas were not discussed, please see Appendix 2 for MPRINT Knowledge Gap Graph analyses that were prepared to help identify knowledge gaps in the types of studies that will be needed to advance therapeutic research for PPL women. Graphs represent the number of publications referencing clinical studies of drug nominations in the respective therapeutic areas by study type and by population type.

Abbreviations

ACE	angiotensin converting enzyme
ACOG	American College of Obstetricians and Gynecologists
ADHD	attention-deficit/hyperactivity disorder
AE	adverse event
aPTT	activated partial thromboplastin time
ARB	angiotensin receptor blocker
ASCVD	atherosclerotic cardiovascular disease
ASH	American Society of Hematology
AUC	area under the curve
BMI	body mass index
BPCA	Best Pharmaceuticals for Children Act
CDE	common data elements
CVD	cardiovascular disease
CUDDLE	Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfed Infants
cUTI	complicated urinary tract infection
Cmax	maximum concentration
CT	clinical trial
DAA	direct acting antiviral
DART	developmental and reproductive toxicology
DOAC	direct oral anticoagulants
DVT	deep vein thrombosis
EDIVA	Efficacy and Demonstration of IntraVenous Iron for Anemia in Pregnancy
EEG	electroencephalogram

EHR	electronic health records
ESBL	extended spectrum beta-lactamases
FAST RCT	Randomized Clinical Trial of Fetal Atrial Flutter & Supraventricular Tachycardia Therapy
FDA	Food and Drug Administration
GABA	gamma-aminobutyric acid
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide 1
HCV	hepatitis C virus
HDP	hypertensive disorders of pregnancy
HF	heart failure
HIV	human immunodeficiency virus
IDA	iron deficiency with anemia
IDWA	iron deficiency without anemia
IL	interleukin
IRB	institutional review board
IV	intravenous
IVIDA2	Intravenous Versus Oral Iron for Treating Iron-Deficiency Anemia in Pregnancy
LAI	long-acting injectable
LDL-C	low density lipoprotein-C
LMWH	low molecular weight heparin
MDD	major depressive disorder
MFM	maternal fetal medicine
MFMU	Maternal Fetal Medicine Units
M:P	milk to plasma ratio
MPRINT	Maternal and Pediatrics Precision in Therapeutics

MRSA	methicillin-resistant *Staphylococcus aureus*
MRI	magnetic resonance imaging
NACHHD	National Advisory Child Health and Human Development
NAMs	new approach methodologies
NICHD	*Eunice Kennedy Shriver* National Institute of Child Health and Human Development
NIH	National Institutes of Health
NRN	Neonatal Research Network
ORWH	Office of Research on Women's Health
OTC	over the counter
PABA	para-aminobenzoic acid
PAH	pulmonary arterial hypertension
PBPK	physiologically based pharmacokinetic modeling
PCSK9	proprotein convertase subtilisin/kexin type 9
PD	pharmacodynamics
PDE5	phosphodiesterase-5
PE	pharmacoepidemiological
PGF2-alpha	prostaglandin F2 alpha
PK	pharmacokinetics
PopPK	population pharmacokinetics
PRGLAC	Task Force on Research Specific to Pregnant Women and Lactating Women
PPL	pregnant, postpartum and lactating
PT	prothrombin time
PTN	Pediatric Trials Network
RCT	randomized controlled trial

REVAMP-TT	Randomized trial of intravenous iron for anemia in Malawian pregnant women in the third trimester
RFI	Request for information
RID	relative infant dose
RSV	respiratory syncytial virus
RWD	real world data
RWE	real world evidence
SCA	sickle cell anemia
SCD	sickle cell disease
SGLT2	sodium-glucose co-transporter-2
SNRIs	selective norepinephrine reuptake inhibitors
SPF	sun protection factor
SSRIs	selective serotonin reuptake inhibitors
TB	tuberculosis
Tmax	time to maximum plasma concentration
TMS	transcranial magnetic stimulation
TNF	tumor necrosis factor
UCSD	University of California, San Diego
UFH	unfractionated heparin
VTE	venous thromboembolism

References

1. Bateman BT, Hernandez-Diaz S, Fischer MA, Seely EW, Ecker JL, Franklin JM, Desai RJ, Allen-Coleman C, Mogun H, Avorn J, Huybrechts KF. Statins and congenital malformations: cohort study. BMJ (Clinical research ed). 2015;350:h1035. Epub 20150317. doi: 10.1136/bmj.h1035. PubMed PMID: 25784688; PMCID: PMC4362473.

2. Costantine MM, Tamayo E, Lu F, Bytautiene E, Longo M, Hankins GDV, Saade GR. Using pravastatin to improve the vascular reactivity in a mouse model of soluble fms-like tyrosine kinase-1-induced preeclampsia. Obstet Gynecol. 2010;116(1):114–20. doi: 10.1097/AOG.0b013e3181e10ebd. PubMed PMID: 20567176.

3. Costantine MM, Cleary K. Pravastatin for the prevention of preeclampsia in high-risk pregnant women. Obstet Gynecol. 2013;121(2 Pt 1):349–53. doi: 10.1097/AOG.0b013e31827d8ad5. PubMed PMID: 23344286; PMCID: PMC3880675.

4. Kumasawa K, Ikawa M, Kidoya H, Hasuwa H, Saito-Fujita T, Morioka Y, Takakura N, Kimura T, Okabe M. Pravastatin induces placental growth factor (PGF) and ameliorates preeclampsia in a mouse model. Proceedings of the National Academy of Sciences of the United States of America. 2011;108(4):1451–5. Epub 2010/12/29. doi: 10.1073/pnas.1011293108. PubMed PMID: 21187414; PMCID: PMC3029692.

5. Fox KA, Longo M, Tamayo E, Kechichian T, Bytautiene E, Hankins GD, Saade GR, Costantine MM. Effects of pravastatin on mediators of vascular function in a mouse model of soluble Fms-like tyrosine kinase-1-induced preeclampsia. Am J Obstet Gynecol. 2011;205(4):366.e1–5. Epub 20110629. doi: 10.1016/j.ajog.2011.06.083. PubMed PMID: 22083058.

6. Saad AF, Kechichian T, Yin H, Sbrana E, Longo M, Wen M, Tamayo E, Hankins GD, Saade GR, Costantine MM. Effects of pravastatin on angiogenic and placental hypoxic imbalance in a mouse model of preeclampsia. Reproductive sciences (Thousand Oaks, Calif). 2014;21(1):138–45. Epub 20130607. doi: 10.1177/1933719113492207. PubMed PMID: 23749761.

7. Winterfeld U, Allignol A, Panchaud A, Rothuizen LE, Merlob P, Cuppers-Maarschalkerweerd B, Vial T, Stephens S, Clementi M, De Santis M, Pistelli A, Berlin M, Eleftheriou G, Maňáková E, Buclin T. Pregnancy outcome following maternal exposure to statins: a multicentre prospective study. BJOG : an international journal of obstetrics and gynaecology. 2013;120(4):463–71. Epub 20121130. doi: 10.1111/1471-0528.12066. PubMed PMID: 23194157.

8. Karadas B, Uysal N, Erol H, Acar S, Koc M, Kaya-Temiz T, Koren G, Kaplan YC. Pregnancy outcomes following maternal exposure to statins: A systematic review and meta-analysis. Br J Clin Pharmacol. 2022;88(9):3962–76. Epub 20220610. doi: 10.1111/bcp.15423. PubMed PMID: 35639354.

9. Costantine MM, Cleary K, Hebert MF, Ahmed MS, Brown LM, Ren Z, Easterling TR, Haas DM, Haneline LS, Caritis SN, Venkataramanan R, West H, D'Alton M, Hankins G,

Eunice Kennedy Shriver National Institute of Child Health and Human Development Obstetric-Fetal Pharmacology Research Units Network. Safety and pharmacokinetics of pravastatin used for the prevention of preeclampsia in high-risk pregnant women: a pilot randomized controlled trial. Am J Obstet Gynecol. 2016;214(6):720 e1– e17. Epub 20151223. doi: 10.1016/j.ajog.2015.12.038. PubMed PMID: 26723196; PMCID: PMC4884459.

10. Costantine MM, West H, Wisner KL, Caritis S, Clark S, Venkataramanan R, Stika CS, Rytting E, Wang X, Ahmed MS. A randomized pilot clinical trial of pravastatin versus placebo in pregnant patients at high risk of preeclampsia. Am J Obstet Gynecol. 2021;225(6):666.e1–.e15. Epub 20210524. doi: 10.1016/j.ajog.2021.05.018. PubMed PMID: 34033812; PMCID: PMC8611118.

11. Pravastatin. Drugs and Lactation Database (LactMed®). Bethesda (MD): National Institute of Child Health and Human Development, Bethesda (MD); 2006. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501357.

12. Rosuvastatin. Drugs and Lactation Database (LactMed®). Bethesda (MD): National Institute of Child Health and Human Development; 2006.

13. Costantine MM, Clifton RG, Boekhoudt TM, Lawrence K, Gyamfi-Bannerman C, Wisner KL, Grobman W, Caritis SN, Simhan HN, Hebert MF, Longo M, Saade GR. Long-term neurodevelopmental follow-up of children exposed to pravastatin in utero. Am J Obstet Gynecol. 2023;229(2):153.e1–.e12. Epub 20230224. doi: 10.1016/j.ajog.2023.02.016. PubMed PMID: 36842489; PMCID: PMC10440254.

14. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, Deswal A, Drazner MH, Dunlay SM, Evers LR, Fang JC, Fedson SE, Fonarow GC, Hayek SS, Hernandez AF, Khazanie P, Kittleson MM, Lee CS, Link MS, Milano CA, Nnacheta LC, Sandhu AT, Stevenson LW, Vardeny O, Vest AR, Yancy CW. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2022;145(18):e876–e94. Epub 20220401. doi: 10.1161/CIR.0000000000001062. PubMed PMID: 35363500.

15. De Backer J, Haugaa KH, Hasselberg NE, de Hosson M, Brida M, Castelletti S, Cauldwell M, Cerbai E, Crotti L, de Groot NMS, Estensen ME, Goossens ES, Haring B, Kurpas D, McEniery CM, Peters SAE, Rakisheva A, Sambola A, Schlager O, Schoenhoff FS, Simoncini T, Steinbach F, Sudano I, Swan L, Valente AM. 2025 ESC Guidelines for the management of cardiovascular disease and pregnancy. Eur Heart J. 2025;46(43):4462–568. doi: 10.1093/eurheartj/ehaf193. PubMed PMID: 40878294.

16. Grünert SC, Rosenbaum-Fabian S, Schumann A, Selbitz A-C, Merz W, Gieselmann A, Spiekerkoetter U. Two successful pregnancies and first use of empagliflozin during pregnancy in glycogen storage disease type Ib. JIMD Rep. 2022;63(4):303–8. doi: 10.1002/jmd2.12295. PubMed PMID: 35822091; PMCID: PMC9259388.

17. Falconi S, Okimi A, Wesley S, Sethi P, Datta P, Krutsch K. Corrigendum: The concentration of maternal sacubitril/valsartan transferred into human milk is negligible. Frontiers in public health. 2024;12:1517339. Epub 20241113. doi: 10.3389/fpubh.2024.1517339. PubMed PMID: 39606073; PMCID: PMC11600444.

18. American Diabetes Association Professional Practice Committee for Diabetes. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2026. Diabetes Care. 2026;49(Suppl 1):S183–S215. doi: 10.2337/dc26-S009. PubMed PMID: 41358900; PMCID: PMC12690185.

19. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Jr., Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, Sperling LS. 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes: A Report of the American College of Cardiology Solution Set Oversight Committee. Journal of the American College of Cardiology. 2020;76(9):1117–45. Epub 20200805. doi: 10.1016/j.jacc.2020.05.037. PubMed PMID: 32771263; PMCID: PMC7545583.

20. Muller DRP, Stenvers DJ, Malekzadeh A, Holleman F, Painter RC, Siegelaar SE. Effects of GLP-1 agonists and SGLT2 inhibitors during pregnancy and lactation on offspring outcomes: a systematic review of the evidence. Front Endocrinol (Lausanne). 2023;14:1215356. Epub 20231010. doi: 10.3389/fendo.2023.1215356. PubMed PMID: 37881498; PMCID: PMC10597691.

21. Parker CH, Slattery C, Brennan DJ, le Roux CW. Glucagon-like peptide 1 (GLP-1) receptor agonists' use during pregnancy: Safety data from regulatory clinical trials. Diabetes, obesity & metabolism. 2025;27(8):4102–8. Epub 20250506. doi: 10.1111/dom.16437. PubMed PMID: 40329607; PMCID: PMC12232371.

22. Ozbek L, Shah E, Al-Shiab R, Inal A, Guldan M, Afsar B, Covic A, Kanbay M. Safety of GLP-1 and Dual GLP-1/GIP Receptor Agonists in Preconception, Pregnancy, and Lactation: A Systematic Review of Maternal, Fetal, and Neonatal Outcomes. Diabetes, obesity & metabolism. 2026;28(6):4503–28. Epub 20260326. doi: 10.1111/dom.70699. PubMed PMID: 41885132.

23. Diab H, Fuquay T, Datta P, Bickel U, Thompson J, Krutsch K. Subcutaneous Semaglutide during Breastfeeding: Infant Safety Regarding Drug Transfer into Human Milk. Nutrients. 2024;16(17):2886. doi: 10.3390/nu16172886. PubMed PMID: 39275201.

24. Halpern DG, Weinberg CR, Pinnelas R, Mehta-Lee S, Economy KE, Valente AM. Use of Medication for Cardiovascular Disease During Pregnancy: JACC State-of-the-Art Review. Journal of the American College of Cardiology. 2019;73(4):457–76. doi: 10.1016/j.jacc.2018.10.075. PubMed PMID: 30704579.

25. Abduljalil K, Pansari A, Jamei M. Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy. J Pharmacokinet Pharmacodyn. 2020;47(4):361–83. doi: 10.1007/s10928-020-09711-2. PubMed PMID: 32840724.

26. O'Hare MF, Murnaghan GA, Russell CJ, Leahey WJ, Varma MP, McDevitt DG. Sotalol as a hypotensive agent in pregnancy. British journal of obstetrics and gynaecology. 1980;87(9):814–20. doi: 10.1111/j.1471-0528.1980.tb04618.x. PubMed PMID: 7426541.

27. Pressly MA, Schmidt S, Guinn D, Liu Z, Ceresa C, Samuels S, Madabushi R, Florian J, Fletcher EP. Informing a Comprehensive Risk Assessment of Infant Drug Exposure From Human Milk: Application of a Physiologically Based Pharmacokinetic Lactation Model for Sotalol. J Clin Pharmacol. 2023;63 Suppl 1:S106–S16. doi: 10.1002/jcph.2242. PubMed PMID: 37317500.

28. Writing Committee Members, Blumenthal RS, Morris PB, Gaudino M, Johnson HM, Anderson TS, Bittner VA, Blankstein R, Brewer LC, Cho L, de Ferranti SD, Gianos E, Gluckman TJ, Gradney KF, Isiadinso I, Lloyd-Jones DM, Marrs JC, Martin SS, McLain KH, Mehta LS, Mora S, Mulugeta WM, Natarajan P, Navar AM, Orringer CE, Polonsky TS, Reynolds HR, Saseen JJ, Shapiro MD, Soffer DE, Tynes SA, Villavaso CD, Virani SS, Wilkins JT, Rohatgi A, Kim SM, Alexander KP, Anderson C, Benziger CP, Dixon DL, Duprez D, Ferdinand KC, Goldberg AC, Joshi P, Knowles JW, Lavie Jr CJ, Linderbaum JA, McEvoy JW, Mehta A, Merz CNB, Nambi V, Orkaby AR, Peña, Jessica M., Rosenson R, Ruisinger J, Sandner SE, Schott SL, Sperling L, Stone NJ, Toth P, Ware AL, Whelton SP, Young J. 2026 ACC/AHA/AACVPR/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Dyslipidemia: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2026;153(17):e1154–e276. doi: doi:10.1161/CIR.0000000000001423. PubMed PMID: 41824552.

29. Noronha Neto C C, Maia SSB, Katz L, Coutinho IC, Souza AR, Amorim MM. Clonidine versus Captopril for Severe Postpartum Hypertension: A Randomized Controlled Trial. PloS one. 2017;12(1):e0168124. doi: 10.1371/journal.pone.0168124. PubMed PMID: 28125624; PMCID: PMC5268489.

30. Taslimi MM, Harbin AR, Gonzalez-Ruiz A. Captopril in severe preeclampsia. J Natl Med Assoc. 1991;83(8):721–3. PubMed PMID: 1956084; PMCID: PMC2627125.

31. Ormesher L, Higson S, Luckie M, Roberts SA, Glossop H, Trafford A, Cottrell E, Johnstone ED, Myers JE. Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP):: A Randomized Double-Blind Placebo-Controlled Feasibility Trial. Hypertension. 2020;76(6):1828–37. Epub 20201005. doi: 10.1161/hypertensionaha.120.15875. PubMed PMID: 33012200; PMCID: PMC7610547.

32. Yoselevsky EM, Seely EW, Celi AC, Robinson JN, McElrath TF. A randomized controlled trial comparing the efficacy of nifedipine and enalapril in the postpartum period. Am J Obstet Gynecol MFM. 2023;5(12):101178. Epub 20231006. doi: 10.1016/j.ajogmf.2023.101178. PubMed PMID: 37806651.

33. Bach N. [Enalapril treatment of a pre-eclamptic woman]. Ugeskrift for laeger. 1995;157(9):1203–4. PubMed PMID: 7701668.

34. Piotrkowicz E, Skrzypczyk P, Prejbisz A, Dobrowolski P, Gawlak M, Kosinski P. Safety and Risks of Antihypertensive Medications During Breastfeeding: A Review of Current Guidelines. J Clin Med. 2025;14(11). Epub 20250526. doi: 10.3390/jcm14113722. PubMed PMID: 40507483; PMCID: PMC12156924.

35. Chugh J, Dai J, Datta P, Krutsch K. Investigating the Transfer of Lisinopril Into Human Milk: A Quantitative Analysis. J Cardiovasc Pharmacol. 2025;85(1):84–7. Epub 20250101. doi: 10.1097/FJC.0000000000001642. PubMed PMID: 39405564.

36. Leggett C, Lwin EMP, Ritchie U, Song Y, Gerber JP, Turner S, Hague WM, Stark M, Upton R, Garg S. Perindopril in Breast Milk and Determination of Breastfed Infant Exposure: A Prospective Observational Study. Drug design, development and therapy. 2020;14:961–7. Epub 20200302. doi: 10.2147/DDDT.S239704. PubMed PMID: 32184565; PMCID: PMC7060030.

37. Vazquez-Rodriguez JG, Mendez-Rodriguez YI. [Treatment of postpartum arterial hypertension with losartan in severe preeclampsia]. Rev Med Inst Mex Seguro Soc. 2020;58(5):574–82. Epub 20200901. doi: 10.24875/RMIMSS.M20000087. PubMed PMID: 34520145.

38. Zoet GA, Paauw ND, Veerbeek JHW, Groenhof TKJ, Spiering W, Verhaar MC, Franx A, Titia Lely A. Differential effects of renin-angiotensine-aldosteron system inhibition, sympathoinhibition and low sodium diet on blood pressure in women with a history of preeclampsia: A double-blind, placebo-controlled cross-over trial (the PALM study). Pregnancy hypertension. 2022;27:173–5. Epub 20220106. doi: 10.1016/j.preghy.2021.12.016. PubMed PMID: 35074611.

39. Coberger ED, Jensen BP, Dalrymple JM. Transfer of Candesartan Into Human Breast Milk. Obstet Gynecol. 2019;134(3):481–4. doi: 10.1097/AOG.0000000000003446. PubMed PMID: 31403599.

40. Falconi S, Okimi A, Wesley S, Sethi P, Datta P, Krutsch K. The concentration of maternal sacubitril/valsartan transferred into human milk is negligible. Frontiers in public health. 2024;12:1389513. Epub 20240522. doi: 10.3389/fpubh.2024.1389513. PubMed PMID: 38841677; PMCID: PMC11150817.

41. Aphena Pharma Solutions. Tadalafil package insert. Available from: https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/351e28ca-3ae6-e535-e063-6394a90a9fb7/spl-doc?hl=tadalafil.

42. Preferred Pharmaceuticals Inc. Sildenafil Citrate package insert. Available from: https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/878b4c44-cddc-42cb-b9b5-911451ad1530/spl-doc?hl=sildenafil#section-8.1.

43. Nauwelaerts N, Ceulemans M, Deferm N, Eerdekens A, Lammens B, Armoudjian Y, Van Calsteren K, Allegaert K, de Vries L, Annaert P, Smits A. Case Report: Bosentan and Sildenafil Exposure in Human Milk - A Contribution From the ConcePTION Project. Frontiers in pharmacology. 2022;13:881084. doi: 10.3389/fphar.2022.881084. PubMed PMID: 35784689; PMCID: PMC9240352.

44. Wollein U, Schech B, Hardt J, Schramek N. Determination and quantitation of sildenafil and its major metabolite in the breast milk of a lactating woman. Journal of pharmaceutical and biomedical analysis. 2016;120:100–5. Epub 20151211. doi: 10.1016/j.jpba.2015.12.006. PubMed PMID: 26717019.

45. Abarca J, Odilla Arrollo C, Blanch S, Arellano G. [Melasma in pregnancy: reduction of its appearance with the use of a broad-spectrum photoprotective agent]. Med Cutan Ibero Lat Am. 1987;15(3):199–203. PubMed PMID: 3312862.

46. Gozen D, Caglar S, Bayraktar S, Atici F. Diaper dermatitis care of newborns human breast milk or barrier cream. J Clin Nurs. 2014;23(3-4):515–23. Epub 20130319. doi: 10.1111/jocn.12047. PubMed PMID: 23506257.

47. Group EW. EWG's 19th Annual Guide to Sunscreens 2026 [cited 2026]. Available from: https://www.ewg.org/sunscreen/report/executive-summary/.

48. Matta MK, Zusterzeel R, Pilli NR, Patel V, Volpe DA, Florian J, Oh L, Bashaw E, Zineh I, Sanabria C, Kemp S, Godfrey A, Adah S, Coelho S, Wang J, Furlong LA, Ganley C, Michele T, Strauss DG. Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients: A Randomized Clinical Trial. JAMA : the journal of the American Medical Association. 2019;321(21):2082–91. doi: 10.1001/jama.2019.5586. PubMed PMID: 31058986; PMCID: PMC6549296.

49. Australian New Zealand Clinical Trials Registry. Efficacy and Demonstration of Intravenous Iron for Anaemia in Pregnancy (EDIVA). Available from: https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382186&isReview=true.

50. Duke Clinical Research Institute, Pedaitric Trials Network. CUDDLE: Pharmacokinetics and Safety of Commonly Used Drugs in Lactating Women and Breastfeeding Infants. Available from: https://dcri.org/cuddle.

51. National Library of Medicine. ClinicalTrials.gov. Intravenous Versus Oral Iron for Treating Iron-Deficiency Anemia in Pregnancy (IVIDA2). Available from: https://clinicaltrials.gov/study/NCT05462704.

52. Butler AS, Cole S, Arya R, Patel JP. Considerations of safety for women prescribed apixaban or rivaroxaban who breastfeed-a physiologically based pharmacokinetic analysis. Journal of thrombosis and haemostasis : JTH. 2026;24(2):520–9. Epub 20251027. doi: 10.1016/j.jtha.2025.09.040. PubMed PMID: 41161415.

53. Harding R, Moya E, Ataide R, Truwah Z, Mzembe G, Mhango G, Demir AV, Stones W, Randall L, Seal M, Johnson K, Bode S, Mwangi MN, Pasricha SR, Braat S, Phiri KS. Protocol and statistical analysis plan for a randomized controlled trial of the effect of intravenous iron on anemia in Malawian pregnant women in their third trimester (REVAMP - TT). Gates Open Res. 2023;7:117. Epub 20231218. doi: 10.12688/gatesopenres.14710.2. PubMed PMID: 38343768; PMCID: PMC10858019.

54. Mian P, Watt K, Chambers C, Allergaert K, Krutsch K, Ito S, Edgington A. Design and mechanics of five major human milk drugresearch biobanks: Time to cross borders and

barriers. Clinical Pharmaccology & Therapeutics. 2024;115:PII–199). doi: doi/10.1002/cpt.3167.

55. Wiesen MH, Blaich C, Muller C, Streichert T, Pfister R, Michels G. The Direct Factor Xa Inhibitor Rivaroxaban Passes Into Human Breast Milk. Chest. 2016;150(1):e1–4. doi: 10.1016/j.chest.2016.01.021. PubMed PMID: 27396794.

56. Saito J, Kaneko K, Yakuwa N, Kawasaki H, Yamatani A, Murashima A. Rivaroxaban Concentration in Breast Milk During Breastfeeding: A Case Study. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2019;14(10):748–51. Epub 20191120. doi: 10.1089/bfm.2019.0230. PubMed PMID: 31746638.

57. Muysson M, Marshall K, Datta P, Rewers-Felkins K, Baker T, Hale TW. Rivaroxaban Treatment in Two Breastfeeding Mothers: A Case Series. Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine. 2020;15(1):41–3. Epub 20190918. doi: 10.1089/bfm.2019.0124. PubMed PMID: 31532233.

58. Zhao Y, Arya R, Couchman L, Patel JP. Are apixaban and rivaroxaban distributed into human breast milk to clinically relevant concentrations? Blood. 2020;136(15):1783–5. doi: 10.1182/blood.2020006231. PubMed PMID: 32488251.

59. Yamashita Y, Hira D, Morita M, Katsube Y, Takakura M, Tomotaki H, Tomotaki S, Xiong W, Shiomi H, Horie T, Ueshima S, Mizuno T, Terada T, Ono K. Potential treatment option of rivaroxaban for breastfeeding women: A case series. Thrombosis research. 2024;237:141–4. Epub 20240405. doi: 10.1016/j.thromres.2024.04.003. PubMed PMID: 38593524.

60. Wang L, He K, Maxwell B, Grossman SJ, Tremaine LM, Humphreys WG, Zhang D. Tissue distribution and elimination of [14C]apixaban in rats. Drug Metab Dispos. 2011;39(2):256–64. Epub 20101111. doi: 10.1124/dmd.110.036442. PubMed PMID: 21071521.

61. Ayuk P, Kampouraki E, Truemann A, Sidgwick F, McDonald L, Bingham J, Murphy P, Kamali F. Investigation of dabigatran secretion into breast milk: Implications for oral thromboprophylaxis in post-partum women. Am J Hematol. 2020;95(1):E10–E3. Epub 20191017. doi: 10.1002/ajh.25652. PubMed PMID: 31599003.

62. Willmann S, Becker C, Burghaus R, Coboeken K, Edginton A, Lippert J, Siegmund HU, Thelen K, Muck W. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. Clin Pharmacokinet. 2014;53(1):89–102. Epub 2013/08/06. doi: 10.1007/s40262-013-0090-5. PubMed PMID: 23912563; PMCID: PMC3889826.

63. Kubitza D, Willmann S, Becka M, Thelen K, Young G, Brandao LR, Monagle P, Male C, Chan A, Kennet G, Martinelli I, Saracco P, Lensing AWA. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: an EINSTEIN-Jr phase I study. Thrombosis journal. 2018;16(1):31. Epub 20181204. doi: 10.1186/s12959-018-0186-0. PubMed PMID: 30534007; PMCID: PMC6278122.

64. Willmann S, Thelen K, Kubitza D, Lensing AWA, Frede M, Coboeken K, Stampfuss J, Burghaus R, Muck W, Lippert J. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thrombosis journal. 2018;16(1):32. Epub 20181204. doi: 10.1186/s12959-018-0185-1. PubMed PMID: 30534008; PMCID: PMC6278136.

65. Willmann S, Zhang L, Frede M, Kubitza D, Mueck W, Schmidt S, Solms A, Yan X, Garmann D. Integrated Population Pharmacokinetic Analysis of Rivaroxaban Across Multiple Patient Populations. CPT: pharmacometrics & systems pharmacology. 2018;7(5):309–20. Epub 20180416. doi: 10.1002/psp4.12288. PubMed PMID: 29660785; PMCID: PMC5980303.

66. Xu R, Tang H, Chen L, Ge W, Yang J. Developing a physiologically based pharmacokinetic model of apixaban to predict scenarios of drug-drug interactions, renal impairment and paediatric populations. Br J Clin Pharmacol. 2021;87(8):3244–54. Epub 20210505. doi: 10.1111/bcp.14743. PubMed PMID: 33528059.

67. Merali SJ, Byon W, Patel YT, Elsrougy A, Marchisin D, Perera V, Chen W, He B, Murthy B. Evaluation of safety, pharmacokinetics, and pharmacodynamics of apixaban in pediatric subjects at risk of venous or arterial thrombotic disorder. CPT: pharmacometrics & systems pharmacology. 2023;12(4):500–12. Epub 20230305. doi: 10.1002/psp4.12935. PubMed PMID: 36861188; PMCID: PMC10088081.

68. Ajavon-Hartmann A, Jarugula P, Back H, Obianom O, Ludwig E, Crevar C, Marchisin D, Wang Z, Chen W, He B, Payne RM, Burns KM, Glatz AC, Male C, Monagle P, Perera V, Murthy B, Merali S. Characterization of Apixaban Pharmacokinetics/Pharmacodynamics and Dose Assessment in Pediatric Patients with Congenital or Acquired Heart Disease. Clin Pharmacol Ther. 2025;118(2):365–77. Epub 20250624. doi: 10.1002/cpt.3689. PubMed PMID: 40551722; PMCID: PMC12272319.

69. Maas H, Gropper S, Huang F, Stangier J, Tartakovsky I, Brueckmann M, Halton JML, Mitchell LG. Anticoagulant Effects of Dabigatran in Paediatric Patients Compared with Adults: Combined Data from Three Paediatric Clinical Trials. Thrombosis and haemostasis. 2018;118(9):1625–36. Epub 20180815. doi: 10.1055/s-0038-1668132. PubMed PMID: 30112751; PMCID: PMC6202931.

70. Roshammar D, Huang F, Albisetti M, Bomgaars L, Chalmers E, Luciani M, Halton J, Mitchell LG, Bergstrand M, Ibrahim MMA, Joseph D, Tartakovsky I, Gropper S, Brueckmann M, Brandao LR. Pharmacokinetic modeling and simulation support for age- and weight-adjusted dosing of dabigatran etexilate in children with venous thromboembolism. Journal of thrombosis and haemostasis : JTH. 2021;19(5):1259–70. Epub 20210326. doi: 10.1111/jth.15277. PubMed PMID: 33636042; PMCID: PMC8251571.

71. Zou P, Atluri A, Chang P, Goedecke M, Leil TA. Population pharmacokinetics and pharmacodynamics of edoxaban in pediatric patients. CPT: pharmacometrics & systems pharmacology. 2025;14(1):118–29. Epub 20241111. doi: 10.1002/psp4.13248. PubMed PMID: 39526427; PMCID: PMC11706424.

72. Komori M, Hayata E, Nakata M, Yuzawa H, Oji A, Morita M. Apixaban therapy in a pregnant woman with heparin-induced thrombocytopenia and venous thromboembolic events caused by congenital antithrombin deficiency: A case report. Case Rep Womens Health. 2020;27:e00200. Epub 20200403. doi: 10.1016/j.crwh.2020.e00200. PubMed PMID: 32300539; PMCID: PMC7152699.

73. Nekooghadam SM, Ebrahimi-Dehkordi S, Paraandavaji E, Pishgahi M, Ghadirzadeh E, Charkazi E, Ghorbani P. Heparin induced thrombocytopenia in pregnancy: A therapeutic challenge case report and literature review. Clin Case Rep. 2023;11(8):e7839. Epub 20230821. doi: 10.1002/ccr3.7839. PubMed PMID: 37614288; PMCID: PMC10442474.

74. Govindappagari S, Newman RA, Burwick RM. Iron-deficiency anemia in pregnancy and the role of intravenous iron. Contemporary OB/GYN [Internet]. 2021; 66 7. Available from: https://cdn.sanity.io/files/0vv8moc6/contobgyn/c05fe2a1f221d09bd0c0dfff6efda683ab5d7ecf.pdf/OBGYN0721_020-024_CoverStory-IV.pdf.

75. Ware RE, Marahatta A, Ware JL, McElhinney K, Dong M, Vinks AA. Hydroxyurea Exposure in Lactation: a Pharmacokinetics Study (HELPS). The Journal of pediatrics. 2020;222:236–9. Epub 20200311. doi: 10.1016/j.jpeds.2020.02.002. PubMed PMID: 32171562.

76. Centers for Disease Control and Prevention. Treatment of Severe Malaria Atlanta, GA2024 [cited 2026]. Available from: https://www.cdc.gov/malaria/hcp/clinical-guidance/treatment-of-severe-malaria.html.

77. Scoullar MJL, Melepia P, Peach E, Fidelis R, Supsup H, Davidson EM, Boeuf P, Bradshaw CS, Fehler G, Hezeri P, Kabiu D, Elijah A, Siba PM, Kennedy EC, Umbers AJ, Robinson LJ, Vallely AJ, Badman SG, Vallely LM, Fowkes FJI, Morgan CJ, Pomat W, Crabb BS, Beeson JG. Mycoplasma genitalium in pregnancy, including specific co-infections, is associated with lower birthweight: A prospective cohort study. Med. 2024;5(9):1123–36 e3. Epub 20240612. doi: 10.1016/j.medj.2024.05.007. PubMed PMID: 38870930.

78. Mafirakureva N, Cartledge A, Bradshaw I, Bekker A, Salazar-Austin N, Meehan SA, Myer L, Odayar J, Rangaka MX, Dodd PJ. Global estimates of tuberculosis incidence during pregnancy and postpartum: a rapid review and modelling analysis. Lancet Glob Health. 2026;14(3):e337–e46. Epub 20260107. doi: 10.1016/S2214-109X(25)00431-0. PubMed PMID: 41519136; PMCID: PMC12916327.

79. Centers for Disease Control and Prevention. Annual STI Surveillance Reports Atlanta, GA: U.S. Department of Health and Human Services; 2024 [cited 2026]. Available from: https://www.cdc.gov/sti-statistics/annual/index.html.

80. Errol RN, Charles BH. Syphilis in pregnancy. Waltham, MA: UpToDate; 2024. Available from: https://www.uptodate.com/contents/syphilis-in-pregnancy.

81. Viral Hepatitis in Pregnancy: ACOG Clinical Practice Guideline No. 6. Obstet Gynecol. 2023;142(3):745–59. Epub 2023/08/17. doi: 10.1097/AOG.0000000000005300. PubMed PMID: 37590986.

82. Centers for Disease Control and Prevention. Respiratory Syncytial Virus Hospitalization Surveillance Network (RSV-NET) Atlanta, GA: U.S. Department of Health and Human Services; 2026 [cited 2026]. Available from: https://www.cdc.gov/rsv/php/surveillance/rsv-net.html.

83. American College of Obstetricians and Gynecologists. Maternal Respiratory Syncytial Virus Vaccination Washington, DC: American College of Obstetricians and Gynecologists; 2025 [cited April 6 2026]. Available from: https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2023/09/maternal-respiratory-syncytial-virus-vaccination.

84. Griffin MP, Yuan Y, Takas T, Domachowske JB, Madhi SA, Manzoni P, Simoes EAF, Esser MT, Khan AA, Dubovsky F, Villafana T, DeVincenzo JP, Nirsevimab Study G. Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants. The New England journal of medicine. 2020;383(5):415–25. Epub 2020/07/30. doi: 10.1056/NEJMoa1913556. PubMed PMID: 32726528.

85. Na-Bangchang K, Manyando C, Ruengweerayut R, Kioy D, Mulenga M, Miller GB, Konsil J. The pharmacokinetics and pharmacodynamics of atovaquone and proguanil for the treatment of uncomplicated falciparum malaria in third-trimester pregnant women. Eur J Clin Pharmacol. 2005;61(8):573–82. Epub 20050723. doi: 10.1007/s00228-005-0969-7. PubMed PMID: 16041597.

86. Yamada E, Trehan S, Stark A, Krutsch K, Datta P. Atomoxetine as a Viable ADHD Treatment in Breastfeeding Mothers: Evidence From Human Milk Pharmacokinetic Analysis. J Clin Psychopharmacol. 2026;46(1):16–22. Epub 20251126. doi: 10.1097/jcp.0000000000002109. PubMed PMID: 41427840.

87. Johnson JM, Walsh JD, Okun NB, Metcalfe A, Pastuck ML, Maxey CM, Soliman N, Mahallati H, Kuret VH, Dwinnell SJ, Chada R, O'Quinn CP, Schacher J, Somerset DA, Paterson K, Suchet IB, Silang KA, Paul H, Nerenberg KA, Johnson DW. The Implementation of Preeclampsia Screening and Prevention (IMPRESS) Study. Am J Obstet Gynecol MFM. 2023;5(2):100815. Epub 20221115. doi: 10.1016/j.ajogmf.2022.100815. PubMed PMID: 36400421.

88. Food and Drug Administration, U.S. Department of Health and Human Services. E21 Inclusion of Pregnant and Breastfeeding Women in Clinical Trials; Draft Guidance for Industry. Docket No. FDA-2025-D-1797. 2025. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e21-inclusion-pregnant-and-breastfeeding-women-clinical-trials.

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Appendix 1

July 2024 Meeting Summary

Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) National Institutes of Health (NIH)

Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating (PPL) Persons

Meeting Summary

July 9-10, 2024

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Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating (PPL) Persons

Meeting Summary

Purpose: This meeting, organized with NICHD's Office of the Director, Obstetric and Pediatric Pharmacology and Therapeutics Branch (OPPTB), and Pregnancy and Perinatology Branch (PPB), will begin discussions on prioritization of drugs, vaccines, and dietary supplement research needs for use in pregnant, postpartum, and lactating (PPL) people. The effort directly addresses recommendations from the NICHD-led Task Force on Research Specific to Pregnant Women and Lactating Women to identify gaps in knowledge and needs and prioritize research on therapeutics for PPL persons.

Day 1: Tuesday, July 9, 2024

Welcome, Introductions, and Goals for Meeting

Camille Fabiyi, Ph.D., M.P.H. - Program Officer, OPPTB, NICHD
Diane Gumina, Ph.D. - Program Officer, PPB, NICHD
Alison Cernich, Ph.D. - Deputy Director, NICHD
Aaron Pawlyk, Ph.D. - Branch Chief, OPPTB, NICHD

Dr. Fabiyi welcomed participants to the Inaugural Stakeholder Meeting for the Prioritization of Therapeutic Research Needs for Pregnant, Postpartum, and Lactating Persons. She noted that the topics for this meeting directly address recommendations from the NICHD-led Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC). She introduced Dr. Gumina, PPB Program Officer, and thanked her for her help in preparing for the meeting.

Dr. Cernich thanked the staff at OPPTB and PPB and the PRGLAC members who have been engaged in this work for several years. NICHD's mission is to lead research and training to understand human development, improve reproductive health, enhance the lives of children and adolescents, and optimize abilities for all. This is reflected in its 2020 Strategic Plan's five research themes, three of which have particular relevance to this meeting: promoting gynecologic, andrologic, and reproductive health; setting the foundation for healthy pregnancies and lifelong wellness; and advancing safe and effective therapeutics and devices for pregnant and lactating women, children, and people with disabilities. NICHD is heavily invested in research to address the maternal morbidity and mortality (MMM) crisis in the United States. In addition to its broad and robust maternal health research portfolio and its data and network infrastructure, NICHD engages in partnerships both across NIH to advance

development and implementation of effective therapeutics and with external groups to help guide clinical recommendations that providers need to deliver care.

In coordination with the National Institute of Nursing Research (NINR) and the Office of Research on Women's Health (ORWH), NICHD co-leads the Implementing a Maternal health and PRegnancy Outcomes Vision for Everyone (IMPROVE) initiative. The core principles of the initiative are reducing preventable causes of MMM, ensuring community involvement, focusing on implementation research, and addressing disparities. IMPROVE has funded 12 Maternal Health Research Centers of Excellence, issued a technology challenge for postpartum diagnostics and monitoring, built research infrastructure in communities, increased intervention uptake in community settings, and developed electronic health record (EHR) standards for pregnancy to enable real-world research. NICHD is also developing Common Data Elements (CDEs) for use in pregnancy studies in the Maternal Health Research Centers of Excellence. The CDEs are standardized, precisely defined questions, paired with a set of allowed responses to ensure consistency. They are currently in the first round of Delphi voting to prioritize constructs, and plan to share final recommendations by September 2024.

Dr. Cernich shared several NICHD maternal health research initiatives that are advancing the goals of PRGLAC, including the Maternal and Pediatric Precision in Therapeutics (MPRINT) Hub and the Commonly Used Drugs in Lactating Women and Breastfed Infants (CUDDLE) study. NICHD also leverages the following networks for MMM research: the Maternal-Fetal Medicine Units (MFMU) Network; the Neonatal Research Network (NRN); and the Global Network for Women's and Children's Health Research. The Institute is also advancing research through the NICHD Data and Specimen Hub (DASH), a centralized resource for researchers to share de-identified data from NICHD-funded studies.

NICHD has also used public-private partnerships to accelerate and sustain maternal health research efforts. One example is the Azithromycin-Prevention in Labor Use Study (A-PLUS), which partnered NICHD's Global Network for Women's and Children's Health Research with the Bill & Melinda Gates Foundation and the Foundation for the National Institutes of Health (FNIH). The A-PLUS Study was stopped early due to clear maternal benefit when it found that a single dose of azithromycin can reduce the risk of postpartum sepsis and death by one-third. NICHD is also working with FNIH to look at biomarkers for risk stratification and detection of early-onset preeclampsia.

Due to historical exclusion from clinical trials, researchers and clinicians do not have a good understanding of how disease pathophysiology may differ in pregnant and lactating people, and evidence for safety, efficacy, and dosing of medicinal therapies for these individuals is severely lacking, which complicates their medical decision-making. The PRGLAC Task Force addressed these issues in its 2018 Report to Congress by recommending the inclusion of pregnant and lactating people in clinical research, as well as the expansion of the workforce of clinicians and researchers with expertise in obstetric and lactation pharmacology and therapeutics. Dr. Cernich noted that public-private partnerships and international collaborations will be necessary to advance the 15 recommendations included in the 2018 report. Partnership is also

critical in changing the existing culture to protect pregnant and lactating people and their fetuses through research, rather than from research.

Dr. Pawlyk highlighted this meeting's central issue, which is that physicians and patients must often make decisions on drug, dietary supplement, and vaccine use without rigorously conducted regulatory studies and approval. Although approximately 60% of pregnant and lactating people take one or more prescription medications for pre-existing or pregnancy-induced conditions, approximately 90% of clinically approved medications do not have appropriate drug labeling information for this population. Dr. Pawlyk noted that two of PRGLAC's recommendations focused on the need for a prioritization process. NICHD has charged OPPTB and PPB with developing this process, expanding on OPPTB's work with prioritization under the Best Pharmaceuticals for Children Act (BPCA). The MPRINT Hub also addresses several of PRGLAC's recommendations, as well as aspects of the BPCA mandates, and has the potential to play a pivotal role in the next round of prioritization for pregnancy and lactation.

NICHD and ORWH published a Request for Information (RFI) on prioritization to address the changes that have occurred since the inception of the BPCA prioritization process in 2004. The information collected through this RFI helped assess the landscape of needs, engage key stakeholders, incorporate new data sources and analytical approaches, consider integrating new processes, and discuss who would use a list of therapeutics priorities. Congress has not authorized any new programs specifically focused on therapeutics in response to the PRGLAC recommendations, and NICHD is focusing on leveraging existing programs for the study of existing medications using existing approaches to prioritizing research. Dr. Pawlyk gave specific examples of prioritizing research needs for existing medications: if there is not sufficient pharmacokinetic (PK) data about Drug X during pregnancy to design a large, controlled trial, then obtaining PK data is a priority research need for Drug X and could be achieved via opportunistic studies. If there is a significant amount of PK data on Drug Y during pregnancy and real-world evidence suggests positive outcomes for mothers and newborns at higher doses with no safety signal, a pivotal randomized controlled trial (RCT) is a priority research need to assess the efficacy of Drug Y. He also gave examples of discussions that NICHD did not want to engage in during this meeting, such as designating Drug Y as a higher priority to study than Drug X, or prioritizing the development of a new drug for a condition that does not currently have any drugs. Following this meeting, NICHD anticipates soliciting suggestions for revision of the prioritization framework, establishing working groups to discuss all therapeutic areas, and expanding available curated knowledge on the MPRINT Hub. Ultimately, these efforts will result in the release of an initial list of priority research gaps for drugs, vaccines, and dietary supplements for PPL persons.

PRGLAC Overview: History and Current Status

Emma Carpenter, Ph.D. - Health Science Policy Analyst, Office of Legislation, Public Policy, and Ethics, NICHD
Leyla Sahin, M.D. - Deputy Director for Safety, Division of Pediatrics and Maternal Health, U.S. Food and Drug Administration (FDA)

Dr. Carpenter provided an overview of PRGLAC's history, the PRGLAC Implementation Working Group of the National Advisory Child Health and Human Development (NACHHD) Council, and the status of several PRGLAC recommendations. PRGLAC was formed in 2016 via the 21st Century Cares Act and was led by NICHD, with representation from multiple sectors. The committee developed a Report to Congress in 2018 and an Implementation Plan in 2020 before its charter expired in 2021. The PRGLAC Implementation Working Group was established under the 2023 Consolidated Appropriations Act and reports to the NACHHD Council. The working group's objectives are to review publicly available materials pertaining to implementation progress, invite speakers from relevant federal agencies or non-federal entities to discuss progress on the implementation plan, report their findings to the NACHHD Council, and ultimately submit a report to Congress.

The working group used a cluster format to group their recommendations around common themes; these were discussed at three stakeholder meetings held between November 2023 and March 2024. Five overarching themes emerged: 1) distinguishing between pregnancy and lactation; 2) assigning clear ownership over recommendations; 3) engaging multiple, diverse stakeholders; 4) requiring additional resources and congressional action; and 5) continuing assessment of implementation progress. Dr. Carpenter shared several examples of recommendation subparts that had been implemented, some that were in progress, and others that have not yet been implemented. She noted that the two subparts that formed the basis of this meeting have been implemented: 8B, Develop separate prioritization processes for therapies and/or conditions in pregnant women and lactating women; and 9A, Create separate prioritization processes for pregnant women and lactating women. The working group is currently working to finalize their progress report, which the Council voted to accept at its June meeting, and it will be published and disseminated in late July.

Dr. Sahin spoke about the FDA’s regulatory framework regarding pregnancy and lactation studies and FDA's efforts to address the PRGLAC recommendations. A recent FDA review of pregnancy safety postmarketing requirements showed that it took 11 years after approval of a new drug to update the labeling with human pregnancy safety data. Most of the FDA's pregnancy and lactation data collection activities occur in the postmarketing phase of the drug life cycle. This includes case reports and series published by healthcare providers, clinical trials of approved drugs that may be repurposed, opportunistic lactation studies, pregnancy PK studies, and observational studies. FDA can require pregnancy safety studies under the Federal Food, Drug, and Cosmetic (FD&C) Act and, historically, pregnancy registries have been issued as postmarketing requirements/commitments (PMRs/PMCs). Recently, two types of pregnancy PMRs have been issued in FDA's Center for Drug Evaluation and Research (CDER).

The FDA is involved in several efforts to advance the conduct of studies. These include publishing guidance for industry, conducting workshops and webinars, conducting outreach at scientific meetings, and collaborating with entities such as NICHD. Dr. Sahin provided several examples where FDA is addressing specific PRGLAC recommendations, including their collaboration with NICHD on BPCA lactation studies of off-patent drugs, an FDA Pregnancy Registry Public Workshop planned for March 2025, and several ongoing Pregnancy Safety Demonstration Projects. FDA will also hold a public workshop on Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products on July 11 and 12, 2024. On the global scale, FDA is participating in the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) E21 guideline working group. This working group includes global regulatory agencies and industry, and the purpose is to provide a globally accepted framework and best practices to enable inclusion and/or retention of pregnant and breastfeeding individuals in clinical trials.

Dr. Meg Grabb (National Institute of Mental Health (NIMH)) asked whether the FDA encourages companies to establish registries. Dr. Sahin said that FDA makes recommendations related to issuance of PMRs and pregnancy and lactation during the New Drug Application (NDA) review process, as part of discussions with applicants about what data are missing. Their recent policy is to issue a PMR for a database study as well as a pregnancy registry, as both study designs have their own strengths and limitations.

Overview of Nominations from the RFI and Prioritization Process

Camille Fabiyi, Ph.D., M.P.H

Under the recent RFI, NIH invited nominations of drug, vaccine, and dietary supplement research needs to be considered in the development of a priority list to advance PRGLAC recommendations 8B and 9A. A total of 136 nominations were received during the public comment period, which ran from May 8, 2023, through September 29, 2023. Dr. Fabiyi noted that many of the nominations had incomplete or unclear information and some nominators may have misclassified information in the nomination, highlighting the importance of the discussion and input received during this meeting to shape the prioritization framework. She presented a breakdown of the nominations by type (drug, vaccine, or dietary supplement) and condition category (general medical condition, pregnancy/postpartum-specific, or lactation-specific).

PRGLAC Recommendation 8B specifically recommended considering NIH's BPCA program as a model for developing a prioritization process for testing therapeutics in pregnant and lactating people. The BPCA legislation requires NIH, in consultation with FDA and experts in pediatric research, to develop a priority list of needs in pediatric therapeutics, establish a program for pediatric drug development studies (primarily of off-patent medications) and submit clinical trial findings to the FDA for drug label change consideration. The legislation also mandates the training of experts in pediatric pharmacology research. BPCA's prioritization process emphasizes three guiding principles: 1) a well-defined process that includes a systematic approach and clear objectives and outcomes; 2) well-defined objective criteria for measuring

priorities; and 3) a dynamic but legitimate and fair process that incorporates expert stakeholder input, transparency, and strong leadership. Unlike the BPCA program, the current efforts around prioritization of research needs for PPL people do not have legislative authority or associated funding. The BPCA has an established process for expert involvement and a dedicated research network (the Pediatric Trials Network or PTN). This process is still evolving within the PPL program, and it does not yet have a research network dedicated to the study of therapeutics in PPL persons.

Dr. Fabiyi summarized the objectives of this meeting. NIH is seeking input to identify pharmacological gaps and make prioritization decisions so that they are prepared to facilitate research i, as well as to address pharmacological gaps around existing medications and inform existing NIH research prioritization processes. This meeting will begin discussion with select drug nominations submitted as lactation and pregnancy-specific conditions due to their alignment with the NICHD mission, with plans to discuss the remaining drug nominations across all condition categories at future meetings.

Study Design for Research on Therapeutics in Pregnant and Lactating People, Part 1

CUDDLE Study

Kevin Watt, M.D., Ph.D. - Chief, Professor, Division of Clinical Pharmacology, University of Utah

Dr. Watt presented an overview of opportunistic studies in lactation, including the CUDDLE study. CUDDLE, which is sponsored by NICHD through the PTN, is an opportunistic study that enrolls lactating people who are already on one of several drugs of interest, with samples collected at the time of standard care visits. Participants can provide maternal breastmilk, maternal plasma, and/or infant plasma, and the study also leverages standard of care procedures like laboratory tests. The study began with 10 initial drugs of interest and an additional 12 medications are now open for enrollment. Drug selection criteria included knowledge gaps in the FDA label, frequency of use in the breastfeeding population, potential to cause harm to the infant, and other scientific priorities such as those aligned with BPCA. The primary outcome of the study looks at infant exposure using metrics such as milk to plasma ratio, total infant dose, and relative infant dose.

Dr. Watt shared study results for oxycodone, where researchers found that, even though oxycodone concentrates in milk at a 3:1 ratio, the daily infant dose was orders of magnitude lower than the dose that would be prescribed to an infant to treat pain. They were also able to simulate oxycodone exposure for various doses at the individual as well as the population level using a physiologically-based PK model, which confirmed their observed findings in the CUDDLE study. They submitted these data to the FDA, which resulted in a label change for oxycodone. Dr. Watt and Dr. Tina Chambers (University of California, San Diego) have also been working on an R21 opportunistic study that looks at collecting breastmilk samples in participants' homes, which could greatly increase the number of lactating people who can participate in these studies. The NIH R21 is an exploratory/developmental grant that supports exploratory and

developmental research projects by providing support for the early and conceptual stages of these projects.

Glyburide and Metformin Studies

Mary Hebert, Pharm.D., FCCP - Professor of Pharmacy, Adjunct Professor of Obstetrics and Gynecology; Director, University of Washington Obstetric-fetal Pharmacology Research Unit, Department of Pharmacy, University of Washington

Dr. Hebert spoke about study design in the context of her group's work with glyburide and metformin. In order to have the appropriate data to evaluate changes in PK and pharmacodynamics (PD), the group first had to conduct studies to evaluate glyburide enzymatic pathways and transport and metformin transport. After having done this, they expected both drugs to be altered by pregnancy. Their ideal comparator group was the non-pregnant population for which the drug is approved. They conducted extensive sampling for glyburide both in pregnant people with gestational diabetes mellitus (GDM) and non-pregnant people with Type 2 diabetes mellitus (T2DM), and found significant changes in the PK of the drug. In order to determine the impact on dosing, they used modeling followed by Monte Carlo simulations that found more than double the approved dosage would be needed for pregnant populations and non-pregnant concentrations to match. They also looked at potential gestational age-dependent changes with drugs that are used chronically, such as metformin. They performed intensive PK sampling in individuals who were taking 500 mg of metformin twice daily during early pregnancy, mid-pregnancy, and late pregnancy. In all three phases, the concentration time profiles were significantly lower than the control group of individuals who were three or more months postpartum.

Dr. Hebert noted that metformin has non-linear PK, and while they found that the peak for 1,000 mg of metformin twice daily in the pregnant population was comparable to 500 mg twice daily in the non-pregnant population, it did not mean that the starting dose should be doubled for pregnant individuals. She emphasized the importance of interpreting the data correctly, noting that recommendations have come out of this data that do not align with the results' actual indications. It can be helpful for clinicians to have a correlate with a clinical marker. In addition to PK, PD are important; when looking at drugs for treatment of diabetes Dr. Hebert's group examined the effects of pregnancy on insulin and glucose concentrations. Although GDM is similar to T2DM, they found significant differences in the ability of the pancreas to produce insulin in the setting of high sugars, indicating that the underlying condition is not the same. They included a healthy pregnant arm in their study to account for gestational age-dependent changes and saw a significant change in the overall disposition index between 30 weeks gestation and 36 weeks gestation. They looked at relative oral treatments being used at the time and found that metformin monotherapy brought patients closer to what's considered normal insulin sensitivity in pregnancy, while glyburide did not. They also looked at equal effects on clinical biomarkers, including glucose concentration. Following a mixed-meal tolerance test, patients receiving metformin monotherapy had significantly lower glucose Area Under the Curve (AUC) compared to pre-treatment, as did the combination therapy group.

Looking at fetal exposure, they found that the average umbilical cord to maternal concentration ratio was 0.7 and suggested that neonatal risks should be considered for dosage changes.

Tranexamic Acid (TXA) and Pravastatin Studies
George Saade, M.D. - Professor and Chair, Associate Dean for Women's Health, Obstetrics and Gynecology, Eastern Virginia Medical School

Rates of postpartum hemorrhage (PPH), a major cause of MMM, are increasing while therapies and preventative strategies are decades old. Trials have looked at TXA to treat PPH, which decreases bleeding and saves lives in the case of traumatic injury. Dr. Saade within the MFMU Network published a study in the *New England Journal of Medicine* in 2023 looking at TXA to prevent obstetrical hemorrhage after cesarean delivery. While they could not confirm the benefit of TXA in preventing maternal death or blood transfusion, they did see improvements in interventions in response to bleeding and in the change in pre- and post-operative hemoglobin levels. Incorporating pregnancy into their study design introduced several challenges. They wanted an outcome of clinical relevance, but this is rare in obstetrics, and longer-term follow-up for risk of thromboembolism added to the cost and study size. They also had to delay administration of TXA until cord clamping to avoid exposure to the neonate.

Similar to PPH, rates of hypertensive disorders of pregnancy (HDP) are also rising and a major cause of both maternal and perinatal mortality and morbidity, with a lack of innovative therapies. There is also a pronounced racial disparity in HDP. Dr. Saade's team at the University of Galveston in Texas studied the use of statins to prevent preeclampsia and found that pravastatin improved endothelial function and uteroplacental function in mice. They proposed a PKPD study to the Obstetric-Fetal Pharmacology Research Unit (OPRU) and obtained an Investigational New Drug Application (IND) from the FDA for a Phase I randomized trial. They found an 80% reduction in incidence of preeclampsia in the individuals who took pravastatin, a decrease in preeclampsia with severe features, and a decrease in indicated preterm delivery. Following this study they proposed a Phase III trial with the MFMU Network using pravastatin 20 mg and a composite primary outcome of preeclampsia, maternal death, or fetal loss. This study is currently on a partial clinical hold from the FDA until they can conduct further animal studies and analyze long-term outcomes in the offspring; however, a long-term neurodevelopmental follow-up study of children exposed to pravastatin in utero was conducted and significant negative effects were not observed.

Dr. Saade summarized several of the challenges in obstetrical trials: eligible patients are uncommon, screening and enrollment are expensive, a need for balance between efficacy and safety, clinically relevant outcomes are rare, and long-term follow-up is needed. All of these factors drive up cost and uncertainty, and the return on investment is small for drug companies due to the short duration of treatment and limited number of patients who will use the medication making large scale funding uncommon. Dr. Saade emphasized the need for solutions, similar to the Cancer Moonshot initiative, to overcome these challenges.

Real-World Evidence

Shaun Grannis, M.D., M.S., FAAFP, FACMI, FAMIA - Vice President, Data and Analytics; Regenstrief Professor of Medical Informatics and Professor, Family Medicine, IU School of Medicine

Chris Bartlett, Ph.D., MHA - Associate Chief Data Sciences Officer, Abigail Wexner Research Institute at Nationwide Children's Hospital; Professor of Pediatrics and Biomedical Informatics, The Ohio State University (OSU) College of Medicine

As defined by the FDA, real-world data (RWD) refers to data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, while real-world evidence (RWE) is clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD. Since 2005 there has been an increase in reliance on RWD/RWE in RCTs as well as externally controlled trials and observational studies. In the MPRINT Real-world Evidence Core, Drs. Grannis and Bartlett are using RWD to develop a hybrid deterministic and algorithmic method of identifying mother-child linkages. This method uses commonly available public health natality data, information from EHRs, and a machine learning method that utilizes demographic data.

While RWE is not the gold standard, it is timely and cost effective; it can be used to identify discrepancies in care, and to work with special populations. It also includes data on patients with multiple comorbidities and drug interactions, which are often excluded from RCTs, and RWE allows for the analysis of different dosing regimens as practiced in real-world studies, helping to optimize dosage recommendations. Dr. Bartlett presented an example of RWD where information on drugs prescribed during pregnancy, pulled from the OSU EHR, could be compared to the MPRINT Knowledgebase data to see what drugs are most often prescribed in the pregnancy interval and how often those drugs are studied during pregnancy and lactation intervals. This can allow researchers to identify real-world patterns, discuss possible new priorities, and find over-studied outliers.

Discussion

Ms. Julie Grimes (Lactation Education Resources) asked Dr. Watt if his team documents the stage of lactation for the milk collected during CUDDLE, and if they use any time intervals shorter than 24 hours in their at-home milk collection study. Dr. Watt said they do collect information about the lactation stage in CUDDLE, primarily as age of the infant or days postpartum. They were not able to get to a more granular level than 24 hours in the at-home condition study, but that would be fairly easy to do in a more in vitro way. Dr. Kaytlin Krutsch (Texas Tech University Health Sciences Center) asked if they looked at any lab work for mammary epithelial permeability in the course of their studies, and Dr. Watt explained they had not done this but acknowledged that it would be important.

Dr. Hebert asked if the FDA was requiring Dr. Saade's team to do further pravastatin studies before a Phase III trial because the drug company was not asked to do those studies before, or because they could not get the data from the drug company. Dr. Saade said that FDA would not share the data from the drug company, and his group did not have access to the past

developmental and reproductive toxicity (DART) studies. He argued that, regardless of those DART studies' results, they should be able to rely on the data that his group has collected through their own studies. They need to accept the fact that medications will be used in pregnancy before there is 100% certainty of safety, because 100% certainty is impossible to achieve.

Dr. Grannis asked if NICHD had a specific strategic plan related to RWD and RWE. Dr. Pawlyk said that one use the NIH is interested in is using RWD/RWE as a regulatory tool to address issues like the one that Dr. Saade brought up with pravastatin. NIH is developing a network to validate and qualify tools for regulatory use, and while NICHD is still exploring its place in those efforts, it will likely be involved in generating linkages and building partnerships. The NIH Common Fund is also starting the Complement Animal Research in Experimentation (Complement-ARIE) Program, which will include an in silico component with RWD.

Introduction to the Review of Drug Nominations within Therapeutic Areas

Overview of Review of Drug Nominations within Therapeutic Areas

Camille Fabiyi, Ph.D., M.P.H.

Dr. Fabiyi gave an overview of the review sessions which are intended to generate input on research needs for drug nominations within the therapeutic areas, with the aim of defining therapeutics and therapeutic needs and gathering data to identify knowledge gaps. Moderators and discussants will cover the background, research landscape or key literature, and proposed recommendations for each area. Following each presentation participants will engage in open discussion, guided by the following questions:

- What information is needed to make prioritization decisions for this area? (i.e., new report on the knowledge gaps, epidemiology, and current treatment option landscape; updates to a existing reports, workshops, or other modes of reaching consensus)
- What considerations are most important for determining topic and therapeutic prioritization? (i.e. severity of condition, population(s) impacted, time to impact, ethical considerations, etc.)
- What types of research infrastructure are needed to address the primary questions? (i.e. utilizing existing clinical trial networks, formation of new networks, retrospective reviews to guides on prospective study design, etc.)
- What types of studies are needed for this topic area (i.e., PK, efficacy, safety)?
- Are the drugs represented in the RFI nominations representative of the topic area and align with standards of care? If not, what is needed to assess missing therapeutics?

The Role of MPRINT Hub's Knowledgebase Portal and Pharmacoepidemiologic Analytic Capabilities in the Review of Drug Nominations

Lang Li, Ph.D. - Professor and Chair, Department of Biomedical Informatics, College of Medicine, The Ohio State University

Dr. Li presented an overview of the silver and gold versions of MPRINT Hub's Knowledgebase-Portal (KBP) and its pharmacoepidemiologic analytic capabilities. The silver version was generated by artificial intelligence (AI). An initial PubMed query using a series of key terms generated nearly 3 million maternal publications and 2.2 million pediatric publications. Dr. Li summarized the large language models (LLMs) and active learning methods that his group used to scan the PubMed abstracts and identify a total of 758,560 publications and 5,062 drugs. Users can conduct queries of the database by drug or more sophisticated queries by both drug and disease. The gold version of the KBP was manually curated and contains 252 drugs and a total of 2,573 publications screened from a pool of 7,966 abstracts.

Dr. Li's group has used the KBP to help identify knowledge gaps in a number of areas. They looked at the frequency of drugs studied from the BPCA priority list in the pediatric population since 2019 and found that out of a total of 157 drugs, only 31 had greater than 20 publications. They also sorted opioid PK studies, pharmacoepidemiology (PE) studies, and clinical trial (CT) publications by subpopulations and maternal pregnancy stages, and divided opioid PE/CT publications into different categories by outcomes and data sources to see how information on various topics was collected.

Dr. Li's institute also has access to the MarketScan Database, which draws from private insurance claims with over 58 million enrollees, including insured employees and their dependents. The database contains person-specific clinical utilization, expenditures, and enrollment information across inpatient, outpatient, and prescription drug services. Paid claims and encounter data can be linked over time across sites and types of providers, and there are 576,869 mom-baby pairs linked through family ID. Dr. Li acknowledged that family ID was a crude mechanism for linkage, but the data are still valuable for longitudinal studies. His group analyzed medication usage data in MarketScan to include in the silver version of KBP and calculated frequencies for five populations: 1) pregnancy, 2) postpartum, 3) infants younger than one year, 4) children 1-12 years, and 5) adolescents 12-17 years. They are also participating in a multi-institutional PE drug safety study. Using electronic medical record (EMR) data from these institutions, the study will investigate medication safety in maternal and pediatric patient populations, including approximately 800,000 linked mom-baby pairs.

Review Selected Nominations by Therapeutic Area

Low Milk Supply, Nutritional, Hyperemesis/Vomiting
Moderator: Andrew Bremer, M.D., Ph.D., M.A.S. - Director, Office of Nutrition Research, NIH
Discussant: Sara Quinney, Pharm.D., Ph.D. - Professor and Director, Disease and Therapeutic Response Modeling Program, Indiana University School of Medicine

Low Milk Supply

Background
Many lactating people perceive that their breastmilk supply is too low; a commonly cited reason for early cessation or decreased exclusivity in breastfeeding. Establishing, monitoring, validating, and quantifying milk production is very difficult, and it is often unclear whether milk production is insufficient, or if the problem with the breastfeeding process is insufficient stimulation. As of 2023, there are no FDA-approved medications to treat low milk supply. Eight nominations were received: any supplements directed to pregnant or lactating people to increase milk production; herbal supplements such as galactagogues for insufficient breastmilk; Mother's Milk Tea; shatavari; domperidone (nominated twice); galactagogues, herbs, and drugs (such as Fenugreek); and galactagogues (synthetic and natural).

Key questions still exist around the safety and efficacy parameters of herbal, pharmaceutical, and dietary supplements used as galactagogues, their benefits, and their effectiveness. There are knowledge gaps around studies on effectiveness and safety, predictors of insufficient milk supply such as biomarkers and polymorphisms, and underlying mechanisms of insufficient milk supply.

Research landscape/key literature
An MPRINT analysis of clinical trials, PE studies, and PK studies on milk supply showed that there is a lack of information on most galactagogues, many of the clinical studies that have been conducted lack stringency, and it is difficult to define clinical outcomes.

Discussion
Ms. Grimes noted the importance of asking which supplements mothers are actually using and which ones other countries have shown to be effective. The answers to these questions should help to inform priorities, dispel myths, and prop up research that has already been done. While Fenugreek has more studies than other supplements, it is controversial in the lactation space because of its side effects. Domperidone is studied more frequently outside of the United States and there is good evidence behind it, but it is not approved for use in the United States. Dr. Quinney agreed that turning to resources like the MotherToBaby helpline would be useful to ascertain which products are actually in use.

Dr. Hebert said that even if they are studied in the proper way, herbal supplements present challenges because often the information on the label does not match what is in the product. Dr. Pawlyk asked whether enough was known about milk composition to objectively address

outcome measures like biomarkers. Dr. Bremer said that in this era of omics, the medical and scientific community is better poised than ever before to answer important questions about the contents of human milk, the variability of milk composition among individuals, and the biological function of individual milk components. It is still difficult to quantify the amount of milk a baby is receiving, but if this could be done then milk volume could start being linked to composition and function. Dr. Quinney added that part of the issue with quantifying milk intake is the variability in how and when a baby is being fed, and this has implications when looking at the PK of various drugs.

Dr. Jennita Reefhuis (Centers for Disease Control and Prevention (CDC)) asked if it would be possible to identify the components of herbal supplements that are effective for lactation, making them more measurable and therefore easier for the FDA to regulate. Dr. Quinney said that for some herbal supplements there is synergism between multiple active constituents, and it may be difficult to tease out those dynamics. Dr. Krutsch said that her group heard a large number of requests for information from mothers and providers about herbal supplements. They also know that lactating people in the United States are using domperidone, and there is currently a Phase II trial for a deuterated version of the drug. Dr. Bremer noted that it is challenging but also very necessary to address the psychosocial elements and other maternal factors that influence human milk composition and production.

Dr. Saade said that regulatory agencies had an accelerated approval process that could incentivize more innovation, but this depends on the scientific community coming together to define clinical outcomes. Dr. Bremer said that from a milk composition standpoint, there is now an economy of scale of researchers who are asking those questions, and talking to regulators and investing in long-term studies is extremely important. Dr. Sahin said that it would be difficult to proceed with further study of domperidone, as the FDA has a strong stance that it should not be used due to its pro-arrhythmic properties. Dr. Krutsch said that what she found most concerning with domperidone use was the lack of consultation with providers, which makes it difficult to stratify risk.

<u>Nutrition</u>

Background

Iodine deficiency can lead to hypothyroidism and iron deficiency can result in anemia, both having negative health effects for mothers and babies. Vitamin supplementation is currently a commonly used therapeutic agent for nutritional support. The nominated agents are prenatal multivitamins/minerals with iodine (over-the-counter and prescribed) and prenatal vitamins.

Key questions concern evaluating iodine status in pregnant individuals and infants and assessment of nutritional status. Knowledge gaps exist around which nutrients should be considered for optimal health outcomes in pregnancy and infancy and the potential effects of contamination in dietary supplements.

Research landscape/key literature

The research landscape includes clinical trials and PE and PK studies, though these often focus on individual elements instead of taking a more holistic approach to nutrition. Dr. Quinney stated that it was important to understand how a person's diet informs which micronutrients they need and how much they should consume.

Discussion

Ms. Grimes suggested looking at iodine in lactation as well as in the prenatal context, as iodine levels in breastmilk are affected by the mother's diet. Dr. Jaime Gahche (NIH) said that the Office of Dietary Supplements (ODS) was interested in looking at prenatal vitamins holistically to study the best forms, absorption rates, and what is actually needed. ODS is hosting a prenatal workshop in 2025 to understand the nutrient requirements for a healthy pregnancy and which nutrients are helpful for certain health conditions. Dr. Daniel Robinson (Northwestern University) suggested that the nutrition model that has been developed for precision health could be appropriately applied in this area. Dr. Bremer said that precision medicine elevates the importance of nutritional assessments. The Nutrition for Precision Health study, powered by the *All of Us* Research Program, is currently still enrolling and is a model to capture deep phenotyping of the pregnant person, the lactating person, and the infant.

Dr. David Weinberg (NIH) emphasized the importance of clear messaging to the public, who are bombarded with disinformation about this topic, particularly from the internet. Dr. Quinney added that non-scientific clinicians are an important audience that does not currently receive this information. Dr. Hebert said that her group at the University of Washington has a paper under review that found that prenatal vitamins often do not match well with nutritional intake during pregnancy and lactation.

<u>Hyperemesis/Vomiting</u>

Background

The 2018 PRGLAC Report discusses nausea and vomiting in pregnancy, including in its most severe form, hyperemesis gravidarum, which has the potential to impact a pregnancy in harmful ways for mothers and babies. In addition to the nominated agents, doxylamine and pyridoxine (vitamin B6) are currently used for hyperemesis/vomiting. Dopamine antagonists, antihistamines, serotonin 5-hydroxytryptamine type 3 receptor antagonists, and steroids are also in the clinical guidelines. The nominations are growth differentiation factor 15 (GDF15)/glial cell line-derived neurotrophic factor (GDNF)family receptor alpha-like (GFRAL) inhibitors; and metformin. Dr. Bremer noted that GDF15 and GFRAL are used as antiemetics in oncology but have not been looked at in pregnancy and lactation.

Limited research is available on medicinal therapies for nausea and vomiting in pregnancy. Although supplement products may be widely used for these purposes, few studies have been reported on their composition, safety, or efficacy.

Discussion

Dr. Quinney noted that metformin can increase nausea as a side effect and the group who submitted the nomination hypothesize that giving metformin before pregnancy prevents nausea and vomiting during pregnancy, as those receptors have already been stimulated. The inhibitors are currently in Phase I clinical studies for cancer cachexia and nausea, but little is known about them at this point, and using them in pregnancy may be premature.

Mental Health
Moderator: Meg Grabb, Ph.D. - Program Officer, NIMH, NIH
Discussant: Matthew Rudorfer, M.D. - Chief, Psychopharmacology, Somatic, and Integrated Treatment Research Program, NIMH

Background
Although there is little data to establish whether medications for mental health disorders are safe during pregnancy, untreated mental illness may pose risks for both the pregnant person and the fetus. The decision of whether a pregnant person should take mental health medication during pregnancy is made on a case-by-case basis, taking into account the severity of the symptoms, their ability to take care of themselves, and whether or not they are able to go to OBGYN appointments. Overall, the data on psychotropics has not been conclusive as to potential harm to the infant, except with specific agents. The nominations for mental health are selective serotonin reuptake inhibitors (SSRIs); serotonin and norepinephrine reuptake inhibitors (SNRIs); bupropion; amphetamines; atomoxetine; guanfacine; benzodiazepines; hydroxyzine; buspirone; and gabapentin. The nominated agents include both specific drugs and large drug classes and fall into three therapeutic areas: 1) treatment of mood disorders, 2) treatment of anxiety disorders, 3) and treatment of attention-deficit/hyperactivity disorder (ADHD). Within each area, the amount and quality of data available for use in pregnancy and lactation are highly variable.

Research landscape/key literature
SSRIs and SNRIs (SRIs) are commonly used antidepressants, and the frequency of SRI use during pregnancy in the United States has increased by a third in the last decade. This has been extensively studied, but sample sizes have been small. A 2024 paper on SRI use in late pregnancy found an increased risk of delayed neonatal adaptation and a dose dependent relationship. Another study found evidence that tapering SRI dose to lower fetal exposure reduced NICU admissions, though the impact on maternal postnatal depression was unclear. The SSRI paroxetine has been associated with congenital malformations when used in the first trimester in two studies, while bupropion received reports of cardiac birth defects when used in the first trimester in a small sample.

In the category of mood stabilizers, lithium, which was formerly used to treat bipolar disorder, is widely regarded as safe in pregnancy, though it is contraindicated in nursing mothers due to risk of toxicity to the newborn. Carbamazepine, valproate, and lamotrigine were originally approved as anti-seizure medications and then for treating bipolar disorder. Carbamazepine and valproate are lithium alternatives and should be avoided in pregnancy due to risk of birth defects. Lamotrigine has not been associated with birth defects or pregnancy complications,

and typically requires dose increases during pregnancy, which are lowered after delivery. While it does enter breastmilk, no adverse effects have been seen in nursing newborns.

Brexanolone and zuranolone, both $GABA_A$ receptor positive modulators, have recently been approved for use in treating postpartum depression. While the FDA has endorsed the safety and efficacy of these approaches, their place in treatment protocol remains to be established.

Benzodiazepines can be used intermittently for episodes of anxiety, and they rapidly cross the placenta. Multiple studies have shown lower gestational age at delivery, lower birth weight, and slight to moderately higher risk of preterm delivery associated with use during pregnancy, primarily driven by exposure in the second and third trimester. There is no systematic data available for buspirone, hydroxyzine, or gabapentin, which are all non first-line anxiolytic agents.

Stimulants, the most commonly used drugs to treat ADHD, are of particular concern to infant health as they may impact neurodevelopmental outcomes and growth. A cohort study of Medicaid-insured individuals in the United States observed a small increase in the risk of cardiac malformations during exposure to methylphenidate in the first trimester. The same effect was not observed for amphetamines. Small studies have observed reduced serum prolactin in postpartum women treated with amphetamines.

Nominated agents guanfacine and atomoxetine are both non-stimulants, which are not first in line treatments, and there is currently no systematic data available on their reproductive safety.

Proposed recommendations

- In a clinical context, understanding patients and their mental health challenges during the perinatal period is important for developing optimal safe and effective use of pharmacotherapy options.
- Align with the standard of care.
- More medication registries; the lamotrigine registry in particular helped to establish the drug's safety for use in pregnancy.
- Case-control series, tracking the course of patients on medication throughout pregnancy (or portions of pregnancy) compared with patients who declined medication.
- More PK studies, tracking changes in medication concentrations across pregnancy. There is a particular research gap with regard to mood stabilizers.
- Benefits and risks of combination treatments (e.g., medication and psychotherapy).
- Consider diversity.
- Clinical research should not increase risk to participants; this should be taken into consideration in the timing of medications, timing of nursing, and tapering of medications.
- Follow neonatal health over time.
- Always consider benefit-to-risk ratio, including the risk of untreated mental illness for mothers and their babies.

- Mood stabilizers and atypical antipsychotics should be considered. Many of the latter now have FDA indications for use as adjuncts in depression and bipolar disorder, and were not included in the nomination list.

Additional discussion questions

- Are the examples in the RFI nominations representative of standard of care in psychiatry?
    - Should off label, occasionally used (not regarded as mainstream) drugs be considered? (e.g., intravenous ketamine?)
    - What disorders, drug classes, and drugs are missing?
- Given ethical considerations, what study designs should be prioritized? (e.g., tapering?)
- Would an intensified diagnostic process in patients with perinatal depression identify more cases of bipolar disorder, with implications for treatment?
- What is the role of device-based neuromodulation interventions during pregnancy, including transcranial magnetic stimulation (TMS), electroconvulsive therapy (ECT), and bright light therapy?

Discussion

Dr. Saade advised caution when looking at data that associates drug exposure to outcomes in children; most of this data comes from administrative data sets where it is difficult to know if the mother actually took the medication, for how long, and the outcomes in children are not rigorously assessed. It is difficult to account for all confounders, and researchers often do not adjust for multiple comparisons. Dr. Grabb agreed, stating that the intent of their presentation was to highlight the multiple gaps existing in this area.

Dr. Reefhuis said that there are case control studies that look at antidepressants and birth defects, and there are methodologies to analyze published studies, though they are not perfect. Studies looking at multiple designs, data sets, and countries are needed before making clinical decisions, but all epidemiological studies should not be discounted. She suggested venlafaxine as an additional medication for consideration; though the case control studies are small and have limitations, they have shown some association with birth defects. Dr. Rudorfer agreed and noted that, while non-pregnancy clinical studies are able to design efficacy trials to control for as many variables as possible, they do not have that luxury in studying people during pregnancy and postpartum.

Hypertensive Disorders
Moderator: Jasmina Varagic, M.D., Ph.D., FAHA - Program Director, National Heart, Lung, and Blood Institute (NHLBI)
Discussant: George Saade, M.D.

Background
Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia-eclampsia, chronic hypertension, and chronic hypertension with superimposed preeclampsia. Preeclampsia is a new onset of high blood pressure (>140/90 mmHg) after 20 weeks of gestation with signs of damage to another organ system, typically kidney or liver. Delivery is the only cure for preeclampsia and may lead to neonatal morbidity and mortality. HDPs are very common in pregnancy in the United States, and all pose health risks for pregnant people and fetuses. In addition to immediate adverse effects, people with HDP are at risk of developing cardiovascular risk factors very soon after delivery, as well as full-blown cardiovascular disease in subsequent years. Current commonly used therapeutic agents for treatment of hypertension in pregnancy include methyldopa, labetalol, nifedipine, verapamil, clonidine, hydrochlorothiazide, and hydralazine. The nominated therapeutic agents for treatment of HDPs are labetalol, nifedipine, and Procardia XL (the extended release version of nifedipine). The nominations for prevention of preeclampsia are acetylsalicylic acid (aspirin) and statins.

Labetalol and nifedipine, first-line therapies for hypertension in pregnancy and postpartum, cross the placental barrier in humans, and are transferred through breastmilk. No evidence of fetal malformations were observed in animals that received several times the maximum human recommended dose of labetalol, though there are no adequate and well-controlled studies in pregnant people. Some non-teratogenic effects have been observed in infants of mothers who were treated with labetalol during pregnancy. For nifedipine, embryotoxic, placentotoxic, and fetotoxic effects were found in animal models when they received several times the recommended human dose, but there are no adequate and well-controlled studies in humans.

Aspirin is a nonsteroidal anti-inflammatory drug, and at low dose (81 mg/day), initiated after 12 weeks of gestation, is recommended by both the United States Preventive Services Task Force (USPSTF) and the American College of Obstetricians and Gynecologists (ACOG) for use in persons who are at high risk for preeclampsia. Aspirin does not significantly increase serious bleeding complications, and at a low dose is not excreted in breastmilk. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors and some studies suggest they could be used in prevention of preeclampsia. They are found to cross the placenta in animal studies and may cause fetal harm when administered to pregnant patients. Pravastatin has a favorable safety profile, good PK properties, and was found to be present in human milk in one study. A series of case reports and observational cohort studies on the use of statins in pregnant people found no major congenital malformations. There is no information on the effects of statins on breastfed infants or milk production.

Research landscape/key literature

A 2018 Cochrane systematic review of 58 trials concluded that antihypertensive drug therapy for mild to moderate hypertension during pregnancy reduces the risk of severe hypertension. The Chronic Hypertension and Pregnancy (CHAP) trial examined the safety and effectiveness of antihypertensive medication compared to no medication in pregnant women with chronic mild hypertension. Before this trial, chronic hypertension in pregnant people was only treated if the blood pressure exceeded 160/110 mmHg (severe hypertension), but the results from the CHAP trial showed that antihypertensive treatment with a blood pressure target below 140/90 mmHg leads to better pregnancy outcomes and has no negative effect on fetal growth. This led to immediate changes in ACOG's clinical practice guidelines. A recent small RCT compared labetalol to extended-release nifedipine in patients with persistent postpartum hypertension and found that both agents were effective, though labetalol had fewer adverse effects and achieved control more often with the starting dose. The Giant Pregnancy ANtihypertensive Drugs: which Agent is best? (PANDA) trial is currently ongoing in the United Kingdom; this is a pragmatic, open-label, multicenter, RCT in women with pregnancy hypertension which evaluates the effects of labetalol and nifedipine on maternal and fetal/neonatal outcomes.

There are still knowledge gaps about whether labetalol or nifedipine is safer and more effective, and the long-term effects of both in children. While most people are now using the extended release form of nifedipine, it has not been adequately studied in pregnant people. There is a need for research in the United States comparing labetalol and nifedipine, but an individualized approach may be more useful than a direct comparison. In addition to prevention of preeclampsia, interventions are needed to improve outcomes once preeclampsia has already developed.

A meta-analysis of the effectiveness of antiplatelet agents (mostly aspirin) performed by the Perinatal Antiplatelet Review of International Studies (PARIS) Collaboration found that antiplatelet agents produce moderate reductions in preeclampsia. The recent Aspirin Supplementation for Pregnancy Indicated risk Reduction In Nulliparas (ASPIRIN) trial in low- and middle-income countries found that low dose aspirin similarly reduced the risk of preterm birth, HDP, and perinatal mortality in women with and without additional risk factors. For statins, animal studies and human pregnancy exposure cohorts do not support previous teratogenicity claims. NICHD's Obstetric-Fetal Pharmacology Research Centers Network performed a series of pilot double-blind randomized trials using pravastatin as a prophylactic treatment in pregnant women at high risk for preeclampsia and found that the treated group had lower rates of preeclampsia and indicated preterm delivery and no identifiable safety risks.

With regard to aspirin's effectiveness in preventing preeclampsia, questions remain about whether aspirin should be given to all pregnant people versus only those at risk, and which dose is more effective, 81 mg versus 162 mg. For statins, there are questions around the efficacy in preventing preeclampsia, long-term effects on children exposed during pregnancy, and effects on breastfed infants.

Considerations for prioritization of research needs:

- HDP are carrying high risk for moms and babies.
- MMM in the United States is high.
- HDP is a significant contributor to MMM.
- HDP is associated with future cardiovascular disease (CVD).
- CVD is the number one cause of death for women in the United States.
- Lack of high-quality, large, RCTs focused on: 1) head-to-head assessment of antihypertensive drugs in pregnancy and 2) efficacy of statins to prevent preeclampsia in high-risk women and improve maternal and neonatal outcomes.
- Need for additional studies on the effect of hypertension medications on lactation and breastmilk
- Need to study statins viamaternal-fetal transfer, safety, and PK/PD studies.
- Potential of leveraging MFMU Network infrastructure.
- 2018 PRGLAC Report:
    - Need to establish more effective treatment/prevention strategies.
    - Substantial gap in the effect of hypertension medications on lactation and breast milk.

Discussion

Ms. Grimes said that she was surprised to hear a caution attached to using nifedipine during lactation, as it is used routinely and the amount present in breastmilk is only 2% of the pediatric dose. She expressed similar thoughts about the prohibition with statins and breastfeeding, as the relative infant dose of statins in breastmilk is 0.2%, which is much lower than the normal cutoff of 10%. She also noted that her organization advises against taking aspirin while breastfeeding due to the possibility of Reye's syndrome.

Dr. Quinney said that one thing missing from studies on labetalol and nifedipine is the effect of precision therapy and personalized therapy; some patients will most likely respond better to one medication than the other because of their different mechanisms of action, metabolic pathways, et cetera. Dr. Saade agreed that different patient populations would benefit from one versus the other. Dr. Quinney added that immediate release nifedipine is not used in any other population other than tocolysis of pregnancy, it has a short half-life, and it has a variable absorption pattern. She suggested looking at the nifedipine extended-release (XL) with more frequent dosing. Dr. Megan Clowse (Duke University School of Medicine) commented that many processes can lead to preeclampsia, including rheumatological conditions such as lupus. She encouraged the group to keep these other pathways in mind and think about different agents that might be able to interfere with them to prevent preeclampsia, such as immunosuppressant medications.

Cardiovascular
Moderator: Jasmina Varagic, M.D., Ph.D., FAHA
Discussant: Courtney Thornburg, M.D., M.S., Chief Medical Research Officer, Division of Blood Diseases and Resources, NHLBI

Background
Increasing incidents of arrhythmia in pregnancy have been noted in the United States over the past two decades. Maternal arrhythmias include supraventricular tachycardia (SVT), which is the most common arrhythmia during pregnancy; atrial fibrillation; and ventricular arrhythmias (VAs). Fetal tachyarrhythmia occurs in less than 0.1% of pregnancies; the majority of these are benign, but some can lead to adverse fetal outcomes. Beta-blockers are commonly used to treat SVT and VAs, with flecainide as a non first-line therapeutic. For fetal tachyarrhythmia, digoxin and flecainide are recommended. Flecainide is the nominated therapeutic agent for treatment of arrhythmia in pregnancy.

Venous thromboembolism (VTE) includes deep vein thrombosis and pulmonary embolism. The risk of VTE increases with pregnancy, and VTE is a leading etiology of preventable MMM. Anticoagulation is used to treat or prevent VTE before, during and after pregnancy, and commonly used anticoagulants include the low molecular weight heparin enoxaparin (given subcutaneously) and unfractionated heparin (given subcutaneously or intravenously). Rivaroxaban is the nominated therapeutic agent for treatment of VTE.

Flecainide is an antiarrhythmic medication that is safely used to treat maternal and fetal arrhythmias, with rare reports of neonatal cardiotoxicity, though there are no adequate and well-controlled studies in pregnancy. It is not known whether the use of flecainide acetate during labor and delivery has immediate or delayed adverse effects on the mother or fetus. Flecainide is excreted in human breastmilk in concentrations as high as four times the corresponding maternal plasma levels, and absorption into neonatal plasma is very low. Milk may inhibit absorption of flecainide in infants, so a reduction in dose should be considered when milk is removed from an infant's diet if it is used to treat arrhythmias in infants.

Rivaroxaban is a direct oral anticoagulant (DOAC) that decreases thrombin generation to prevent thrombus formation.

Key questions:
- Are more PK data needed to optimize treatment of fetal tachyarrhythmia with flecainide?
    - Considerations for placental transfer and accumulation in the amniotic fluid.
    - Optimal methods for measurement of fetal drug exposure.
- Are more data needed to define the fetal, maternal, and neonatal safety profiles?
    - Fetal echocardiography (ECHO) or fetal magnetocardiography (fMCG) could be optimal methods for measurement of flecainide efficacy and toxicity.

- Does flecainide have immediate or delayed adverse effects on the mother or fetus, affect the duration of labor or delivery, or increase the possibility of forceps delivery or other obstetrical intervention?
- Is rivaroxaban safe and effective in treating and/or preventing VTE in pregnancy? Is the PK/PD the same in pregnancy? Could anticoagulation lead to subclinical placental bleeding and associated complications?
- Is rivaroxaban safe and effective in treatment and/or preventing VTE in postpartum period? Is the PK/PD the same in postpartum period?
- Does rivaroxaban cross the placenta? If so, does it cause harm in the fetus such as teratogenic effects or bleeding, including intracranial hemorrhage?
- If a pregnant person is exposed to rivaroxaban, what should be the monitoring?
- If a pregnant person is on rivaroxaban at the time of delivery, what precautions should be taken? Considerations include risk of bleeding with epidural placement or Cesarean section and risk of post-partum hemorrhage.
- Does rivaroxaban cross into breast milk? If so, does it increase harm in the newborn/infant, particularly related to bleeding?

Knowledge gaps:

- Flecainide:
    - Lack of studies:
        - Limited PK studies.
        - No general guidelines on optimal dosing of flecainide and timing of discontinuation prior to delivery.
        - RCTs evaluating and comparing efficacy and safety of antiarrhythmic drugs for pregnant and lactating persons are needed.
            - Awaiting results of Fetal Atrial Flutter & Supraventricular Tachycardia (FAST) Therapy Trial for fetal arrhythmia.
    - When evaluating the risks and benefits of flecainide, how to account for effects of the underlying arrhythmia on fetal and neonatal outcomes.
        - It is often difficult to tease out outcomes related to the condition versus side effects of medication.
- Rivaroxaban:
    - VTE represents a wide range of conditions that can present as a pre-existing condition at the time of pregnancy or develop during pregnancy or in the postpartum period. Each condition and associated timing of presentation will have specific knowledge gaps.
    - It is known that rivaroxaban passes into breastmilk; currently available preclinical and incidental exposure data in pregnancy are very limited and insufficient to conclude safety of rivaroxaban in this population.
    - The limited available data on rivaroxaban in pregnancy are insufficient to inform a drug-associated risk of adverse developmental outcomes. Adverse effects have been seen in animal studies and reported in a few human case reports.

- There are insufficient data to determine the effects of rivaroxaban on the breastfed child or on milk production.

Research landscape/key literature

Much of the research landscape data for flecainide focuses on fetuses and infants. Case reports indicate flecainide is safe to use to treat fetal tachyarrhythmia, and that it penetrates the placental membrane easily without accumulation in fetal blood. Small observational studies of 14 women who were given flecainide for fetal SVT concluded that it should not be the first drug of choice for atrial flutter. A systematic review and meta-analysis comparing the efficacy, safety, and fetal-maternal tolerance of first-line therapies for fetal SVT and atrial flutter found that flecainide may be more effective than digoxin as a first-line treatment for fetal SVT. The prospective RCT of FAST RCT recently completed enrollment, though no results have been published yet. The study included 600 fetuses with SVT or atrial flutter from at least 70 centers. Flecainide concentration in human milk averages 2.5 times that found in maternal plasma, with a calculated infant plasma level that is negligible for a nursing infant.

The research landscape for rivaroxaban consists of animal studies, database reviews, pharmacovigilance reports, and case reports, with some case reports including drug concentration in breastmilk. As a DOAC, rivaroxaban is not considered safe for pregnant or lactating people, and multiple medical societies recommend against its use in these populations.

Considerations for prioritization of research needs:

- Flecainide:
  - Maternal and fetal arrhythmias are rare but could lead to significant maternal, fetal, and neonatal adverse events.
  - Flecainide is deemed relatively safe during pregnancy and lactation and used in clinical practice. Additional preclinical and clinical data could be used to optimize administration and clinical outcomes.
  - Future studies should consider routes of maternal fetal transfer to inform additional PK studies.
  - Better pharmacological and electrophysiological models could be developed and used to predict effects.
  - To garner more RWE, expand drug usage registries to accurately assess the clinical effects of antiarrhythmic drug treatment on both mother and fetus, including data during the breastfeeding period.
  - Conduct randomized trials evaluating the superiority in efficacy and safety of antiarrhythmic in pregnancy.
  - Leverage MFMU Network infrastructure.
- Rivaroxaban:
  - Consulting with experts in hematology, obstetrics, and perinatology to gather more information, specifically asking if there is additional rationale to study rivaroxaban further, given that is considered unsafe based on limited data.

- Consider multiple levels of efficacy and safety risks to the pregnant person, fetus, and neonate.
    - There are rare contraindications to heparin, as well as special populations with very high risk of thrombosis.
- Research infrastructure is needed.
    - Additional safety and efficacy data may come from RWE, including claims data, pharmacovigilance, and registries/cohort studies and PK studies to inform whether interventional studies may be safely pursued.
    - Investigators should consider available networks and FDA guidance.

Discussion
Dr. Saade noted that antiarrhythmic medications are supposed to treat the fetus without harming the mother, while anticoagulants are supposed to treat the mother without harming the baby. There is an opportunity to develop methods and formulations of these medications to either limit or facilitate their transplacental passage. Dr. Hebert asked if the DOACs should be studied further. Dr. Thornburg said that it was important to get more preclinical data in animal models to look at safety, both in terms of teratogenicity and bleeding risk, before embarking on any clinical trials. Dr. Reefhuis said that they need to prioritize finding a way to capture data on women who are on a drug and happen to get pregnant.

Day 1 Summary and Instructions for Day 2

Diane Gumina, Ph.D.
Camille Fabiyi, Ph.D., M.P.H.

Dr. Gumina summarized key points from the day's discussion. Dr. Fabiyi thanked the presenters and attendees for their time and adjourned the meeting at 4:33 p.m.

Day 2: Wednesday, July 10, 2024

Summarize Day 1 and Discussion

Camille Fabiyi, Ph.D., M.P.H
Diane Gumina, Ph.D.

Dr. Fabiyi welcomed participants to the second day of the meeting. Dr. Gumina summarized the presentations and discussions from Day 1. She noted that, while there were subject-specific discussions around the RFI-nominated therapeutics, some common themes emerged, including: the rigor of prior studies and how that informs the future of research; the possibility of a role for precision medicine; considering preconception health in studies; accounting for and including multiple comparisons; and rooting prioritizations in the standard of care.

Overview and Instructions for Remaining Nomination Review

Camille Fabiyi, Ph.D., M.P.H.

Dr. Fabiyi summarized the format for the nomination presentations and discussions. She thanked the moderators and discussants for their insight and expertise in organizing this meeting.

Review Selected Nominations by Therapeutic Area - Continued

Preterm Birth
Moderator: Monica Longo, M.D., Ph.D. - Medical Officer, Project Scientist, Maternal-Fetal Medicine Units Network; PPB, NICHD
Discussant: Maisa Feghali, M.D. – Assistant Professor, University of Pittsburgh

Background
A preterm delivery, also known as a premature birth, occurs when a baby is born before 37 weeks of pregnancy have been completed. Preterm deliveries can be categorized into different subcategories based on gestational age, including:

- Extremely preterm: Less than 28 weeks
- Very preterm: 28 to less than 32 weeks
- Moderate to late preterm: 32 to 37 weeks

Preterm delivery is the leading cause of neonatal morbidity and mortality and the most common reason for antenatal hospitalization. It accounts for 25-50% of cases of long-term neurologic impairment, cerebral palsy, breathing problems, feeding difficulties, and/or impaired vision or hearing. Current practice for preterm labor involves the use of tocolytic drugs to delay labor and allow for the administration of corticosteroids and magnesium sulfate and transport to a tertiary facility. Common medications to treat preterm birth include nifedipine and indomethacin; terbutaline can be used in acute settings, and magnesium is now used only for neuroprotection for 12 hours. These medications have limited effectiveness in preventing preterm birth and there is a lack of consensus on the optimal tocolytic drug to use, leading to variability in practice. There is a need for more research and evidence-based

guidelines to guide the use of these drugs effectively and safely. The nominated therapeutic agents for this category are hydroxyzine; aspirin; statins; azithromycin; novel synthetic progestin; progesterone; choline/phosphatidylcholine; and prenatal multivitamin/mineral (over-the-counter and prescribed).

Hydroxyzine use during pregnancy has been associated with an increased risk of preterm delivery, but some studies have found different results. One study found that hydroxyzine use during pregnancy was associated with an increased risk of preterm delivery. However, another study found no significant difference in pregnancy outcomes between women who were exposed to hydroxyzine and those who were not. Although the mechanism of action for aspirin is not fully understood, the ASPIRIN trial found that it reduced the incidence of preterm birth and perinatal mortality. Statins are used to treat high cholesterol and prevent heart disease, and in pregnancy they may increase risk of preterm labor. However, some studies suggest that they may help delay premature birth by reducing inflammation and uterine muscle contractions. Azithromycin is an antibiotic used to treat perinatal infection in preterm premature rupture of membrane (PPROM) or advanced cervical dilation. Novel synthetic progestin is another agent to be explored, especially given the FDA final decision ordering the withdrawal of approval for Makena (hydroxyprogesterone caproate). Vaginal progesterone can still be used, but it has not been well-studied for use to prevent preterm labor in women with prior preterm delivery. A series of dietary supplements were also nominated: choline/phosphatidylcholine, which have been studied for prevention of birth defects and preterm birth, have been shown to improve postnatal growth and neuro-cognitive development of infants; and prenatal vitamins/minerals, including vitamin D, vitamin C, iodine, calcium, iron, and folate.

Key questions:

- What are the best therapeutic options for efficacy and safety?
- What are the PK/PD and safety considerations?
    - Transfer of medication across the placenta
    - Transfer of medication across breast milk
    - Long-term neonatal/children follow-up
- Dosage and timing guidelines for administration.
- Route of administration leading to change in PK.

Research landscape/key literature

The research landscape includes several PK and epidemiology studies on progesterone, aspirin, folate, iron, and calcium. Progesterone has been the subject of the most clinical trials in this area, but there is still a significant limitation in understanding what other medications, vitamins, and supplements can be used to prevent preterm birth. Although the research literature on preterm birth is relatively large compared to other conditions covered in the 2018 PRGLAC Report, there is still limited scientific understanding of the underlying mechanisms. There is also a knowledge gap around PK, PD, and pharmacogenetic (PG) considerations specific to pregnant and lactating physiology.

Discussion

Dr. Feghali noted that in the clinical setting there is a distinction between spontaneous preterm delivery related to preterm labor or placental conditions and iatrogenic situations where preterm delivery is indicated, such as preeclampsia. The same medications and interventions would not necessarily apply to both of these scenarios. Dr. Saade emphasized the need to determine what outcome would be adequate to allow regulatory agencies to approve any medication preventing preterm delivery. Dr. Feghali agreed that clinical outcomes related to the success of preterm delivery prevention have varied significantly, and it has become harder to find effective therapies as the goals are moved with higher expectations. The population that is studied can affect these outcomes, as there are baseline differences in preterm delivery risk and recurrence.

Dr. Weinberg said that he did not hear enough compelling evidence to test any of the nominated agents, and the field needs to support more research on the mechanisms of action. He added that he would encourage the group not to treat preterm delivery as a single category, echoing Dr. Feghali's comments about clinical distinctions. Dr. Krutsch encouraged the group to reconsider the justification for excluding parents with preterm delivery from clinical lactation trials, because that population needs better information. Dr. Robinson said that he had expected to see the N-3 fatty acid DHA (docosahexaenoic acid) in the nomination list, as it has a strong foundation of literature for prevention of preterm delivery. Dr. Saade said that there were many other therapeutic agents for preterm delivery that were not on the nomination list. He added that better methods are needed to study pregnancy in utero prospectively, similar to the Human Placenta Project.

Ms. Becky Abbott (Society for Maternal-Fetal Medicine) said they needed to think about whether they are prioritizing obstetric research generally or helping to guide the decision-making process between clinicians and patients. Dr. Feghali said that part of the challenge with preterm delivery is that, because it is a pregnancy-specific condition, it is difficult to use interventions from other areas. In addition, the overall regulatory environment and the concern about research and pregnancy have negatively impacted the ability to evaluate interventions for its treatment and prevention. Dr. Reefhuis said that recurrence is a good starting point because they already know there is increased risk and inequity. Dr. Feghali said that the avoidance of intervention because of theoretical risk comes at the cost of exposure to active conditions with known risks. Studies that are well-organized and well-regulated can still allow for the protection of research participants while advancing knowledge of how to care for these patients. Dr. Krutsch commented that there is a push for more patient-centered research, and they need to make sure they are answering the questions that patients and lactation consultants are actually asking.

Dr. Quinney echoed earlier comments that the nominated agents are not the right drugs to study; instead they should be looking at medications that they already know have the potential to be effective. Dr. Longo asked how they could best reach out to get input about the right drugs to study. Dr. Quinney said that her group was using MPRINT to look at RWE on use of medications and trying to match that up with what is presented in the research. She also

suggested surveying clinicians directly. Dr. Krutsch said that organizations like InfantRisk and MotherToBaby are collecting data on what questions are asked, and this can complement the MPRINT data. Dr. Weinberg suggested that a study could look at why some people have severe adverse side effects to nifedipine while others do not, as this could be valuable from a precision medicine standpoint. Dr. Saade recommended continued focus on treatment or management to improve the outcomes for preterm neonates, as this is where they have been the most successful in the area of preterm delivery.

Infectious Disease

Moderator: Tara DeYampert, M.D. - Program Officer, Division of Extramural Research, NICHD
Discussant: Jeanna Piper, M.D. – Senior Medical Officer, Division of AIDS, National Institute of Allergy and Infectious Diseases (NIAID)

Background

Infections during pregnancy and lactation are common, and infectious diseases in pregnant women can cause substantial maternal and fetal morbidity and mortality. There is limited scientific information for pregnant women and their providers on how and whether to treat infectious diseases during pregnancy and lactation. Other than the well-documented risk of HIV transmission via breastmilk, there are few data available on the effects of infections and their treatment on breastmilk and lactation, as mentioned in the 2018 PRGLAC Report. The nominated therapeutic agents fall into three categories: HIV prevention and treatment (cabotegravir and lenacapavir); hepatitis C treatment (sofosbuvir/velpatasvir and glecaprevir/pibrentasvir); and syphilis treatment (cefixime).

Multiple antiretroviral drugs are currently approved for treatment of HIV, and a few drugs approved for prevention. Cabotegravir has been approved by the FDA for treatment and prevention of HIV, with testing prior to starting its use. Lenacapavir has also been approved for treatment by the FDA and is under investigation for prevention. In June 2024, data from the PURPOSE 1 (https://www.purposestudies.com/purpose1/) study showed a significant reduction in HIV acquisition in cisgender women compared to oral pre-exposure prophylaxis (PrEP). Of the 133,000 estimated perinatal infections worldwide in 2022, 20% were due to acute infection during pregnancy or lactation. Perinatal transmission of HIV has decreased dramatically in the United States since 1995. HIV acquisition during pregnancy and lactation has a higher risk of perinatal transmission due to high viral loads from acute infection and late timing of diagnosis and treatment. Pregnancy and lactation also include physiologic changes that increase the risk of HIV infection if exposed.

In 2022, the CDC reported 67,400 estimated acute hepatitis C infections in the United States. Direct acting antiviral agents have cure rates greater than 95%, but access to diagnosis and treatment is low. Sofosbuvir/velpatasvir was approved by the FDA for treatment of hepatitis C, with ribavirine added for people with decompensated cirrhosis. A sustained virologic response was found in more than 90% of people across multiple clinical studies. Glecaprevir/pibrentasvir is also approved by the FDA and also has a sustained virologic response rate of greater than 90%. 15 million people of child-bearing potential have chronic hepatitis C, and perinatal

transmission occurs in 5-7% of pregnancies with active hepatitis C. There is limited data on the impact of hepatitis C on pregnancy, as well as the impact of pregnancy on hepatitis C, though there is evidence of increased risk of intrahepatic cholestasis of pregnancy associated with hepatitis C infection.

The CDC reported 203,500 new syphilis cases in the United States in 2022, which is a 79% increase from 2018. Maternal syphilis rates in the United States increased by 222% from 2016 to 2022. According to CDC guidelines, benzathine penicillin G is the preferred treatment for all stages of syphilis and the only treatment for syphilis in pregnancy. Outside of pregnancy doxycycline, tetracycline, and ceftriaxone may be used. Syphilis is associated with adverse birth outcomes, including stillbirths, neonatal deaths, low birth weight, and congenital syphilis. The majority of congenital syphilis cases are related to lack of adequate diagnosis and treatment during pregnancy. Cefixime was approved by the FDA in 1986 for bacterial infections and is currently being studied as an alternative treatment for syphilis in non-pregnant people.

Research landscape/key literature
Animal studies done on cabotegravir in pregnancy and lactation have shown generally reassuring results. Data is currently being collected in the Antiretroviral Pregnancy Registry and through International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) studies. The HIV Prevention Trials Network (HPTN) 084 pregnancy substudy is currently collecting safety and PK data from the original Phase III trial and the open-label extension study. Animal studies have shown negative results for reproductive toxicity of lenacapavir, but there is inadequate human data for safety evaluation. The excretion in human breastmilk is unknown, as is the impact of pregnancy and lactation on PK or efficacy in humans. Data is being collected in the Antiretroviral Pregnancy Registry and the PURPOSE 1 and 3 studies. There are gaps in knowledge for both cabotegravir and lenacapavir around the safety for fetuses and infants exposed via pregnancy and lactation, though data is currently being collected for both via registry and from ongoing clinical trials. Data is currently being collected on the impacts of pregnancy on PK and effectiveness for cabotegravir through clinical trials, but the same has not yet been done for lenacapavir.

Animal studies have shown negative results for reproductive toxicity of sofosbuvir/velpatasvir and glecaprevir/pibrentasvir, but there is inadequate human data for safety evaluation. Components of both drugs were detected in animal breastmilk, with unknown excretion in human breastmilk. Data is being collected for both agents in the Treatment in Pregnancy for Hepatitis C (TiP-HepC) Registry. The Hepatitis C in Pregnancy (HIP)-2 PK study of sofosbuvir/velpatasvir (SOF/VEL) in pregnancy has been completed and found that the PK was not clinically significantly different from non-pregnant individuals and there were no concerning adverse events in mothers or fetuses/infants. The SOF/VEL Treatment of Chronic Hepatitis C During Pregnancy (STORC) study of safety of sofosbuvir/velpatasvir in pregnancy is ongoing. There are only case reports of glecaprevir/pibrentasvir use in pregnancy thus far, but an IMPAACT 2014 study to assess PK and safety in pregnancy and lactation is in development. Data is being collected from ongoing clinical trials to assess safety for fetuses/infants exposed during pregnancy/lactation, and the impact of pregnancy on PK and effectiveness for

sofosbuvir/velpatasvir. More trials are needed to collect data on these same areas for glecaprevir/pibrentasvir.

Due to drug shortages of benzathine penicillin G, alternative therapies with adequate placental transfer are needed for treatment of syphilis in pregnant women. Animal studies have found negative results for reproductive toxicity of cefixime, but there is inadequate human data for safety evaluation. There are no controlled studies for treatment of syphilis in pregnancy, but a trial is currently underway to look at cefixime use in non-pregnant women, with a plan to study pregnant women subsequently if successful.

Recommendations

- Prioritization in the infectious disease category should be guided by population frequency, impact on pregnancy/lactation, impact on the fetus/infant, and feasibility.
- The three conditions discussed today were all high priority examples with drugs at different stages in their pregnancy/lactation pathway.
- Other drugs submitted are also high priority, particularly the multiple tuberculosis (TB) drugs submitted, which will need quite a bit of time to fully consider.

Discussion

Dr. Pat Flynn (St. Jude Children's Research Hospital) noted that Gilead, the sponsor of the PURPOSE studies, has significant data on lenacapavir in pregnancy. IMPAACT has some studies on first- and second-line TB drugs, but, given some of the very complex drug regimens TB patients are on, there is an opportunity for more research on drug-drug interactions. She added that she was surprised by the lack of vaccine nominations, particularly flu and COVID vaccines. Dr. DeYampert said that they did receive a nomination for the mRNA vaccine for RSV and one for the COVID vaccine. Dr. Piper mentioned NIAID's Multisite Observational Maternal and Infant Study for COVID-19 (MOMI-VAX study), which is currently analyzing breastmilk data and will be published later this year.

Dr. Saade asked if there were any nominations for the treatment of cytomegalovirus (CMV), which is just as much a problem as syphilis. He added Group B strep to the list of vaccines that should be considered. He said that it was important to determine which was better, giving an RSV vaccine to the mother or treating the baby prophylactically after delivery. Dr. Piper said that CMV did not have any nominations, nor did they see nominations for infectious disease conditions that are specific to pregnancy and lactation, such as mastitis, endometritis, and chorioamnionitis.

Dr. Michael McVoy (Virginia Commonwealth University) suggested prioritizing ways of finding money to support not just the studies but the cost of some of the drugs needed to conduct the studies. Dr. Piper said that PRGLAC often discussed the topic of pharmaceutical companies' attitudes towards testing their products in pregnancy and lactation. They talked about trying to de-risk the process and making it more feasible for companies to put their products into studies. Dr. Hebert commented that companies are responsible for ensuring the safe and effective use of their products. When a drug is approved in the adult population, it is approved

for pregnant and lactating people, and the liability data shows that it is riskier not to study these individuals than to study them. Dr. Sahin added that a recently published report by the National Academies of Sciences, Engineering, and Medicine found no evidence to support an increased risk of liability for including pregnant and lactating people in clinical studies. The real liability occurs once the product is out on the market without data on how it affects this population.

Dr. Saade said that it was not actually an issue of liability, since liability is inherent for drug companies, but there is no financial return on investment in pregnancy. They need to find a way of incentivizing companies to get a return on investment through programs like BPCA or by making trials less costly, which depends on regulation. Dr. Pawlyk said that developing better nonclinical models will also help, and there is potential to improve DART assays, which are currently very expensive. He commented that pregnancy and lactation research could be viewed as being at the point where pediatrics was 30 years ago, and it took congressional action to create incentives and requirements for industry doing clinical trials. One large incentive for the pharmaceutical industry is the extension of exclusivity, which has a high market value for companies.

Dr. Krutsch said that she was surprised not to see treatment for mastitis on the nomination list, as it is currently at the center of a controversy in the lactation world and more information is needed about its physiology. She also talked about the ways that risks and benefits are communicated from studies on the effects of antibiotics in breastmilk, noting that InfantRisk hears from many lactating people who choose to suffer without their antibiotics rather than risk harming their baby.

Dr. Saade noted that many medications used in non-pregnant people were able to progress because they were used first in healthy volunteers, and he wondered if something similar could be done for pregnancy. Dr. Sahin noted that in pediatrics there is a provision of a minor increase over minimal risk where there is potential generalizable knowledge. This topic was raised in PRGLAC but the discussions have not moved forward.

Dr. Krutsch said that she has asked the BPCA program whether lactation trials could qualify for pediatric exclusivity, but she has not received any solid answer. Dr. Feghali said that these discussions highlight just how isolated the pregnancy and lactation world is when it comes to regulatory language. It would be helpful to remedy this to allow more flexibility, given the lack of availability of regulatory space to try to investigate treatments in the setting of pregnancy-specific conditions.

Dr. Fabiyi shared comments from the online chat. One commenter noted that the World Health Organization has a working group focused on drugs for treating and preventing HIV, hepatitis, and STIs in pregnancy and lactation. Another shared that one of the key antibiotics used in multidrug-resistant TB is a later generation fluoroquinolone, which is also relevant to other infections in pregnancy. The commenter asked if any of the nominated drugs cut across several different infectious diseases, as that would seem to give them higher priority. Dr. Piper said

that she did not recall any drugs being submitted for multiple conditions. Another online commenter pointed to a consensus statement on the inclusion of pregnant people in TB research, available on the Treatment Action Group (https://www.treatmentactiongroup.org/) website.

Substance Abuse/Exposure & General Areas
Moderator: Sunila Nair, Ph.D. - Program Officer, Integrative Neuroscience Branch, National Institute on Drug Abuse (NIDA)
Discussant: Carmela Reichel, Ph.D. – Program Officer, Division of Therapeutics and Medical Consequences, NIDA

Substance Abuse/Exposure

Background
The use of alcohol, tobacco, and illicit drugs during pregnancy and lactation is a significant public health concern in the United States, as mentioned in the 2018 PRGLAC Report. In the 2013 National Survey on Drug Use and Health, 5.4% of women reported using illicit drugs (including cocaine, methamphetamine, and marijuana) during pregnancy, 9.4% reported using alcohol, and more than 15% reported using tobacco. The opioid epidemic has also spread among pregnant women, and the incidence of neonatal opioid withdrawal syndrome (NOWS) has increased nationally. Therapeutic agents currently used to treat substance use disorders (SUDs) are nicotine replacement therapies and medication-based treatments for opioid dependence, including methadone and buprenorphine. The nominated therapeutic agents in the abuse category are vape pens (mods, pods, e-cigarettes), medications foropioid use disorder (MOUD), and naltrexone. For the exposure category, the nominations are cannabidiol (CBD), cannabis, marijuana (all components - delta-9 tetrahydrocannabinol (THC), delta-8 THC, et cetera.), and over the counter cannabidiol and/or medical cannabis.

Key questions:
- What is the impact of vaping on the fetus?
- What are the consequences of regular maternal use of CBD on the pregnancy?
- What are the long-term effects of marijuana and its components? Does marijuana have long-term adverse effects on the fetus?
- Do the benefits of cannabis use for hyperemesis gravidarum outweigh the risks to the pregnancy and the fetus?

There are few studies that address how SUDs and their medicinal therapies affect lactation and breastmilk. Basic mechanistic studies of substance use in pregnancy are limited, and relatively few studies of any type exist to inform understanding of possible therapeutic approaches in pregnant people who used several commonly abused illicit drugs.

Research landscape/key literature
This category did not have an associated MPRINT analysis. An electronic search of research articles for studies of naltrexone compounds compared with methadone and buprenorphine in pregnant individuals with opioid use disorder (OUD) yielded a total of five studies that met eligibility criteria. No significant differences in gestational age at delivery were detected, and all

studies with data on neonatal abstinence syndrome (NAS) detected a lower risk of NAS in the naltrexone group compared to methadone and buprenorphine. The data available are limited, and further comparative studies of pregnant people with OUD taking MOUDs and large RCT trials are necessary. In non-pregnant people, methadone and buprenorphine are associated with lower overdose rates and decreased opioid health problems than naltrexone, but all forms of MOUD are superior to no treatment for overdose prevention.

Prenatal cannabis exposure after the middle of the first trimester is associated with attentional, social, and behavioral problems in affected children, which persist as they progress into early adolescence. Analysis using baseline data from the Adolescent Brain Cognitive Development (ABCD) study found an association between prenatal cannabis exposure and behavioral problems in children 9-10 years of age. Other preclinical studies have reported that Delta-9 THC can cross the placenta and potentially affect brain development. The incidence of opioid use at labor and delivery has steadily increased since 1999, with stimulant use in pregnancy characterized as an under-recognized epidemic. Two separate studies found that drug overdose mortality increased in pregnant and postpartum people during the COVID pandemic, with the highest rates during the late postpartum period.

Recommendations

- Additional studies are required prior to forming a consensus on prioritization
    - Studies targeted at delineating changes in the PK of SUD therapeutics during pregnancy and in the postpartum period
    - Studies targeted at the transfer of addictive substances as well as therapeutic agents through the placenta and into breast milk
    - Influence of polysubstance use on maternal and fetal outcomes
    - Identification of brain changes during pregnancy and postpartum
    - Identification of specific windows of vulnerability and biological factors that increase vulnerability during pregnancy and in the postpartum period
    - Mechanisms underlying individual differences in vulnerability
    - Influence of comorbidities such as postpartum depression, sleep disturbances, etc.
- Consideration of non-pharmaceutical interventions:
    - Circumvent polydrug use and exposure as well as drug-drug interactions
    - Cognitive behavioral and digital behavioral therapies
    - Neuromodulation (e.g., TMS, focused ultrasound and low intensity focused ultrasound, phrenic nerve stimulation, etc.)

<u>General</u>

Background

This category is not included in the PRGLAC Report. The nominated agents are drugs frequently taken by pregnant people and drugs used for general anesthesia. Key questions arose from the nomination about studying the mechanism and extent of changes in the PK of drugs in the maternal-fetal unit, including fetal exposure through phenotyping studies and in vitro studies, rather than studying each drug separately. For general anesthetics, there was a question of

whether the advice to pump and dump breastmilk is backed up by actual evidence of transfer or harm to the baby.

Research landscape/key literature
Data from MPRINT studies on general anesthetics showed more studies conducted during pregnancy than in the postpartum period, with almost none during lactation.

Discussion
Ms. Grimes said that lactation circles were moving away from the idea of pumping and dumping breastmilk for surgeries, with the exception of certain procedures and drugs. Dr. Krutsch added that the American Society of Anesthesiologists (ASA) has a new slogan, "sleep and keep," and their guidelines no longer recommend pumping and discarding milk. Dr. Hebert said that they do not want to push pregnant and lactating people into less than optimal treatment strategies. She added that, under the current state of the art strategy for OUD, taking away buprenorphine increases recidivism. Dr. Grabb asked if the ABCD study collects data on the amount of cannabis use in a certain time period. Dr. Nair said that she was not sure about the granularity, but they do collect that information. Dr. Reichel said that they ask participants to self-report cannabis use and then attempt to quantify this with hair samples.

Ms. Grimes asked if anyone was looking at whether the benefits of treatments for withdrawal also pass into breastmilk for babies with NOWS. Dr. Nair said that they needed more small- and large-scale studies to answer that question with respect to individual drugs and polysubstance combinations. Dr. Reichel added that lofexidine is one of the only FDA-approved treatments for opioid withdrawal. While she did not know if it passed into breastmilk, it is under consideration for treatment in younger populations.

Study Design for Research on Therapeutics in Pregnant and Lactating People, Part 2

Mary Hebert, Pharm.D., FCCP

Dr. Hebert summarized the study designs that were discussed on Day 1 and noted that clinicians often face challenges when preclinical work has not been done or is not accessible. Most of the preclinical and clinical work with the pregnant and lactating population is done during the postmarketing period, after the drugs have been approved. DART studies are done during drug development, but the information is often considered proprietary. Phase I studies of safety and dosage have been done for very few medications during pregnancy. Most of the medications used in pregnancy are FDA-approved for the adult population, but their place in therapy, what dose to use, and the safety for pregnant, postpartum, and lactating persons, as well as the embryo, fetus, and neonate, have not been established. Evaluating each individual medication to collect the missing data will be costly and require careful consideration of prioritization. The following elements should be taken into account:

- Pharmacological gaps in knowledge for PK, PD, dosing, efficacy, and safety of each drug in pregnancy and lactation.
- Timing of studies (PK, PD, efficacy, safety) during pregnancy and lactation.

    - Do studies need to be done in all three trimesters? What is the time course of changes postpartum?
- What factors are important to consider in the selection of study design?
    - Dedicate versus nested PK/PD studies? Single dose versus steady state? Population versus intensive sampling?
    - RWD versus prospective, randomized studies for efficacy and safety information?
- Selection of the appropriate control or comparator group depends on the question you are trying to answer.
    - Is the PK/PD changed during pregnancy?
    - Is the PK, PD, dosage, efficacy and safety the same as the population for which the drug has received FDA approval?
    - Is the efficacy/safety better with new treatment versus the standard of care?
- Dosage selection strategies: extensive sampling PK/PD, population PK, non-linear PK, modeling and simulation, cross-sectional dosage studies.
- Consideration of PD changes:
    - Is there a good surrogate marker? Is the underlying condition the same as the improved condition? Is the response to therapy the same as the approved population?
- Efficacy study considerations: Have PK/PD studies been completed? Have dosage and safety been determined during pregnancy/lactation? Is the drug being used for an approved indication?
- Safety study considerations: What are the effects of the drug (maternal, embryo, fetal, neonate)? Is this a first-in-pregnancy study?

Dr. Hebert opened the floor for a discussion on strategies NIH can use for prioritization. Dr. Pawlyk asked how to assess whether sufficient nonclinical studies have been done to initiate additional research studies in pregnant and lactating people. Dr. Sahin said that FDA's M3(R2) guidance discusses the nonclinical studies that need to be done before pregnant individuals can be included in clinical trials. There is a question around when the available RWD from a drug on the market becomes sufficient to obviate the need for those nonclinical studies. Dr. Li said that his group used machine learning to curate six or seven categories of maternal/pediatric information from drug labels, and this is included in the silver version of the KBP. The KBP also contains many well-defined phenotypes curated from published epidemiology studies, and these can serve as a preliminary starting point for future epidemiology studies. Dr. Pawlyk asked if MPRINT could extract a summary of the nonclinical data from the labels, and Dr. Li said that they were already doing that automatically. All of this information can be accessed by querying the silver version of the KBP.

Dr. Reefhuis noted that a case control study is almost always needed to study a specific birth defect because they are such rare outcomes. It is important to keep talking to PPL people to find out whether they are taking their medication, as this can ebb and flow over time and it can be different for different medications. She reiterated the importance of starting a registry for

people who get pregnant during trials and would otherwise be removed from the trial. Dr. Hebert noted that currently that data is owned by the drug companies and cannot be released because it is proprietary. Dr. Reefhuis added that the link to stillbirths is missing from pregnancy outcomes, and they are difficult to find in maternal medical records.

Dr. Saade commented that one of their problems is the lack of standards and guidance to assess how much nonclinical research or RWD is sufficient to proceed with human studies. Dr. Krutsch noted that the public comment period is currently open for the USCDI+ core data elements for the maternal health domain, and they would appreciate feedback on Dr. Reefhuis' point about stillbirths in medical records. She also suggested applying natural language processing to the lactation information from the National Library of Medicine's LactMed database. In response to Dr. Saade's comments, Dr. Pawlyk noted that several NIH Institutes and Centers do have contract services that conduct trials with regulatory consultants, although NICHD does not. There is a knowledge gap when it comes to investigators accessing that regulatory expertise to design studies.

Ms. Grimes echoed Dr. Li's comments about looking at RWD first to see which of the most commonly used drugs have not been studied and then prioritizing those medications for further research. She suggested looking at medications that have already been shown to be efficacious, such as heparin for the treatment of VTE. Dr. Hebert added that conditions that are less common but life-threatening should also be prioritized. Dr. Krutsch suggested looking at drugs for which there are no alternatives, where clinicians currently advise people to stop breastfeeding so that they can continue to use the medication. Dr. Reefhuis commented that, as a pregnancy-only issue, preterm birth should be prioritized. Dr. Hebert agreed and added that the same was true for preeclampsia and hyperemesis gravidarum. Dr. Fabiyi shared a comment from the online chat that they can build in PK early safety assessment among consenting people who become pregnant in registrational trials, especially Phase III. Once dosing is established in non-pregnant adults, and if no concerns are raised by nonclinical fertility and early embryonic development (FEED)/embryo-fetal development (EFD) studies, they could stay on the study drug with consent.

Open Discussion and Plans for the Future

Dr. Fabiyi invited participants to raise questions or comments about topics discussed during the meeting. Dr. Saade said that many studies in this area are negative because the availability of funds determines study design factors such as eligibility, outcome, and sample size. Trials are often stopped early because of poor recruitment, or they are underpowered because investigators picked an outcome and overestimated its rate to keep the budget below the funding requirement. Dr. Krutsch suggested that more lactation physiology expertise should be included in ongoing discussions.

Meeting Adjourned

Dr. Fabiyi thanked the participants for their attendance and noted that they will continue to have future discussions about the remaining nominations, most likely via virtual working groups. There being no further business, she adjourned the meeting at 11:51 a.m.

Appendix 2

Landscape Analyses

MPRINT Landscape Analysis

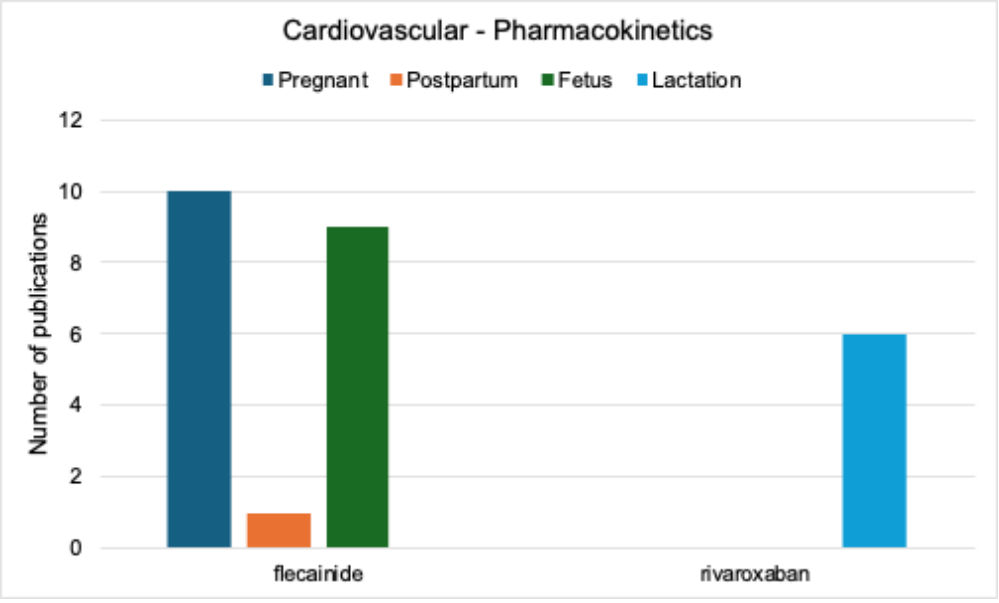
The following figures are from the MPRINT Knowledge Gap Graph analyses that were prepared to help identify knowledge gaps in the types of studies that will be needed to advance therapeutic research for PPL women.

Each graph represents the number of publications identified describing clinical trials (CT), pharmacoepidemiology studies (PE), and pharmacokinetic studies (PK) in pregnant, postpartum, and lactating women of given drugs for the indicated indication(s) or therapeutic area.

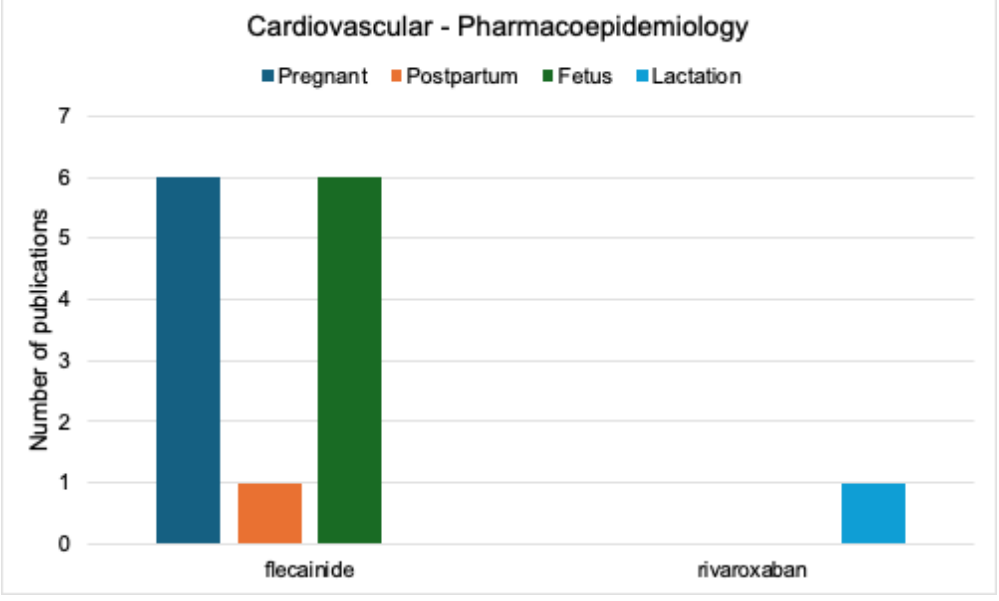
Data was derived from the MPRINT Hub Silver Knowledgebase, which includes articles from PubMed. Figures were generated in June 2024 and summer 2025.

Landscape analysis for nominations discussed in 2024

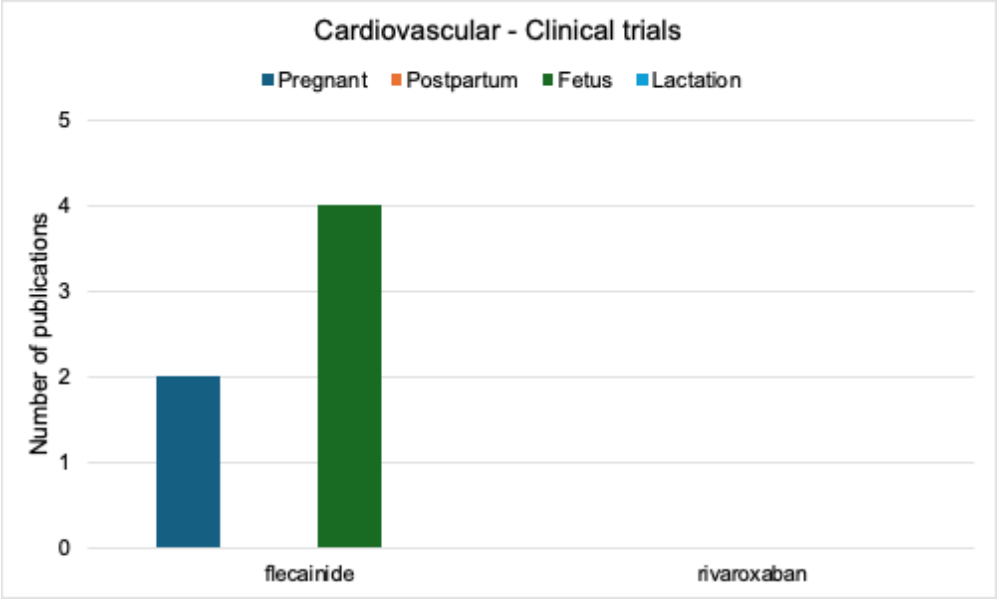
Cardiovascular nominations



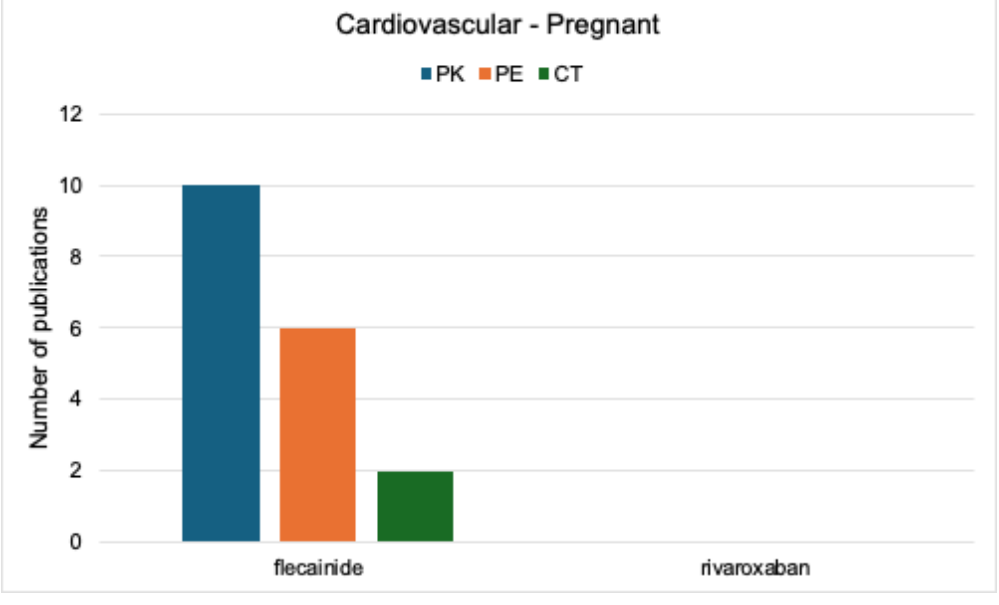
Cardiovascular nominations



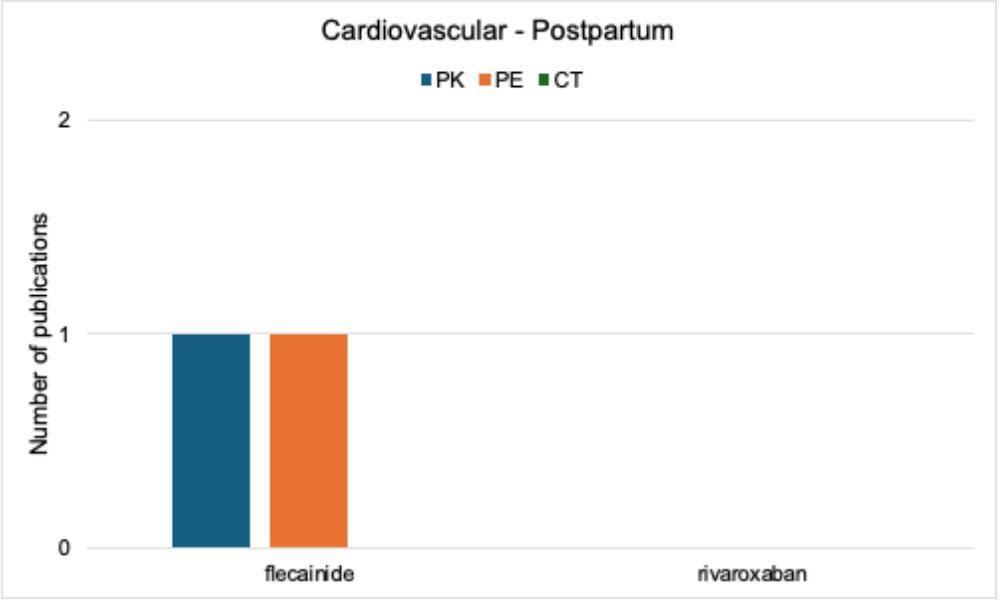
Cardiovascular nominations



Cardiovascular nominations



Cardiovascular nominations



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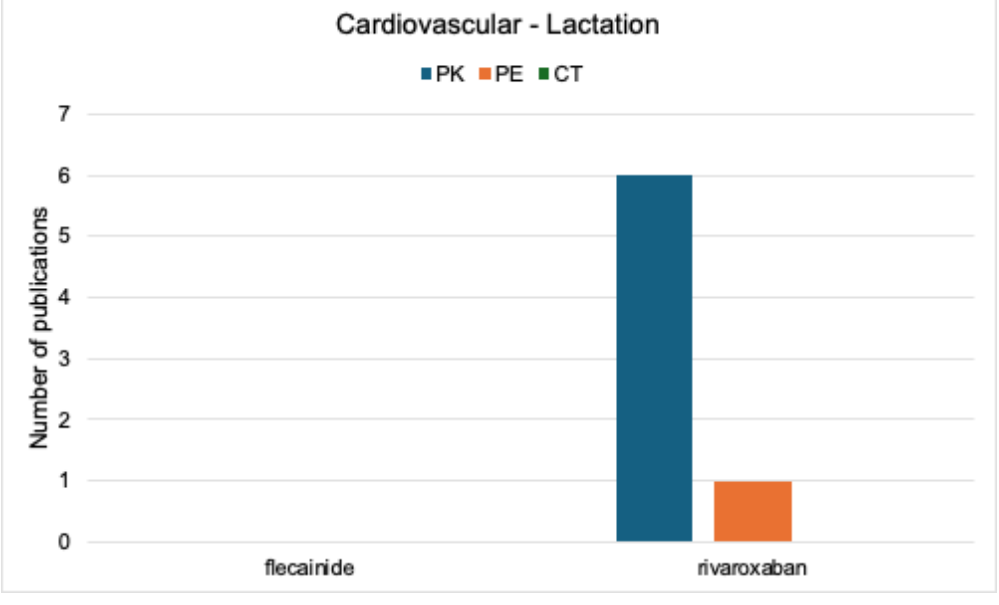
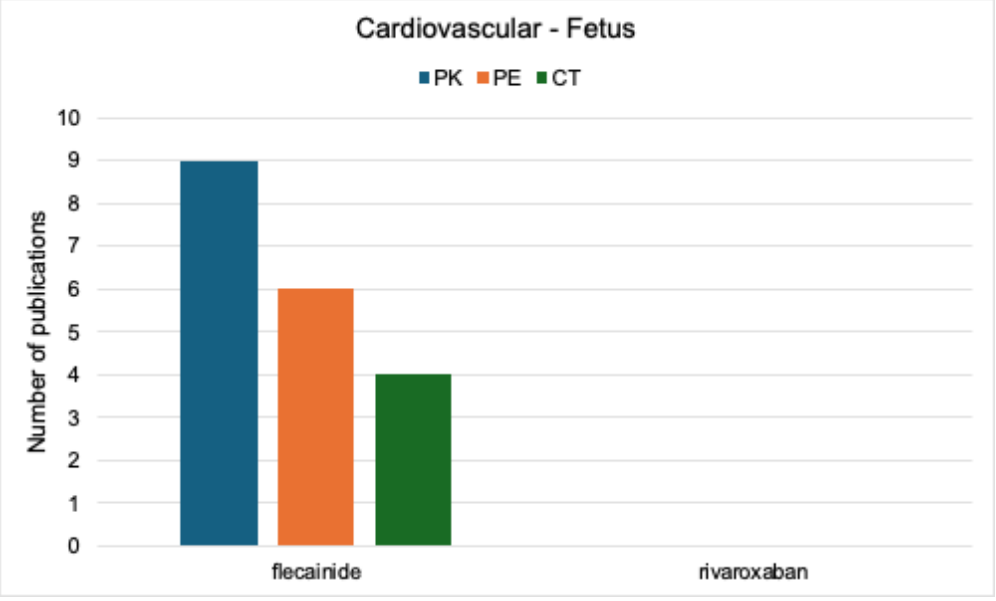
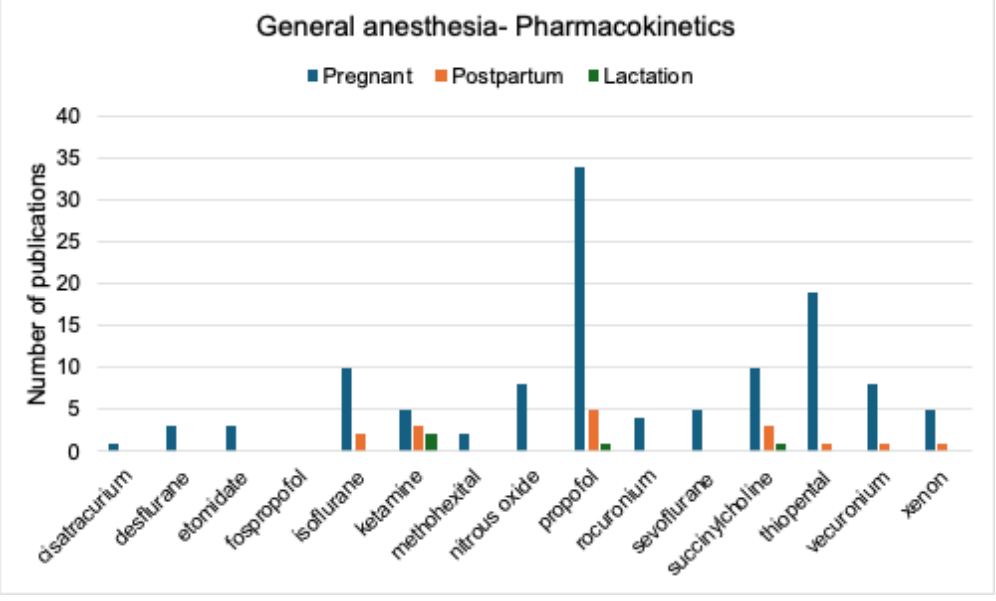


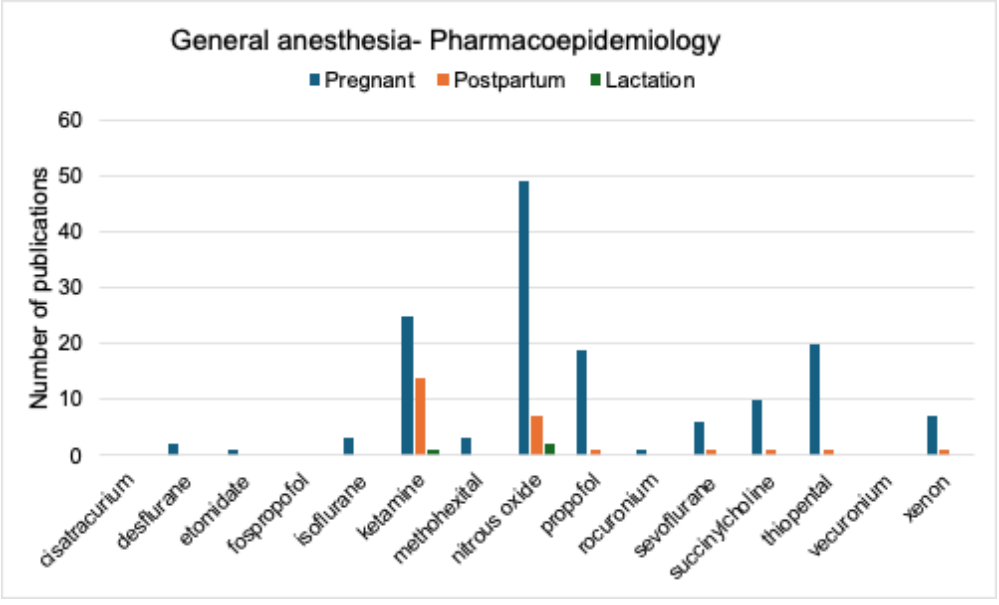
Cardiovascular nominations



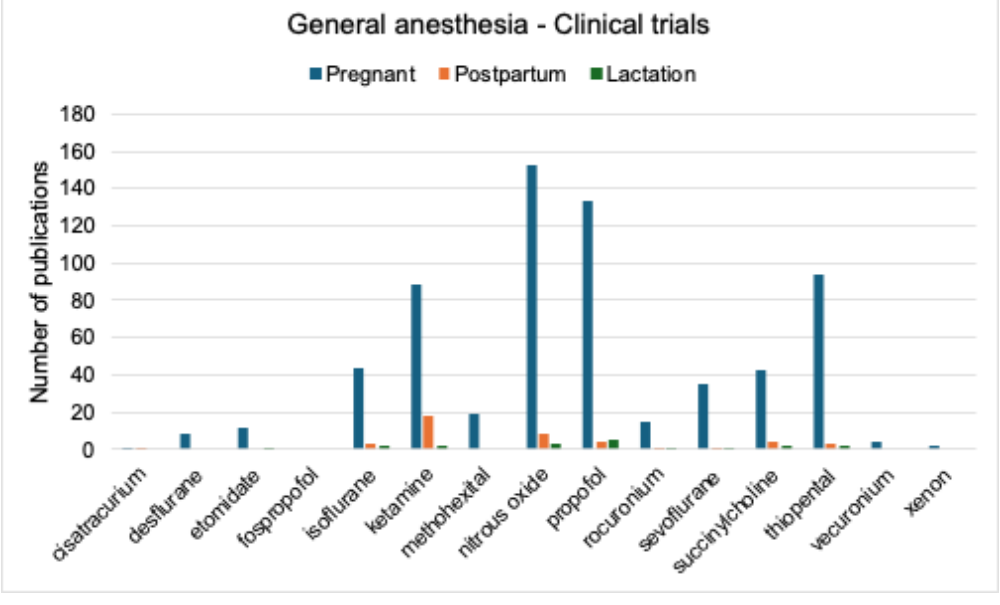
General anesthesia nominations



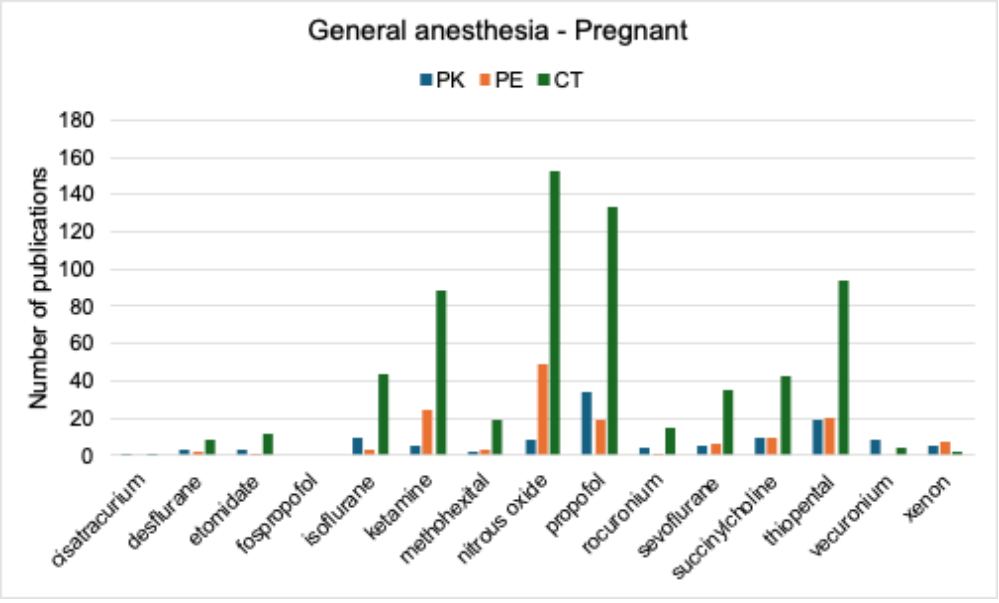
General anesthesia nominations



General anesthesia nominations



General anesthesia nominations



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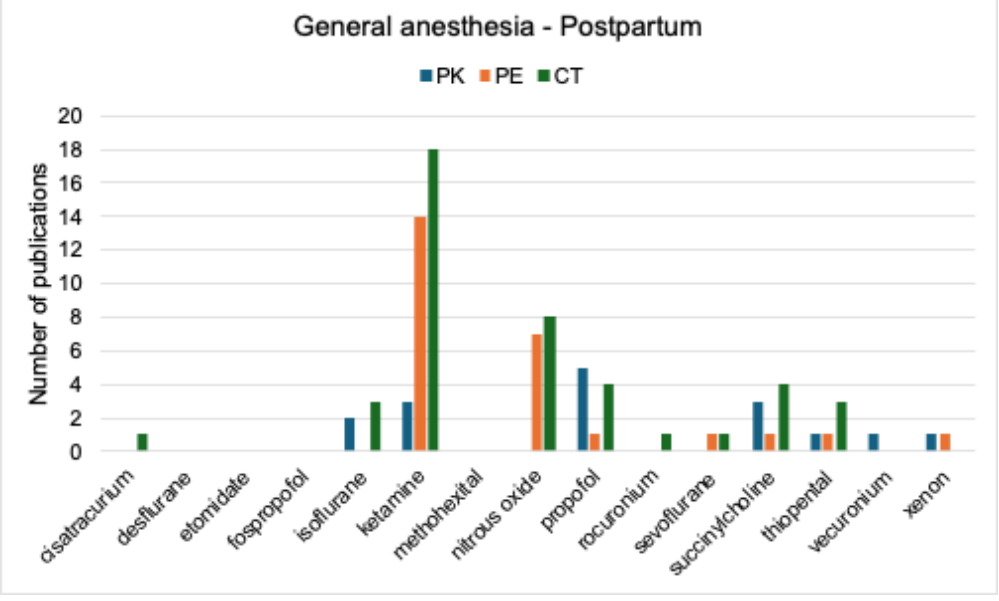
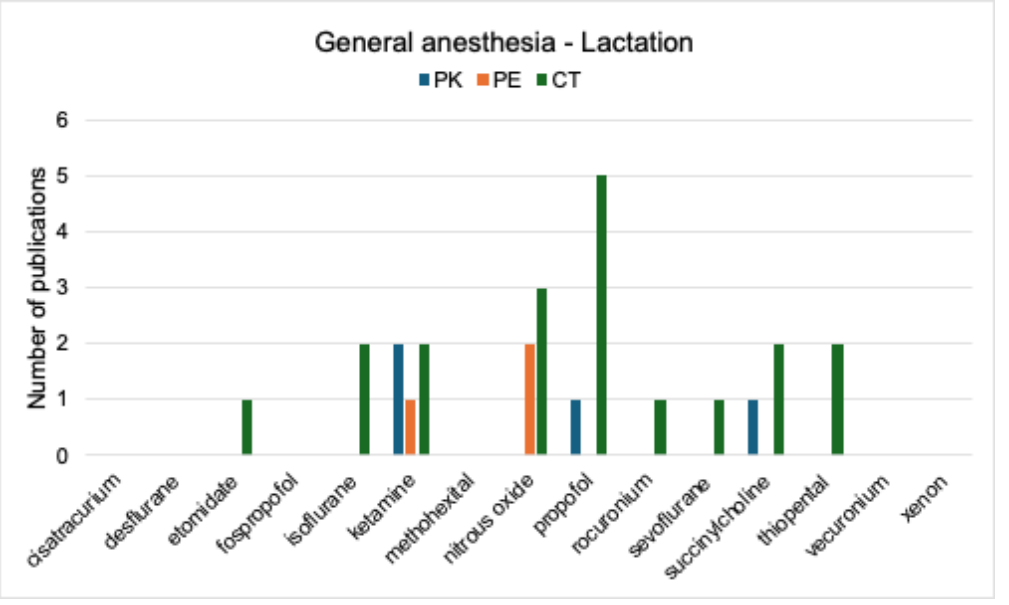
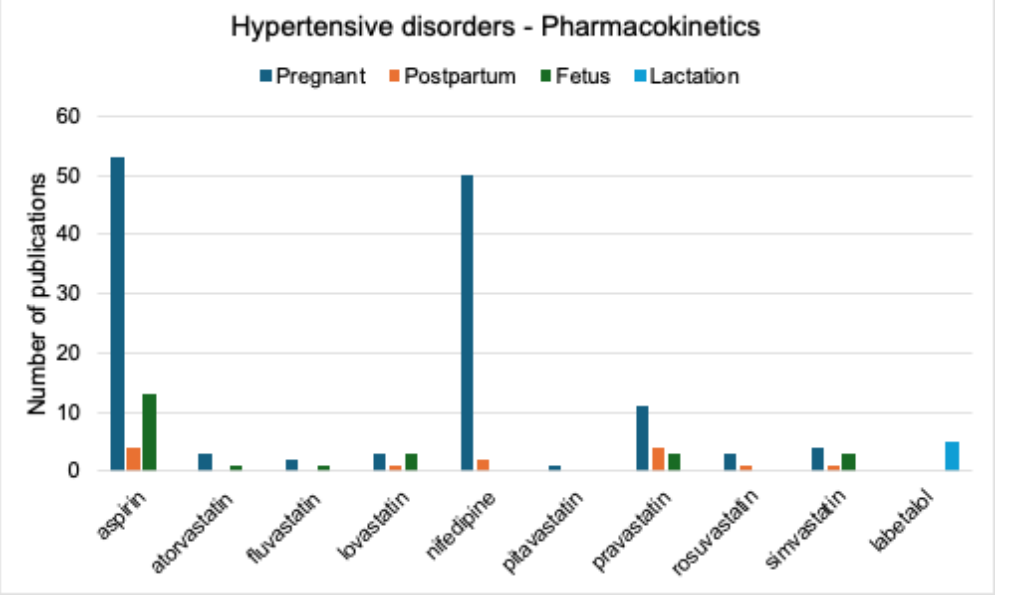


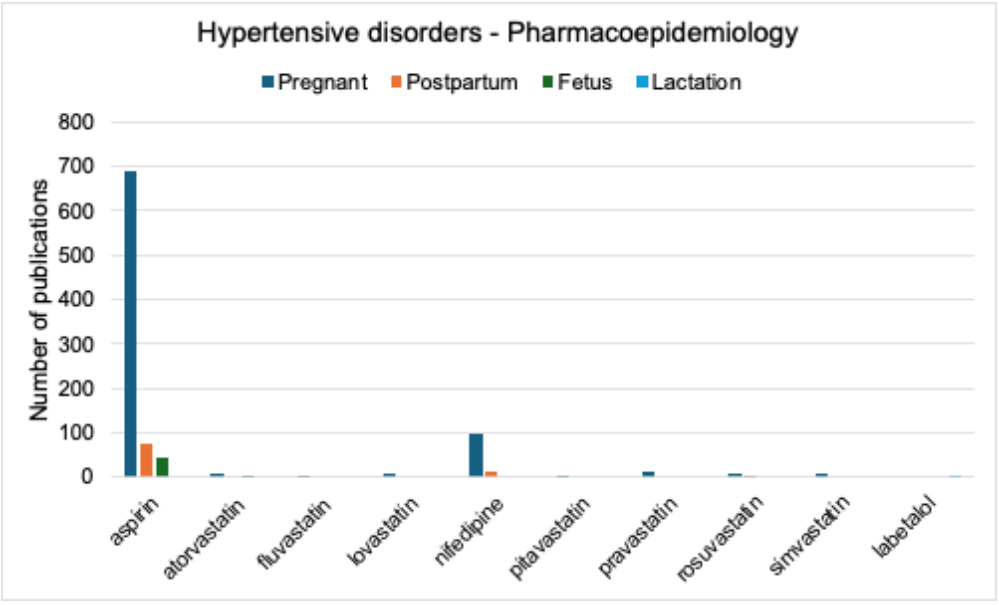
General anesthesia nominations



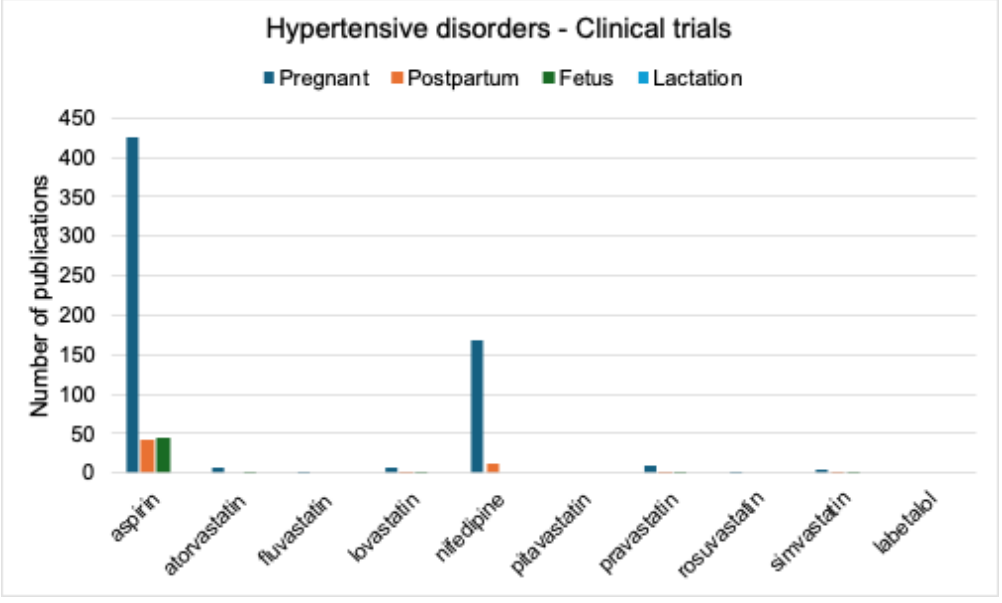
Hypertensive disorders nominations



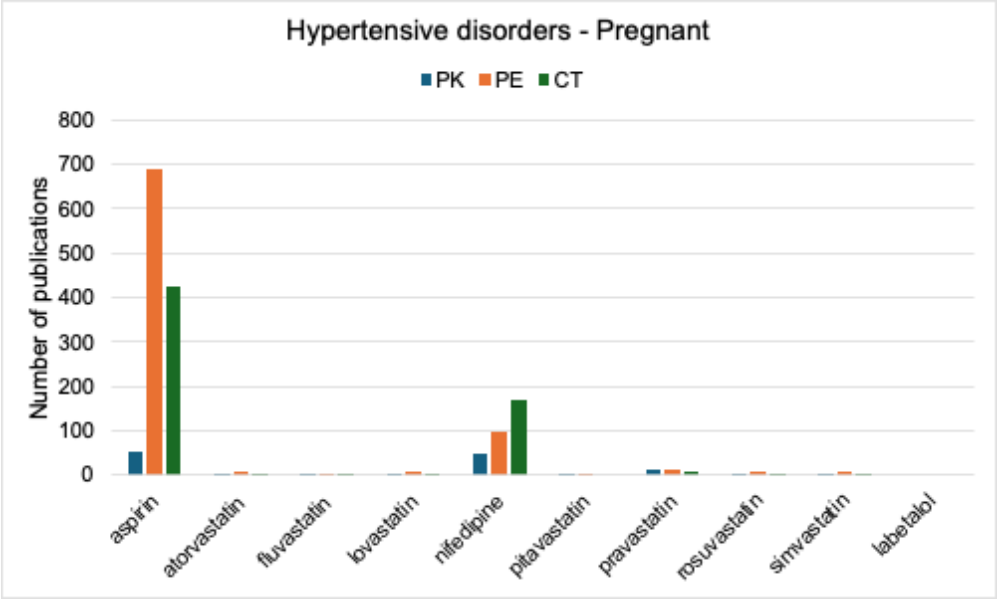
Hypertensive disorders nominations



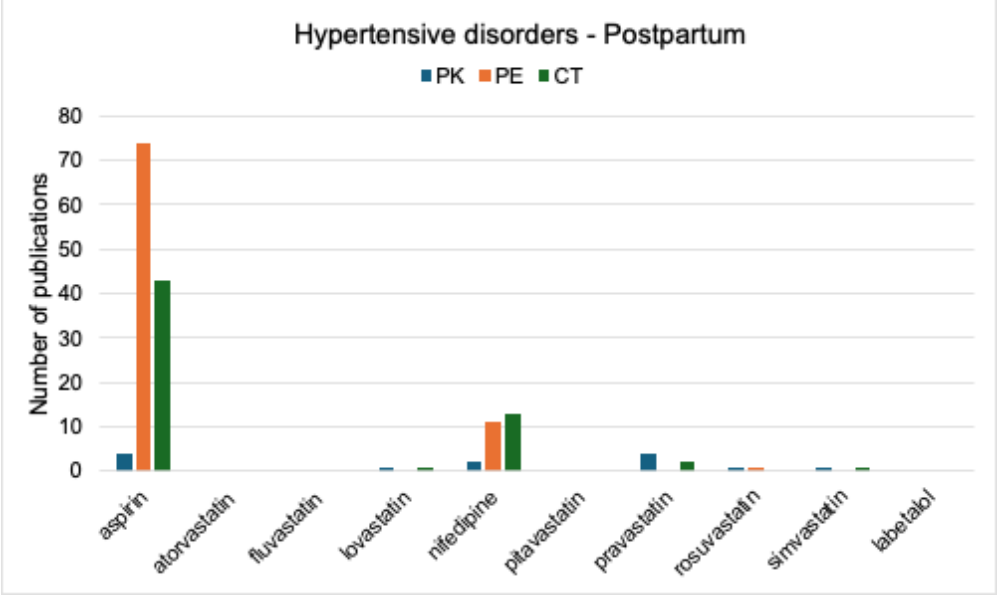
Hypertensive disorders nominations



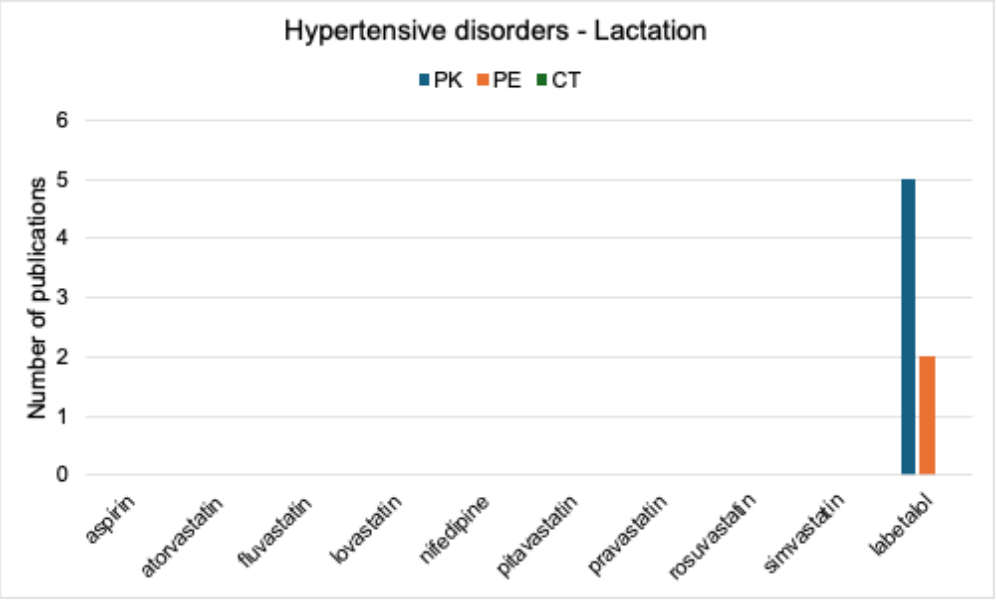
Hypertensive disorders nominations



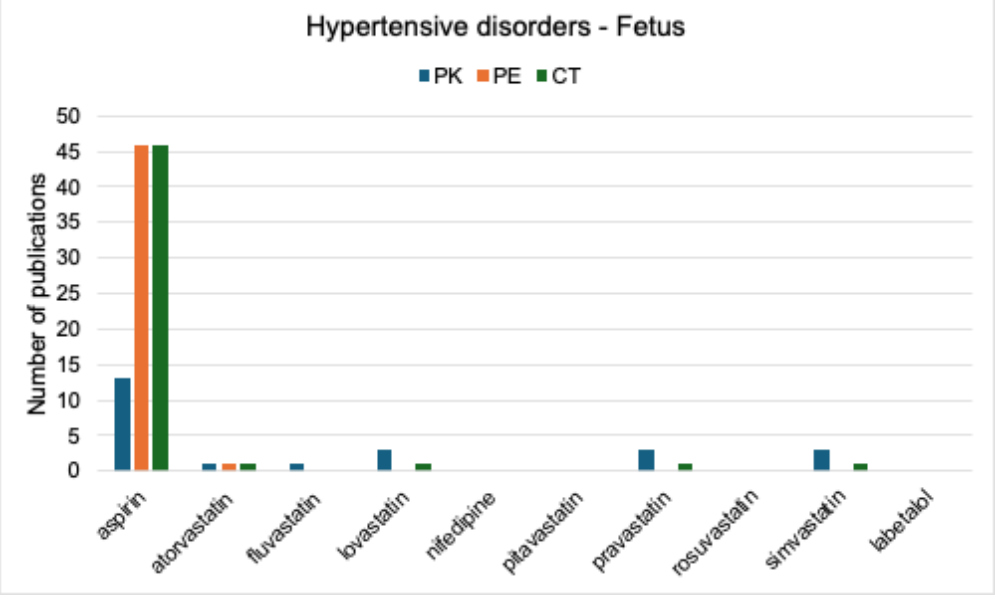
Hypertensive disorders nominations



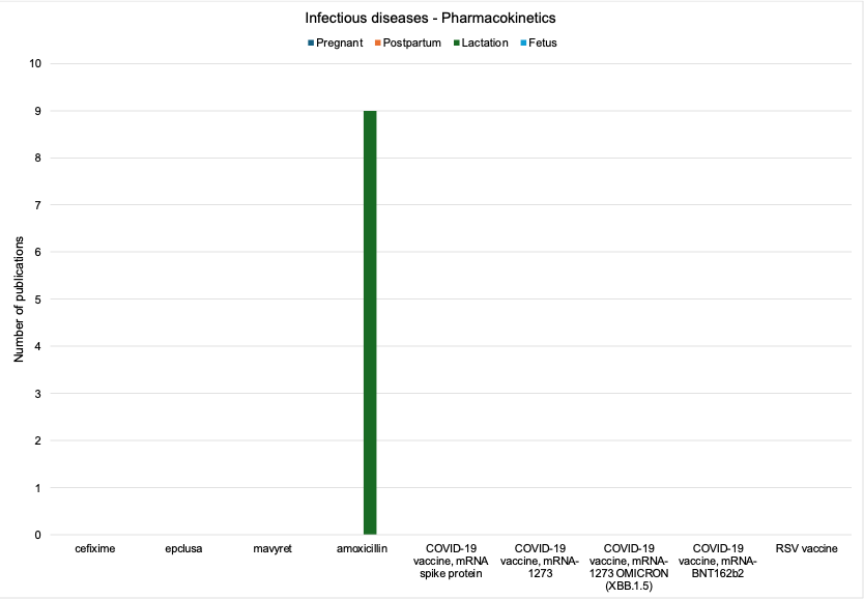
Hypertensive disorders nominations



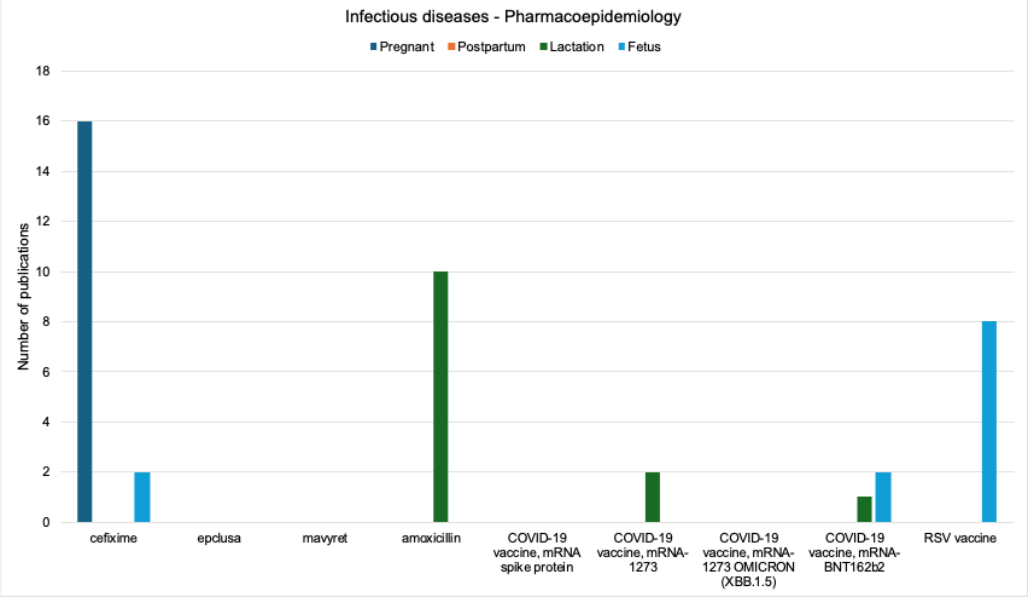
Hypertensive disorders nominations



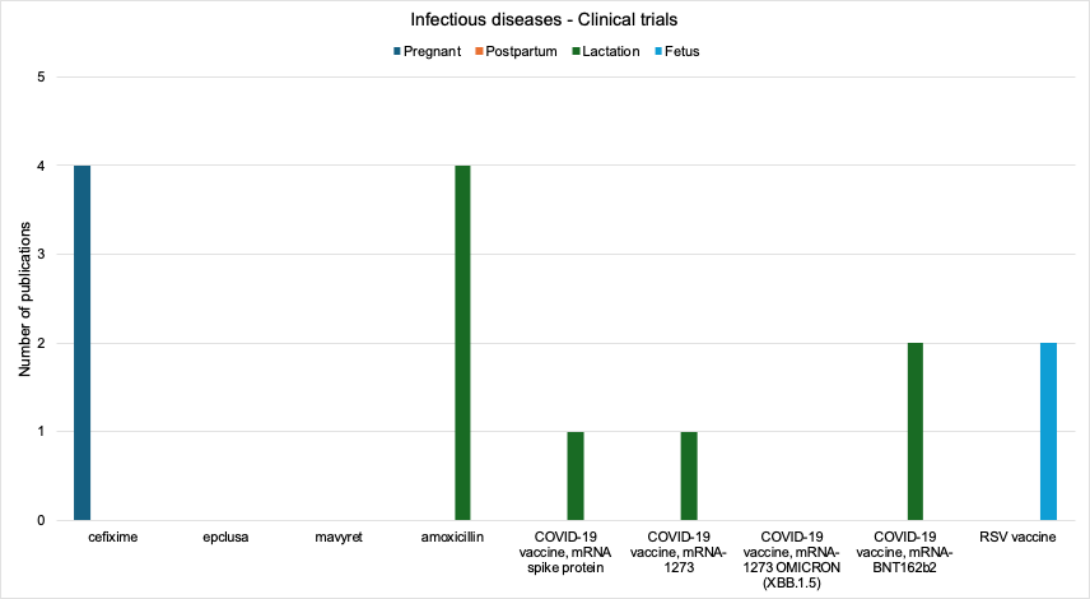
Infectious diseases nominations



Infectious diseases nominations



Infectious diseases nominations



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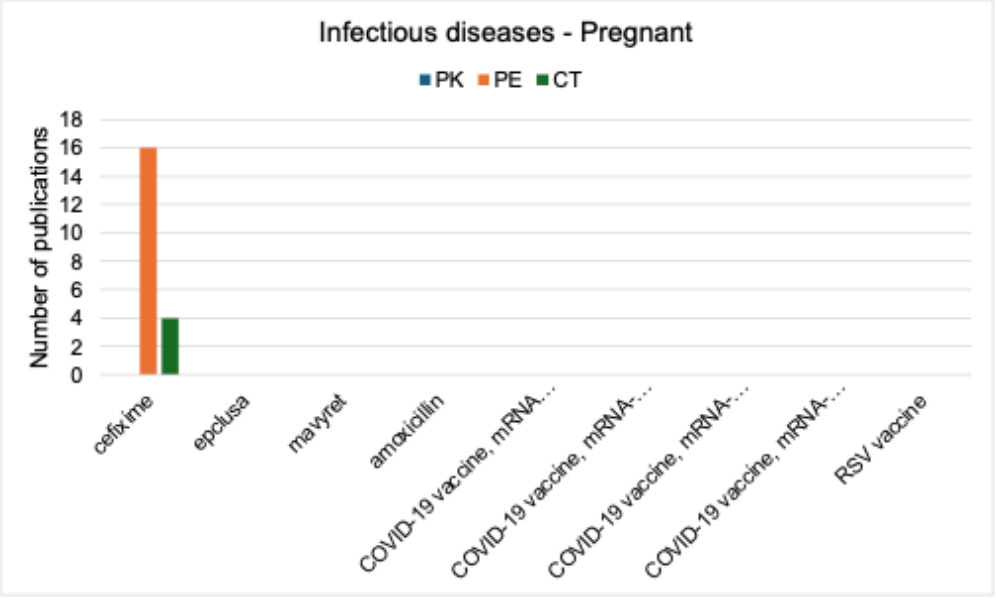
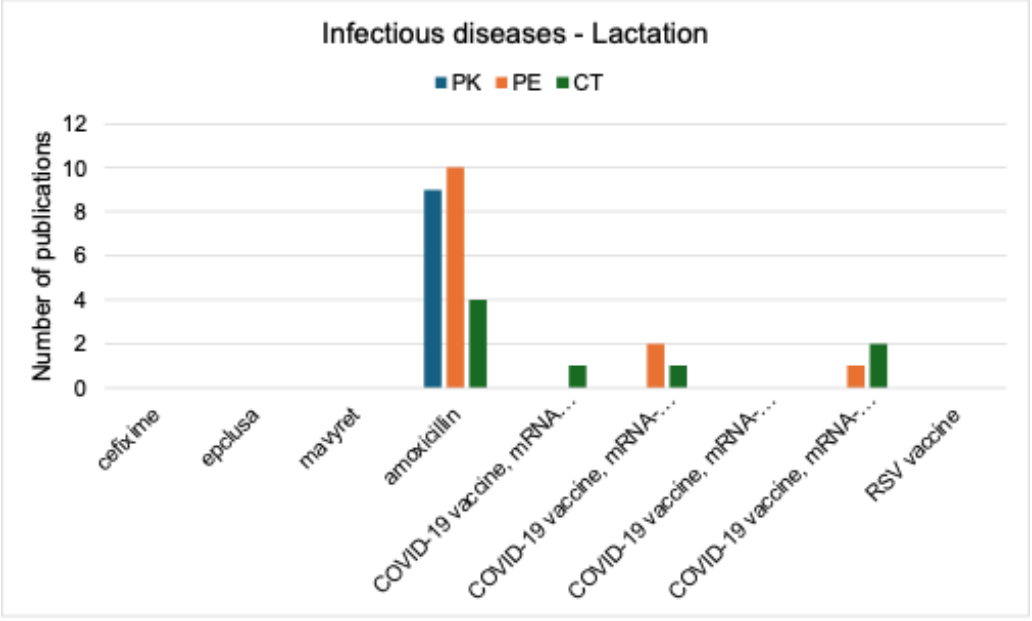
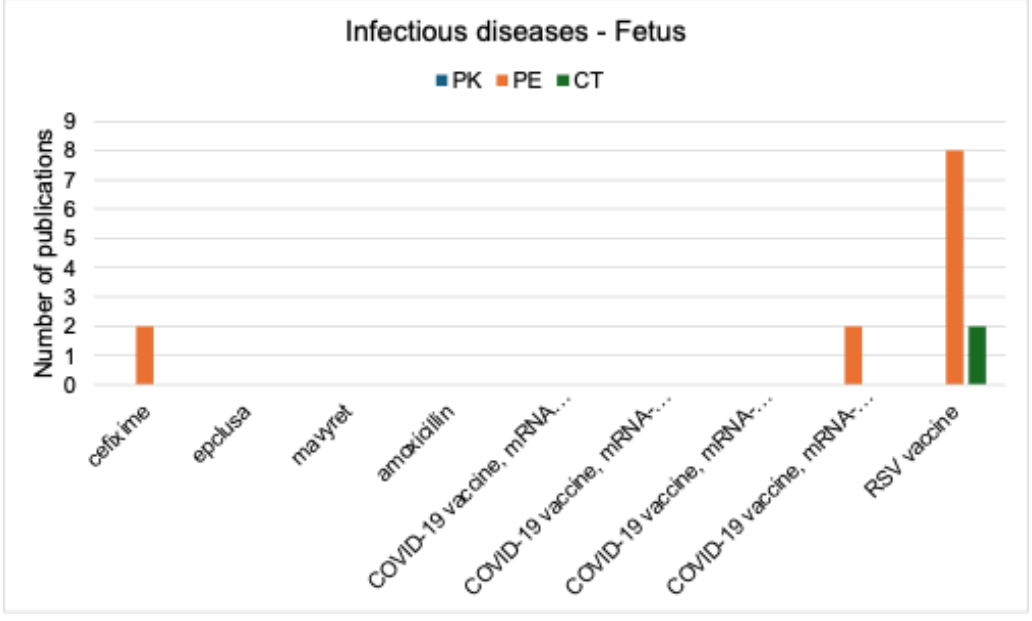


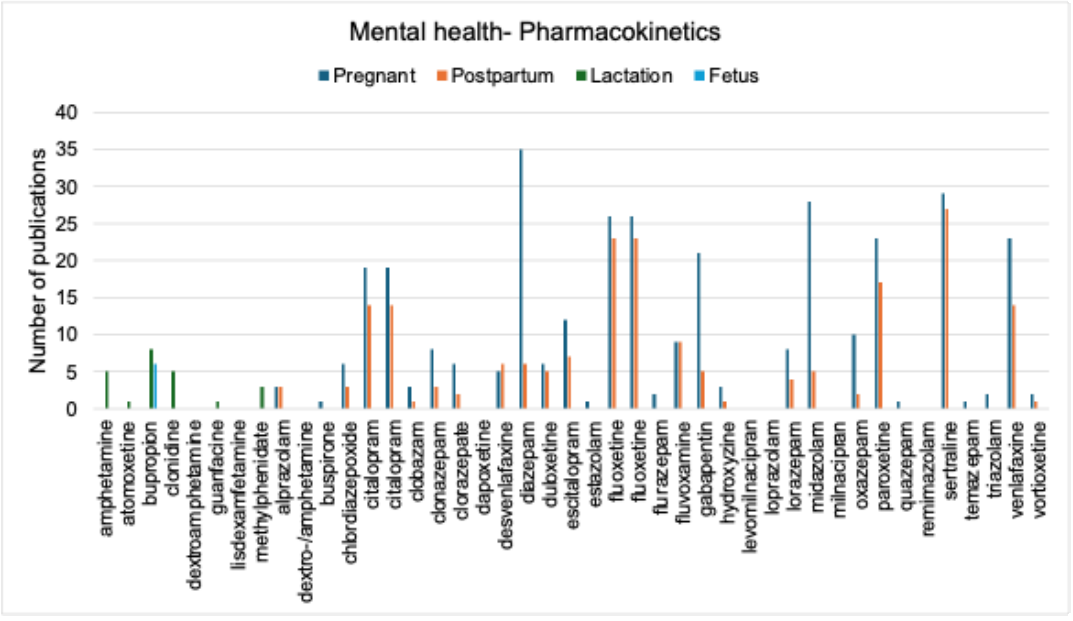
Infectious diseases nominations



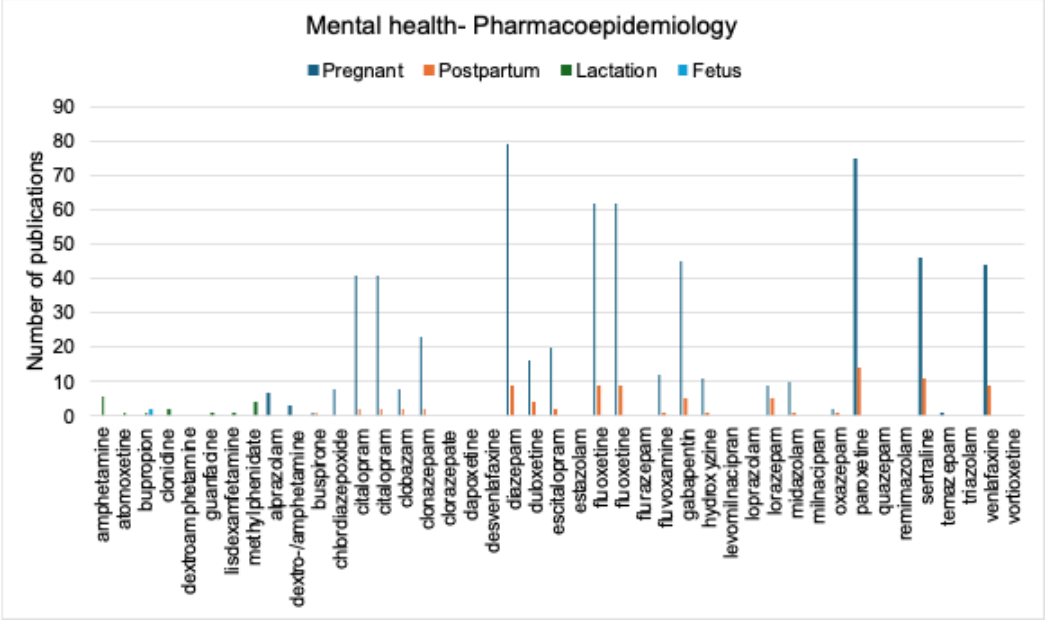
Infectious diseases nominations



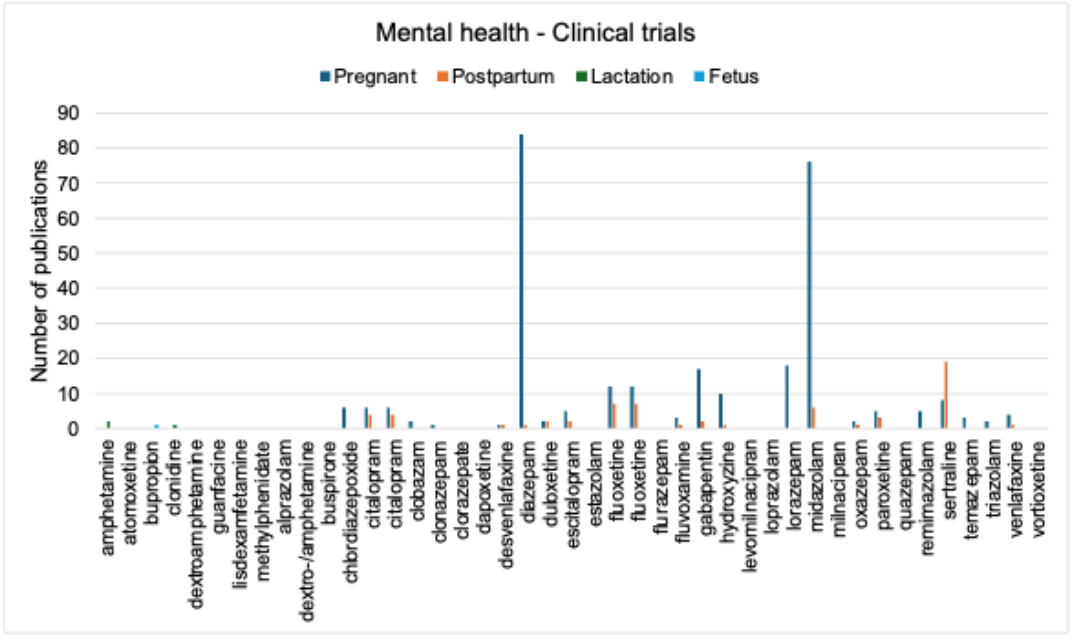
Mental health nominations



Mental health nominations



Mental health nominations



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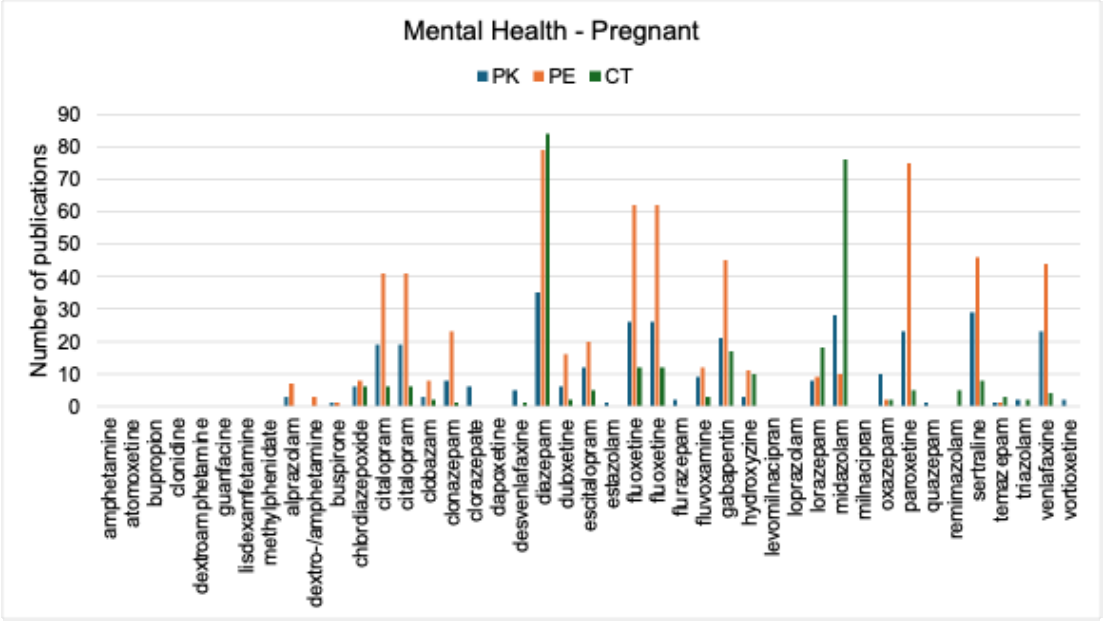
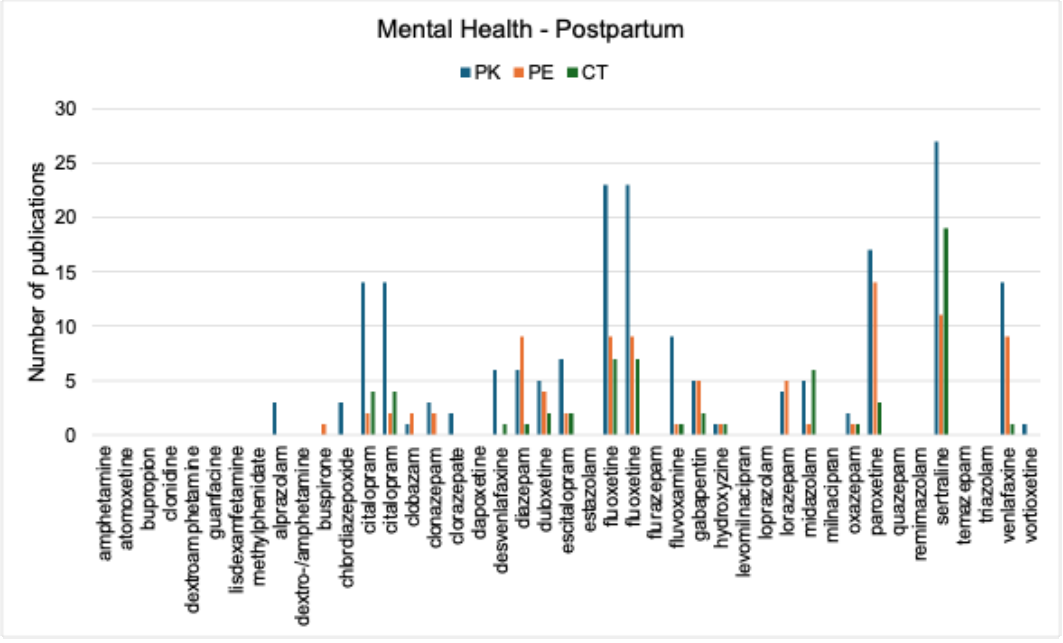
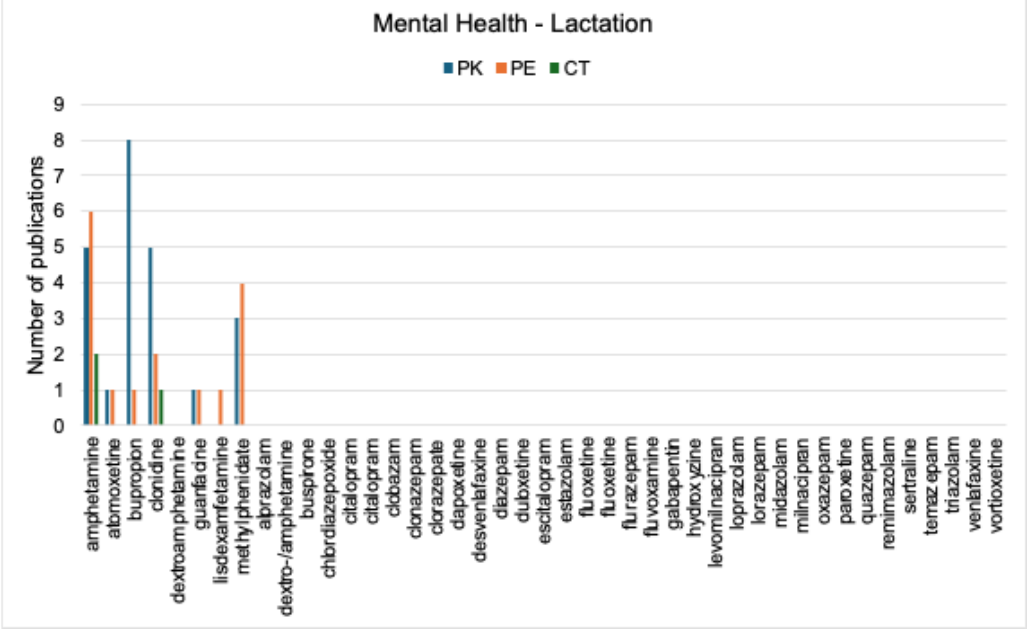


Mental health nominations



Mental health nominations



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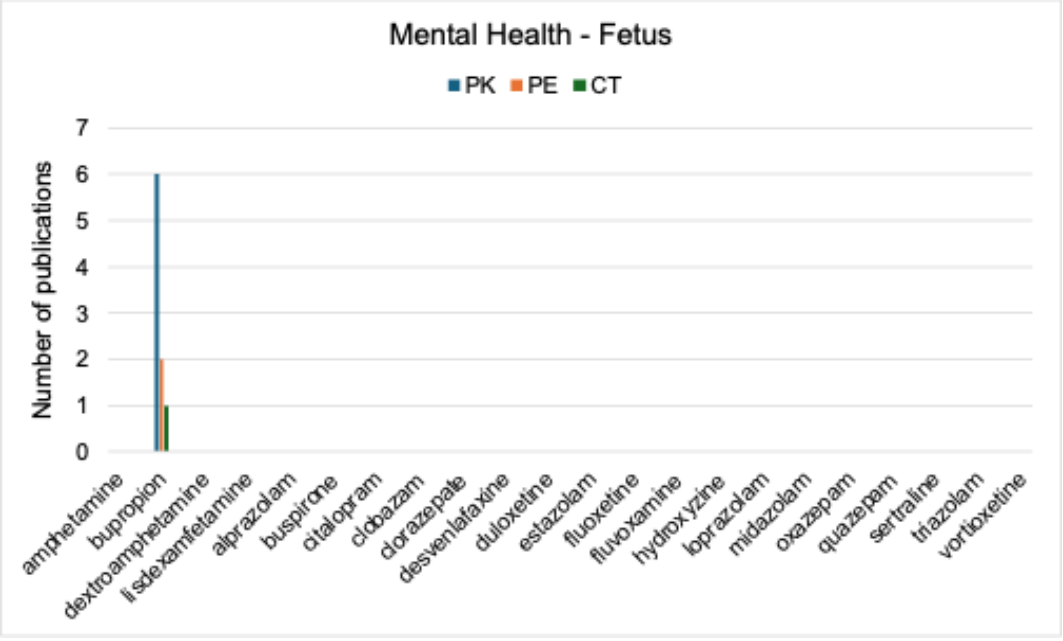
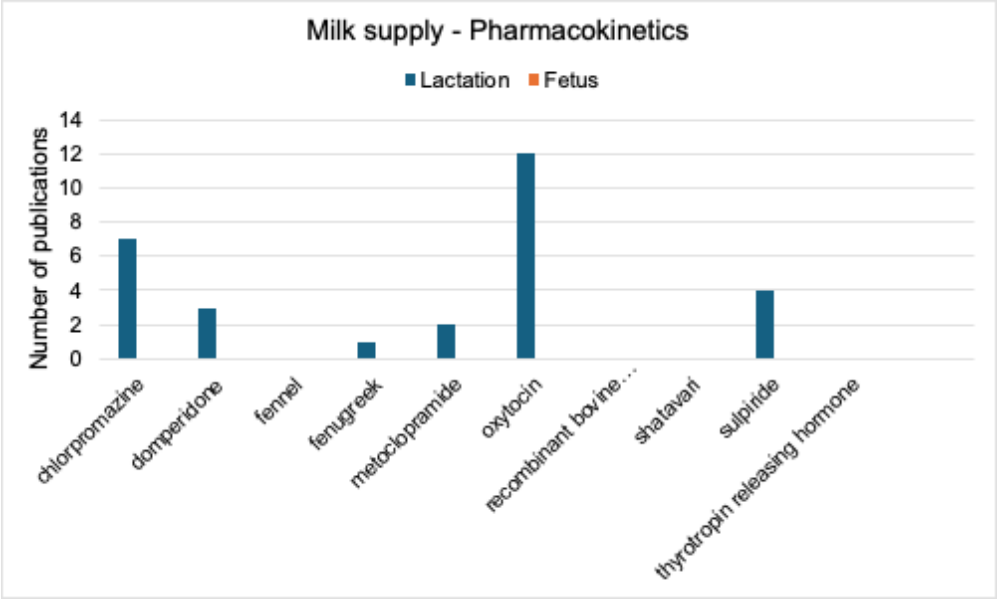
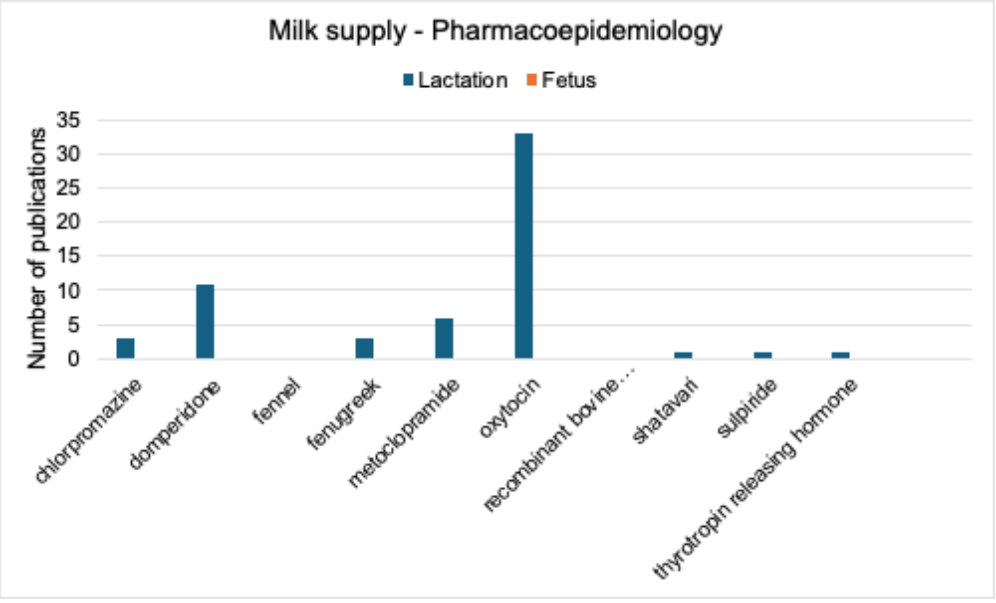


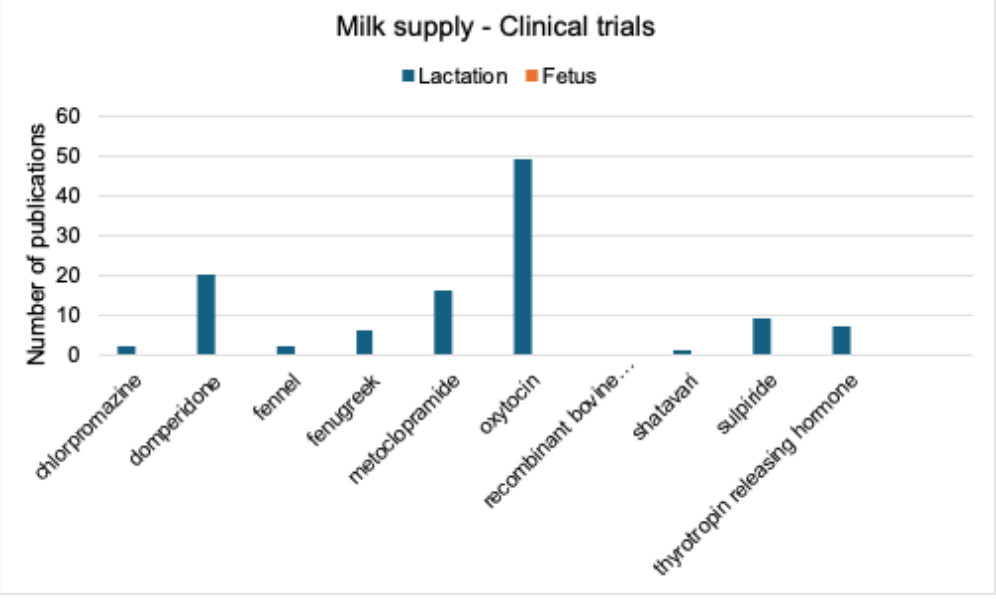
Milk supply nominations



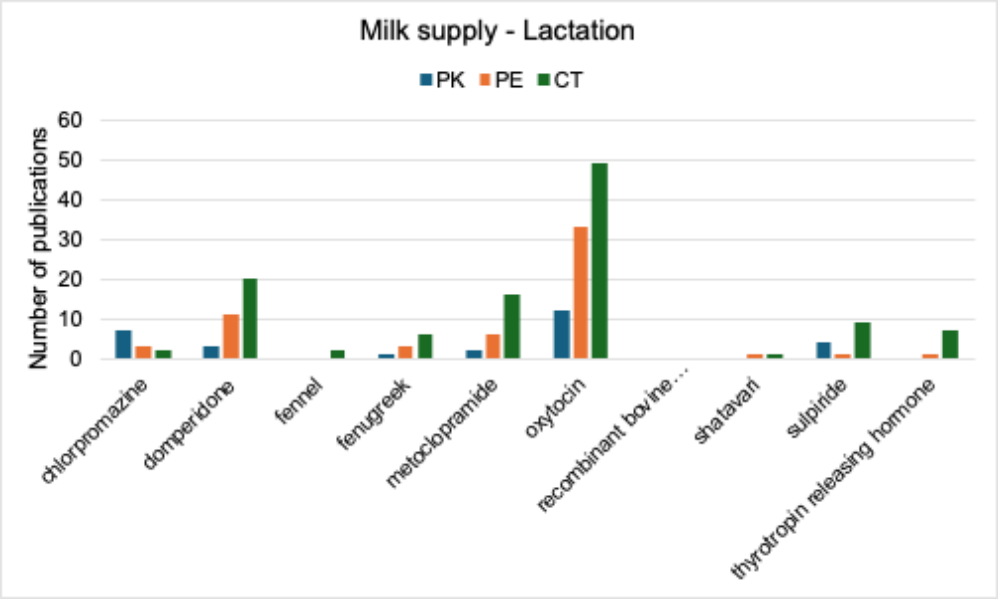
Milk supply nominations



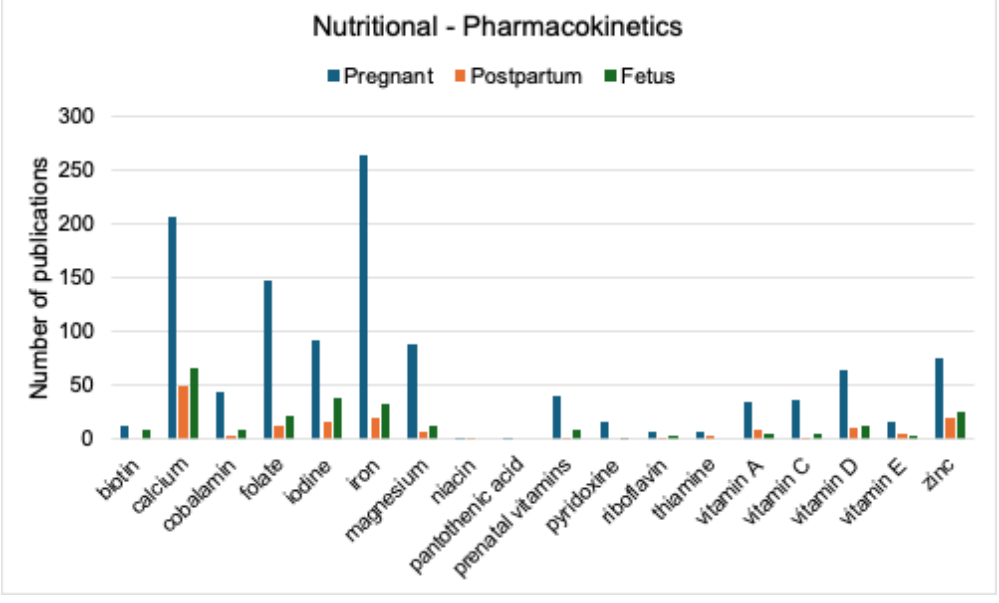
Milk supply nominations



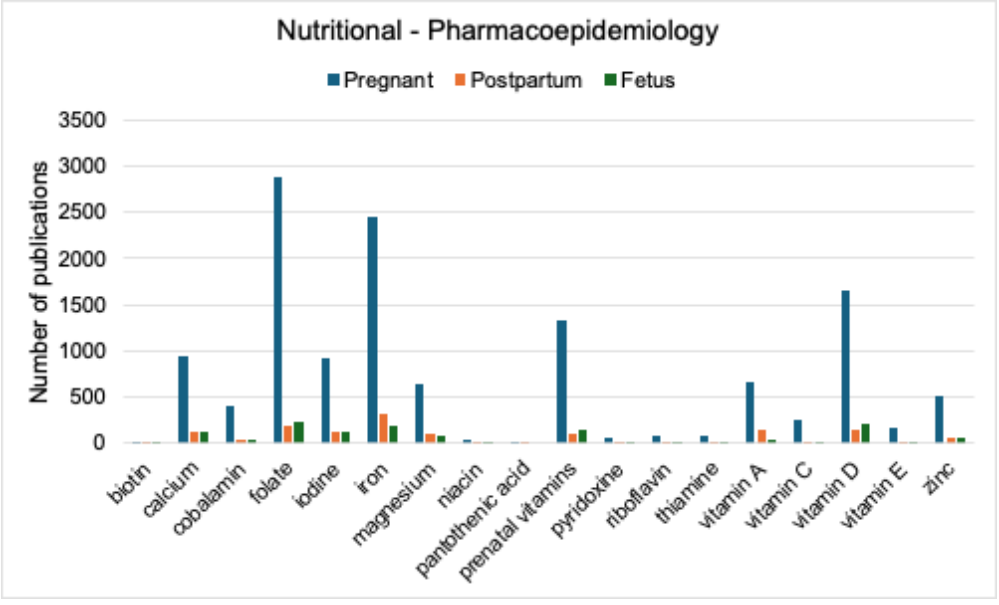
Milk supply nominations



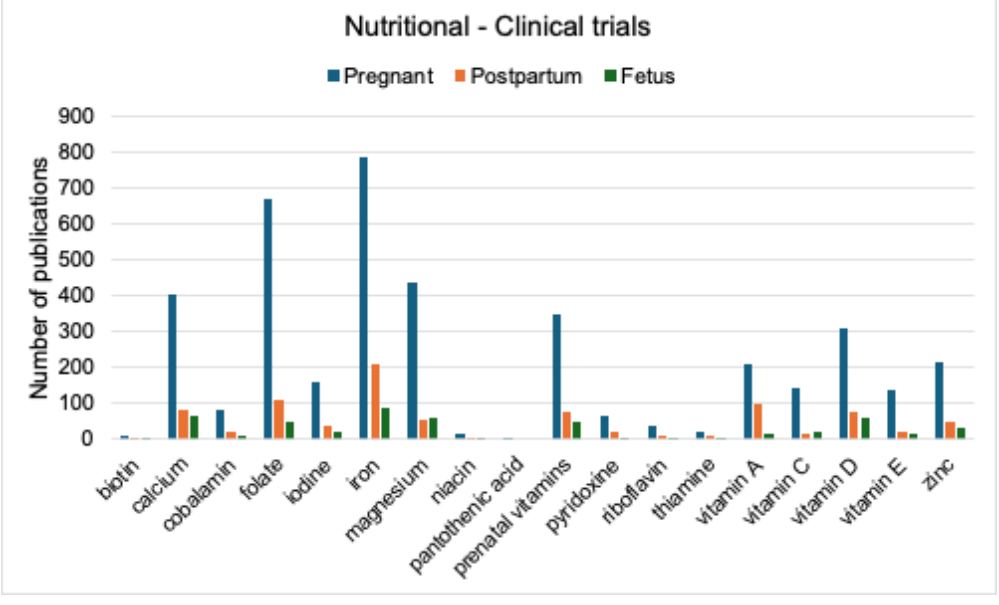
Nutritional nominations



Nutritional nominations



Nutritional nominations



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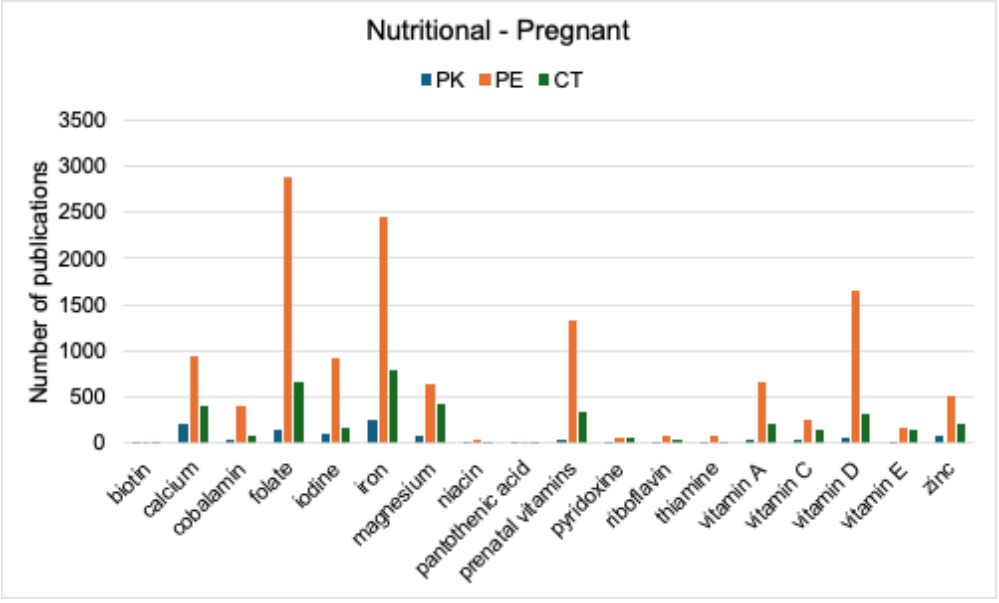

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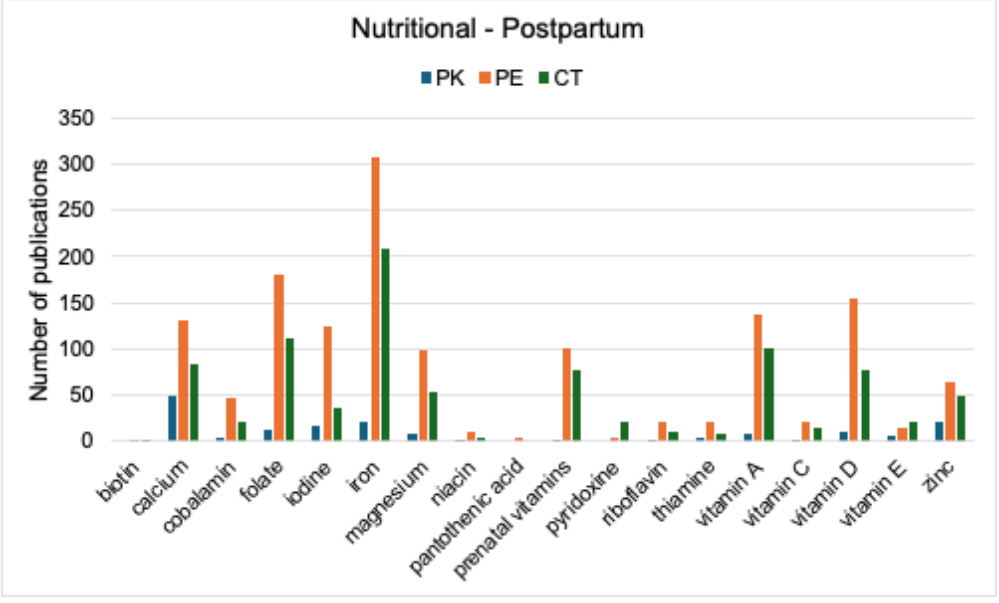

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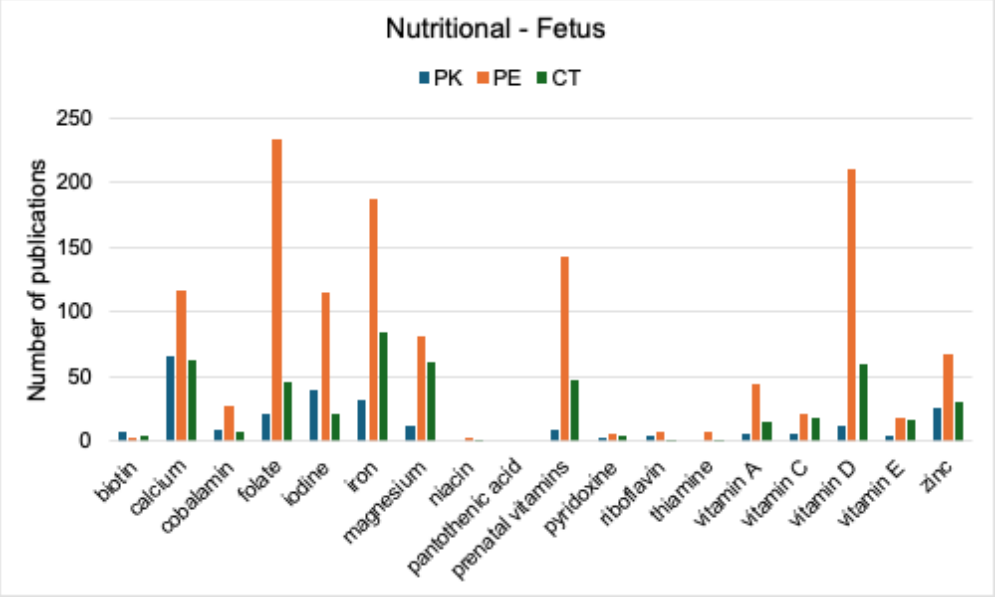
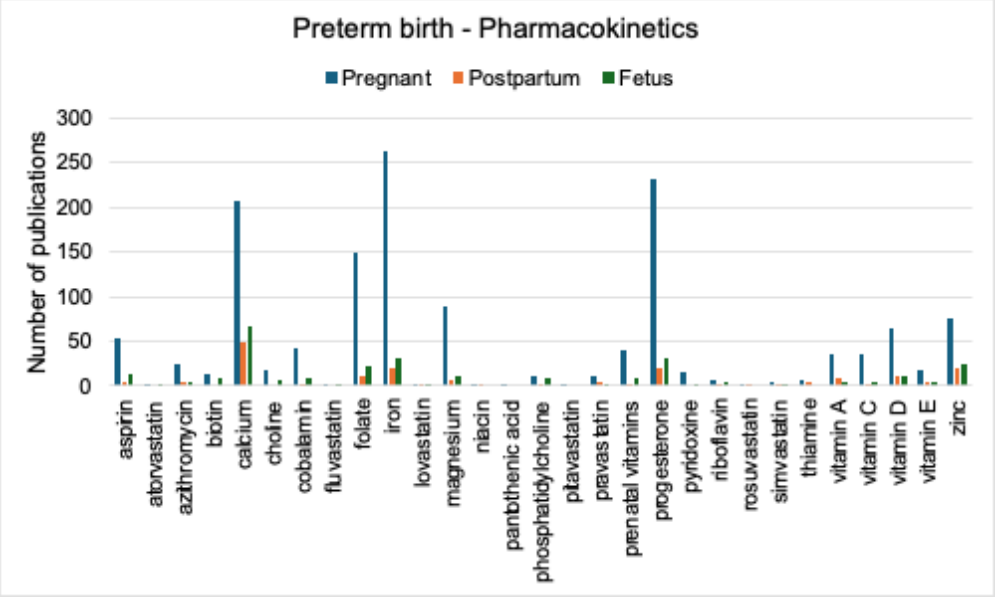
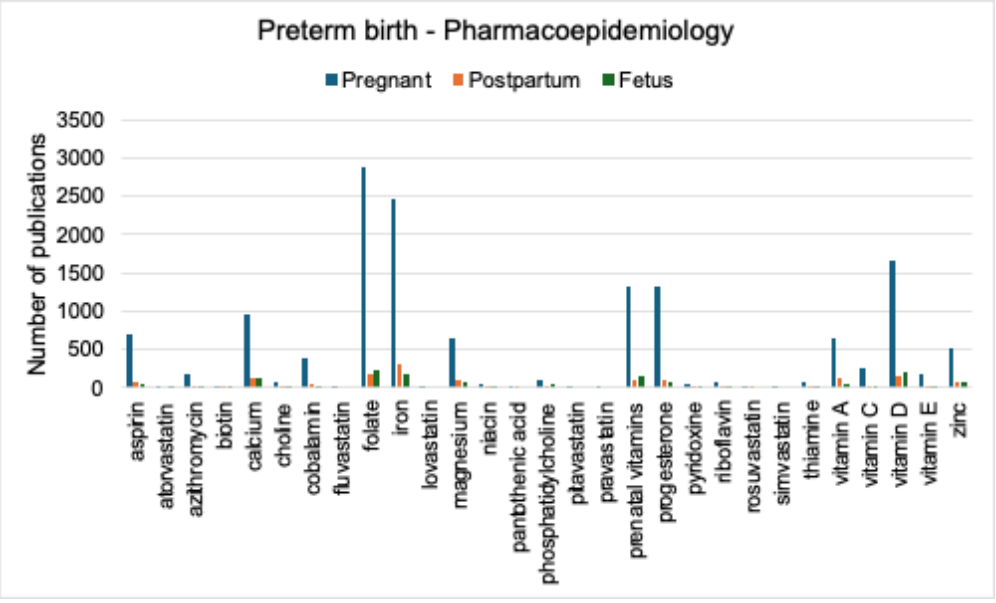


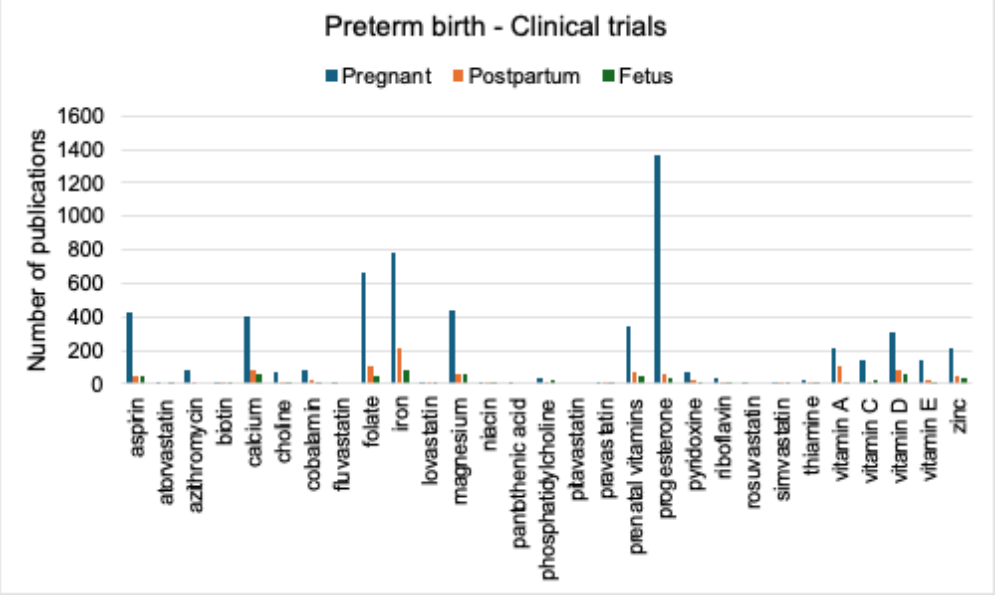
Preterm Birth nominations



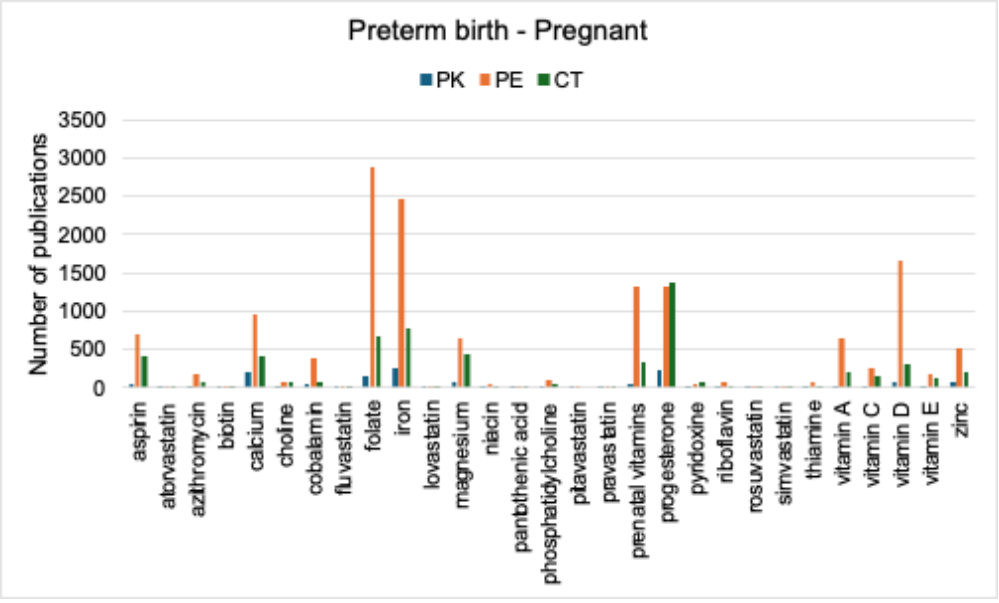
Preterm Birth nominations



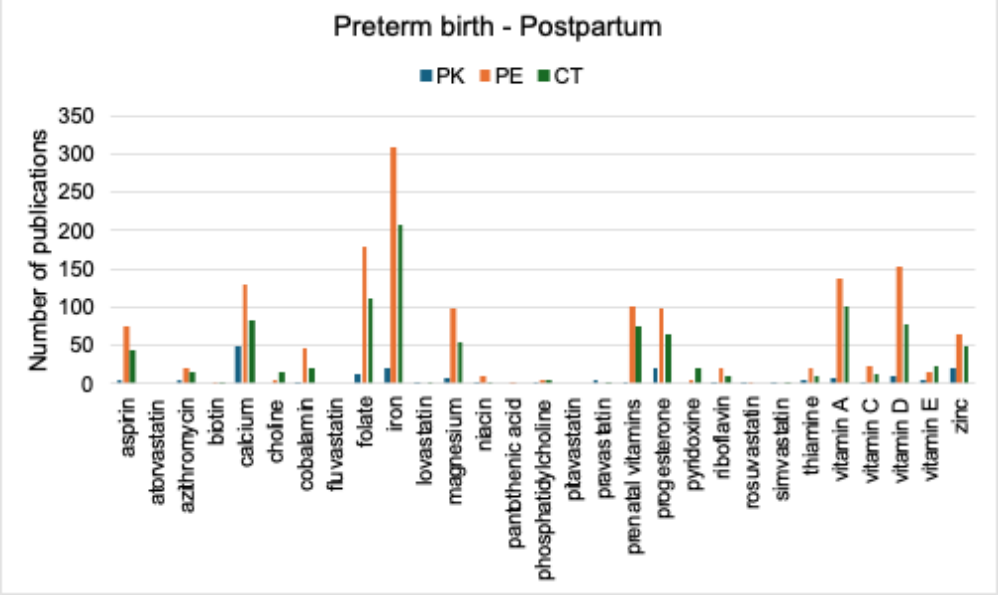
Preterm Birth nominations



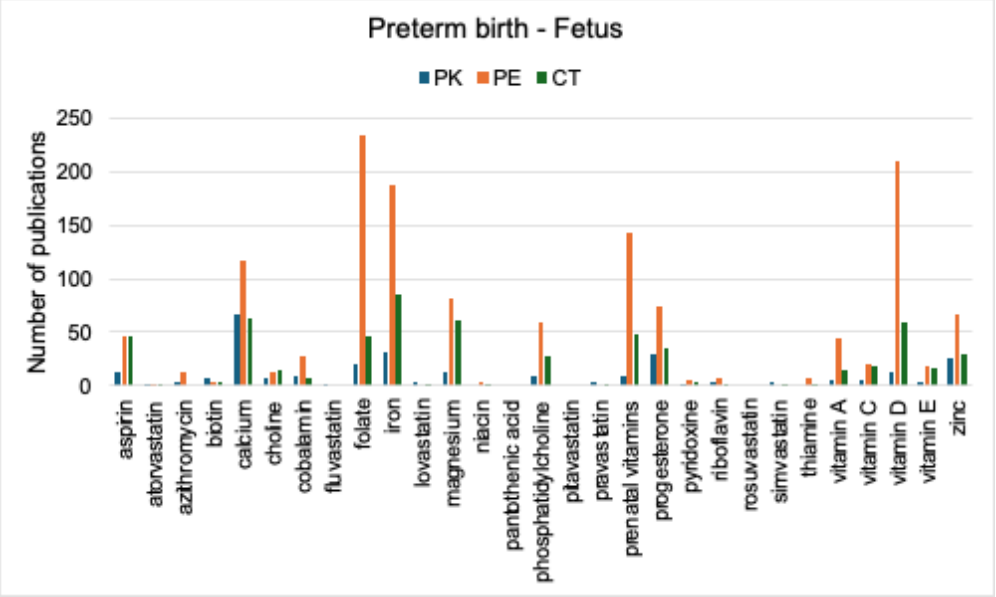
Preterm Birth nominations



Preterm Birth nominations

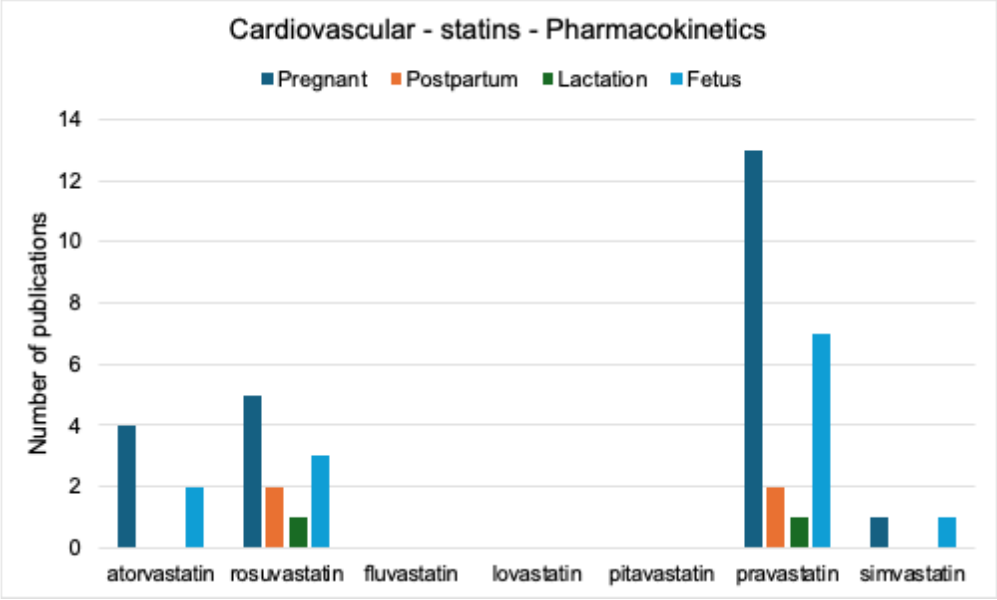


Preterm Birth nominations

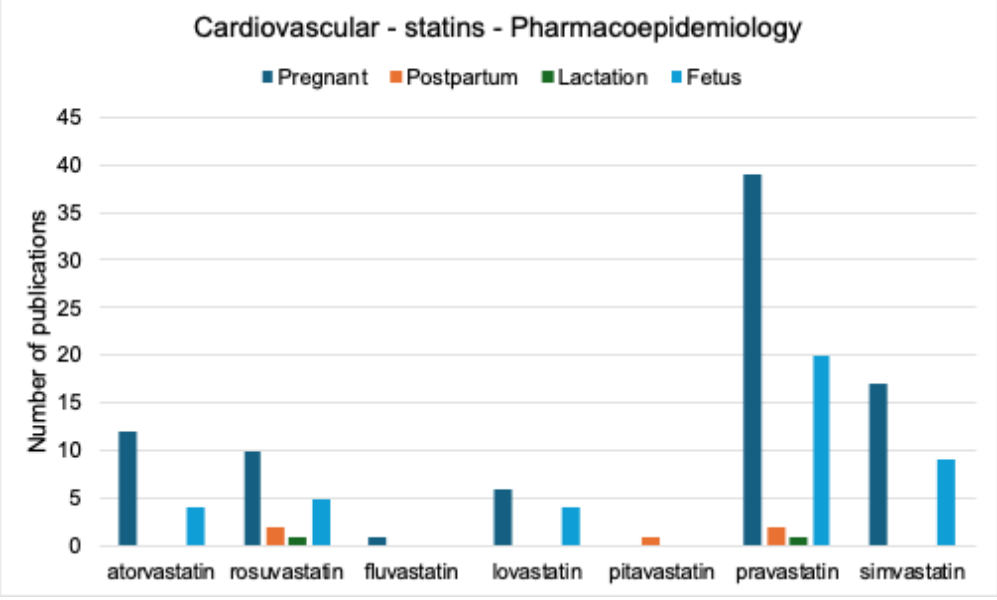


Landscape analysis for nominations discussed in 2025

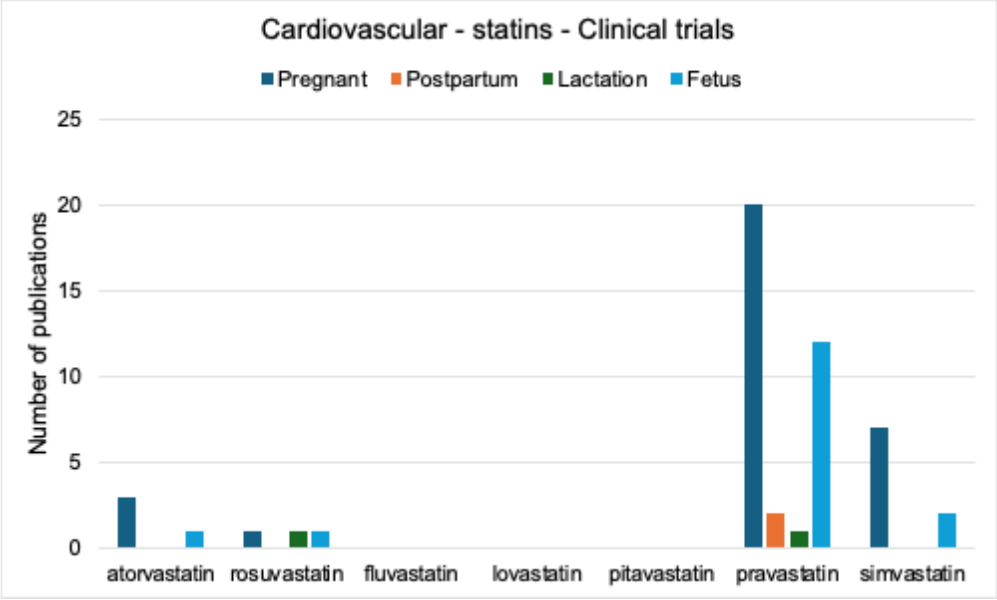
Cardiovascular nominations



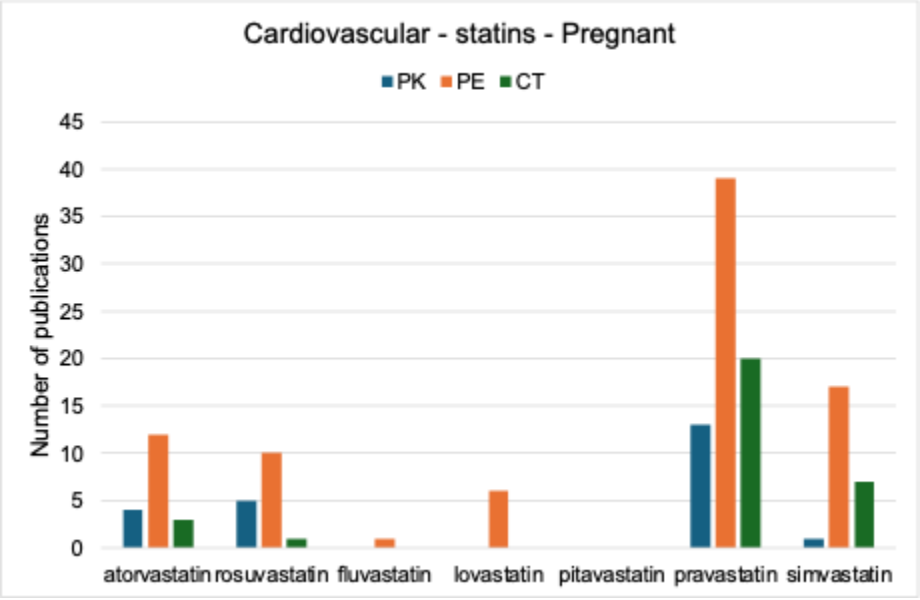
Cardiovascular nominations



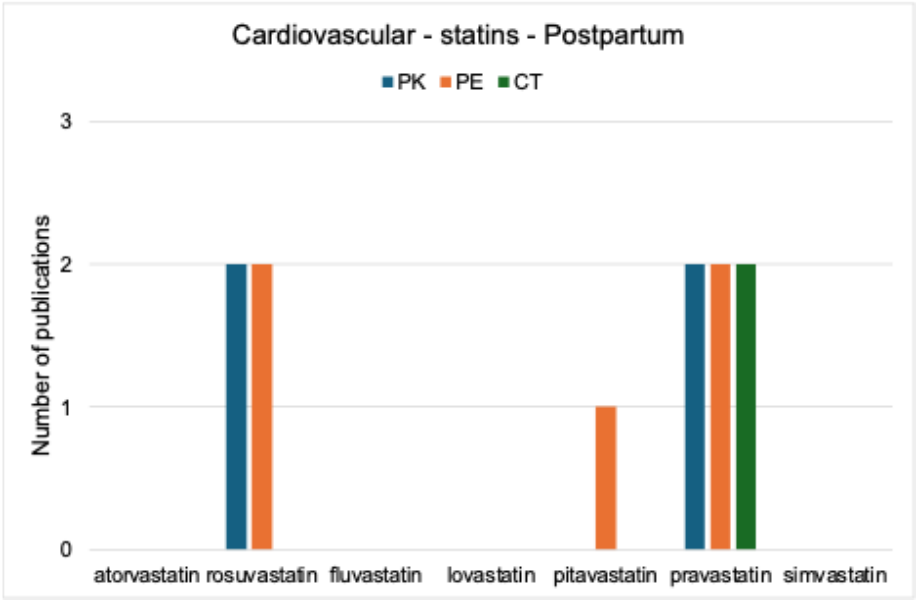
Cardiovascular nominations



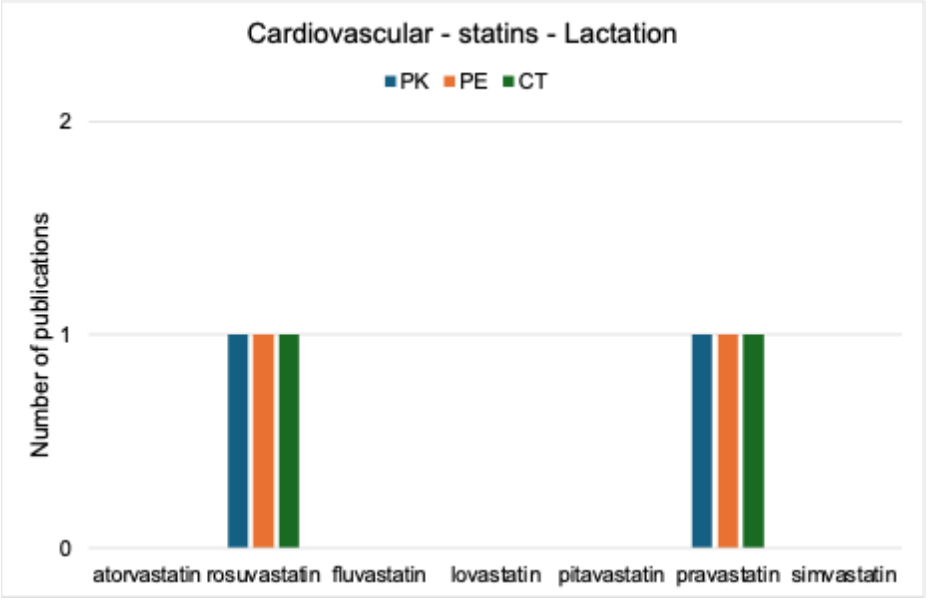
Cardiovascular nominations



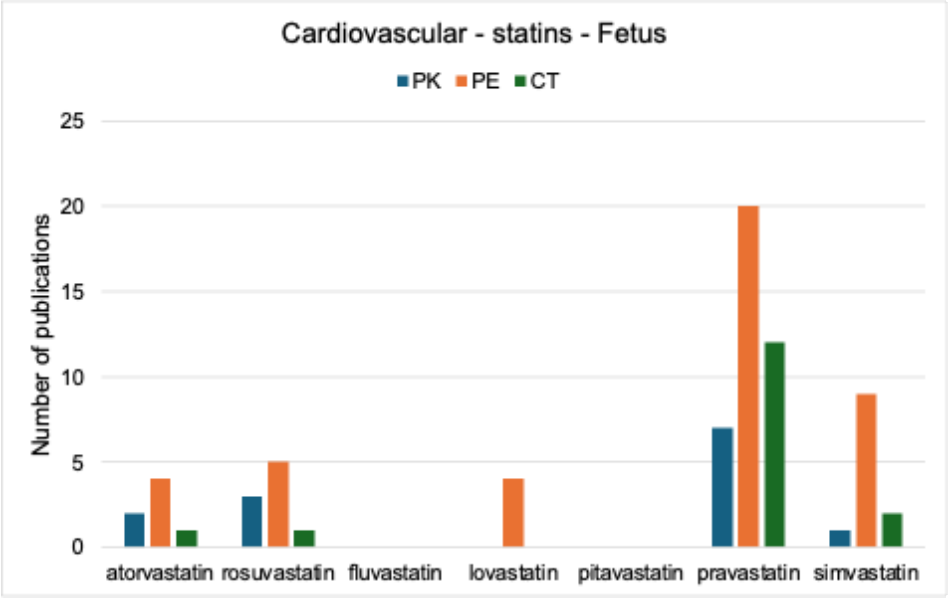
Cardiovascular nominations



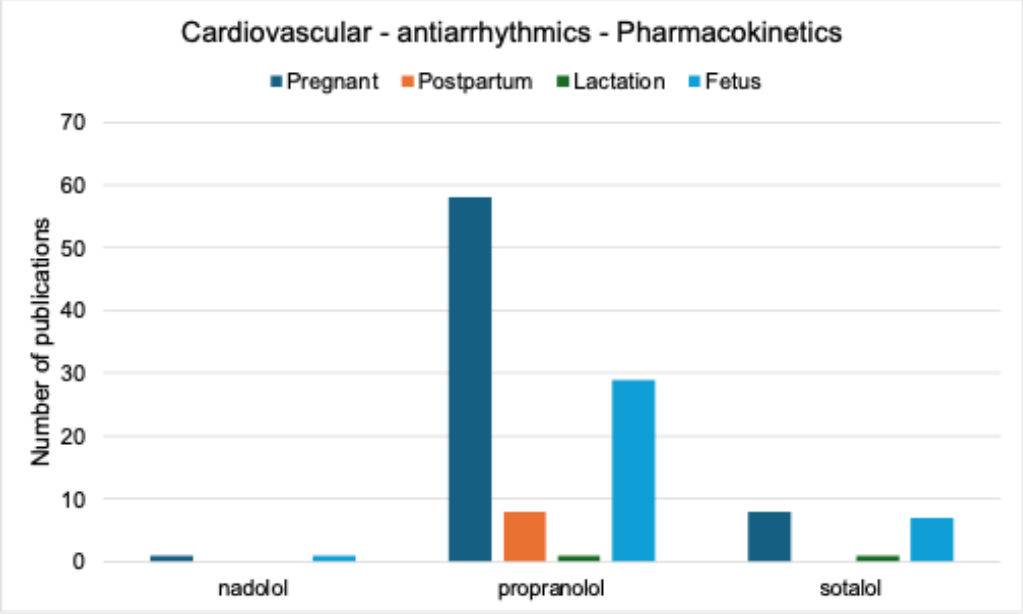
Cardiovascular nominations



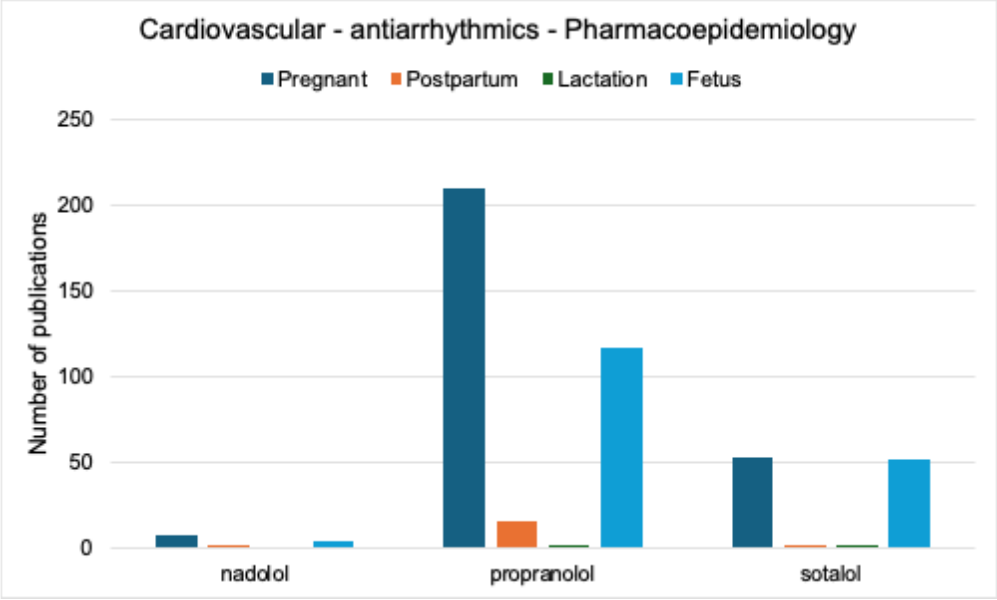
Cardiovascular nominations



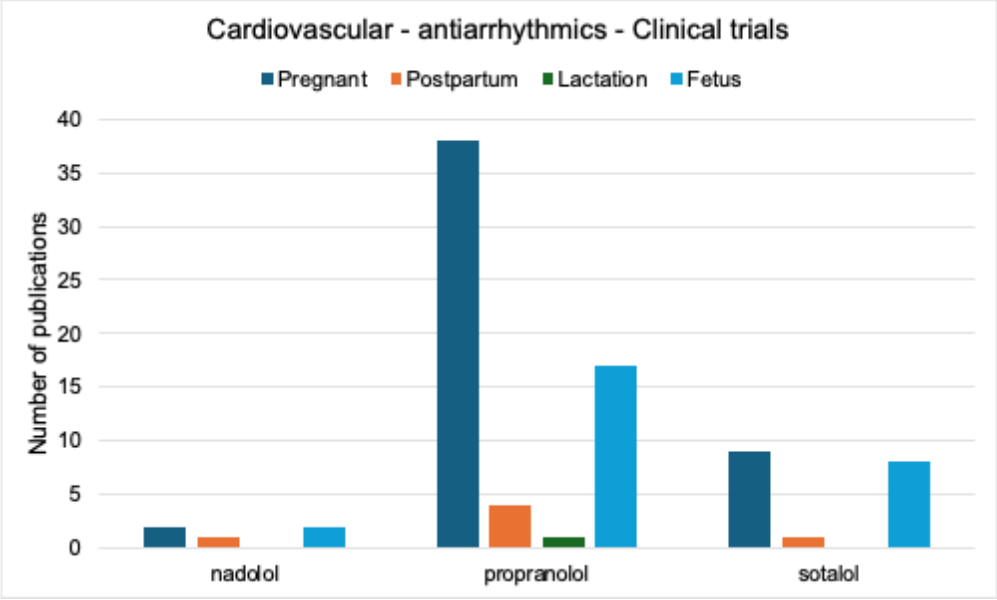
Cardiovascular nominations



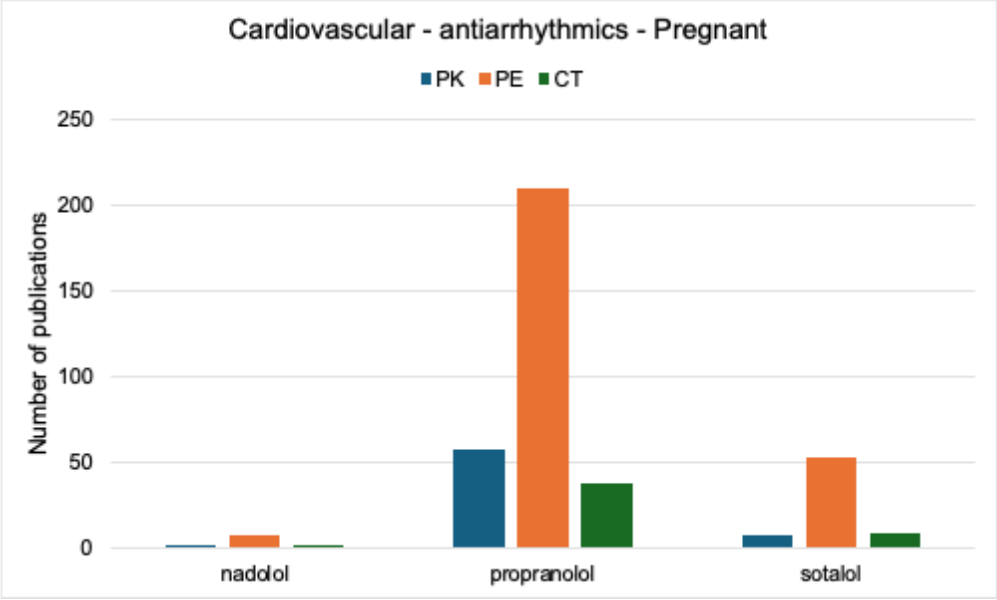
Cardiovascular nominations



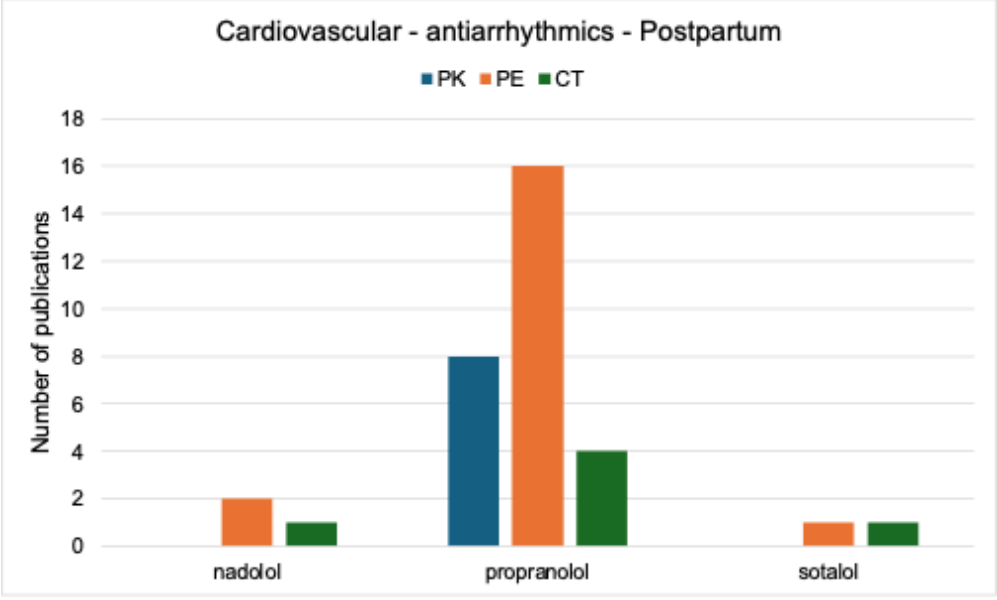
Cardiovascular nominations



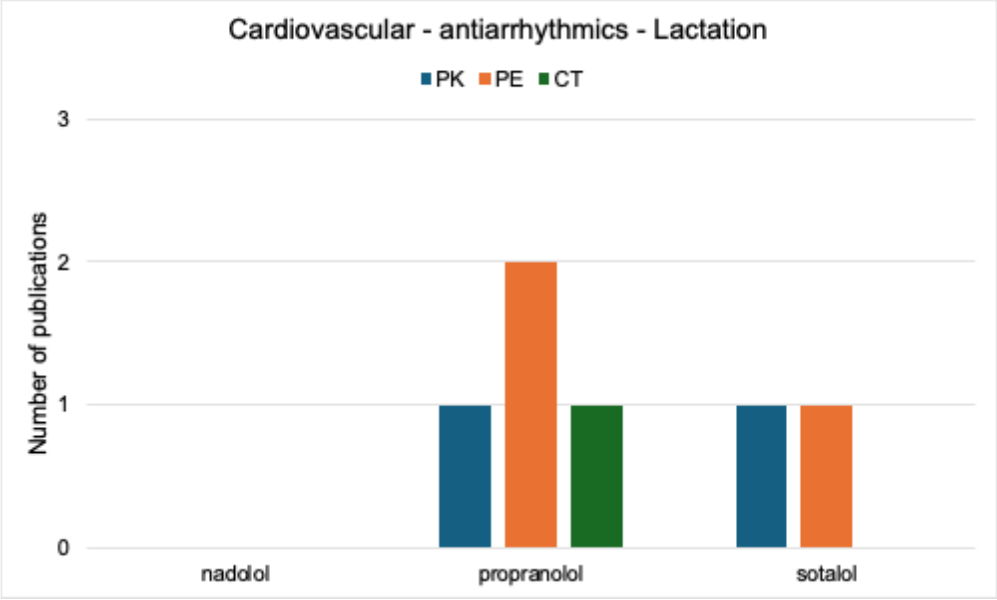
Cardiovascular nominations



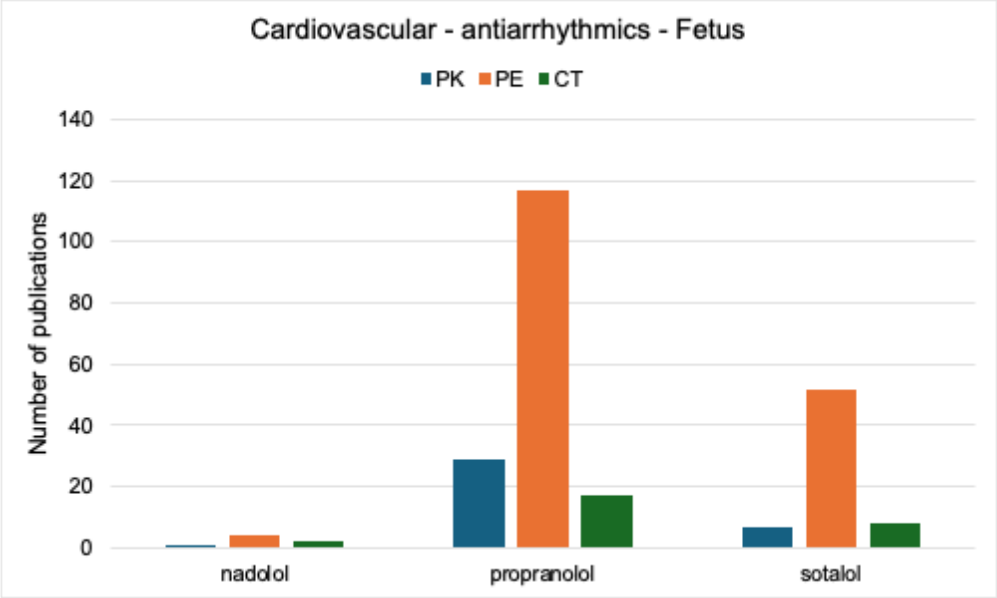
Cardiovascular nominations



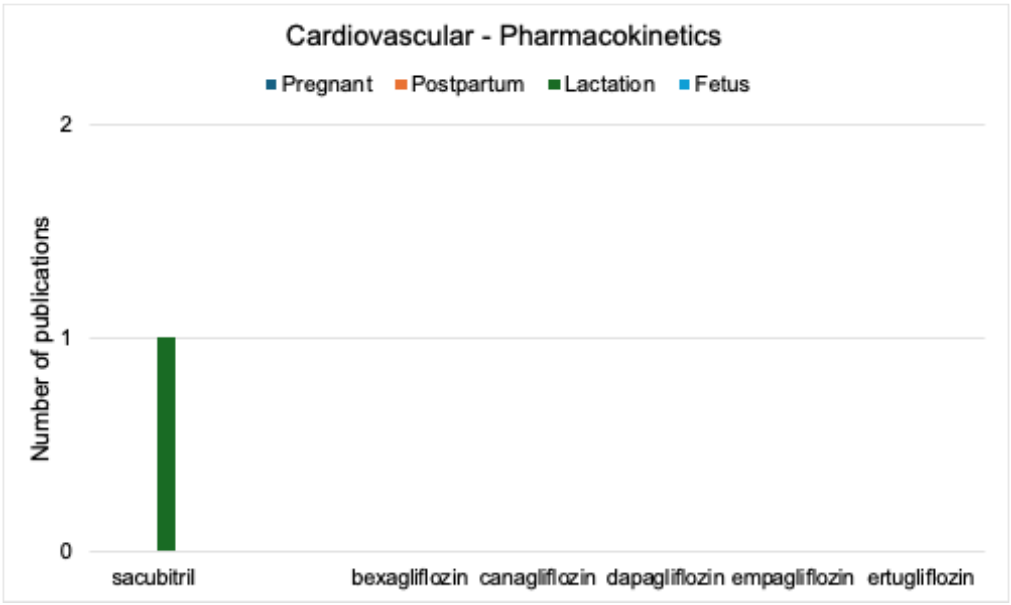
Cardiovascular nominations



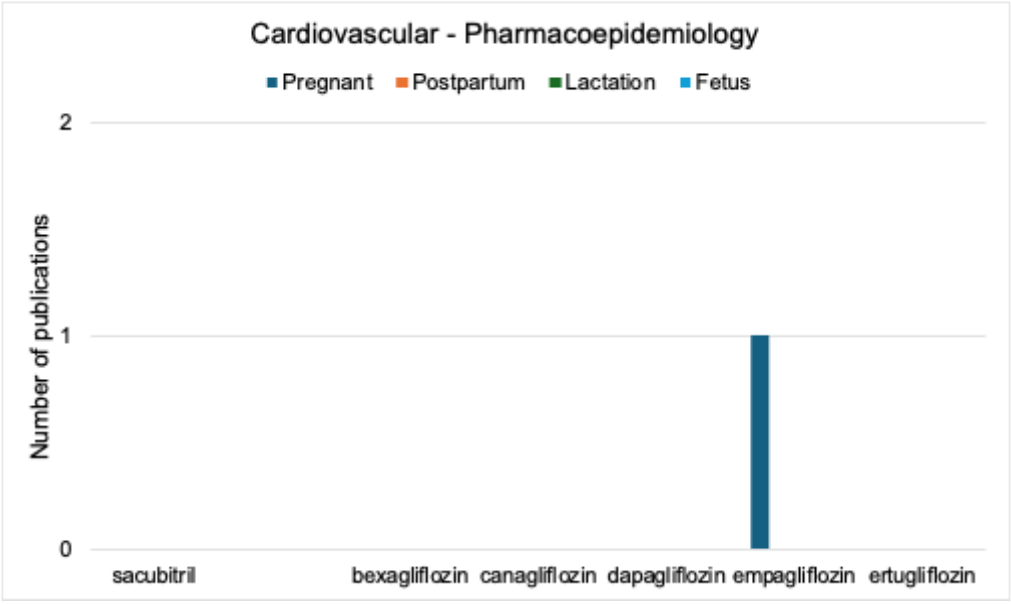
Cardiovascular nominations



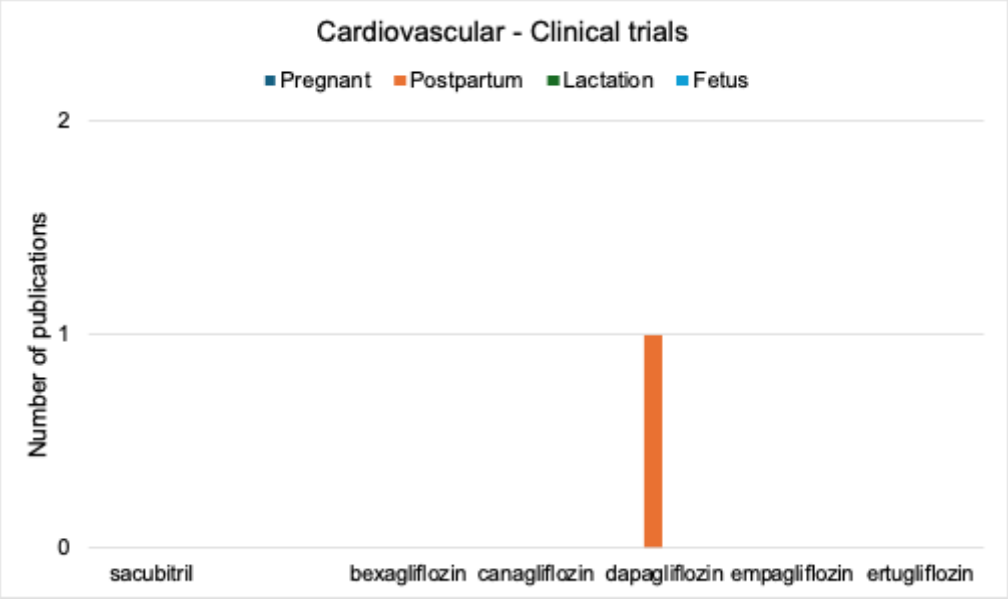
Cardiovascular additional nominations



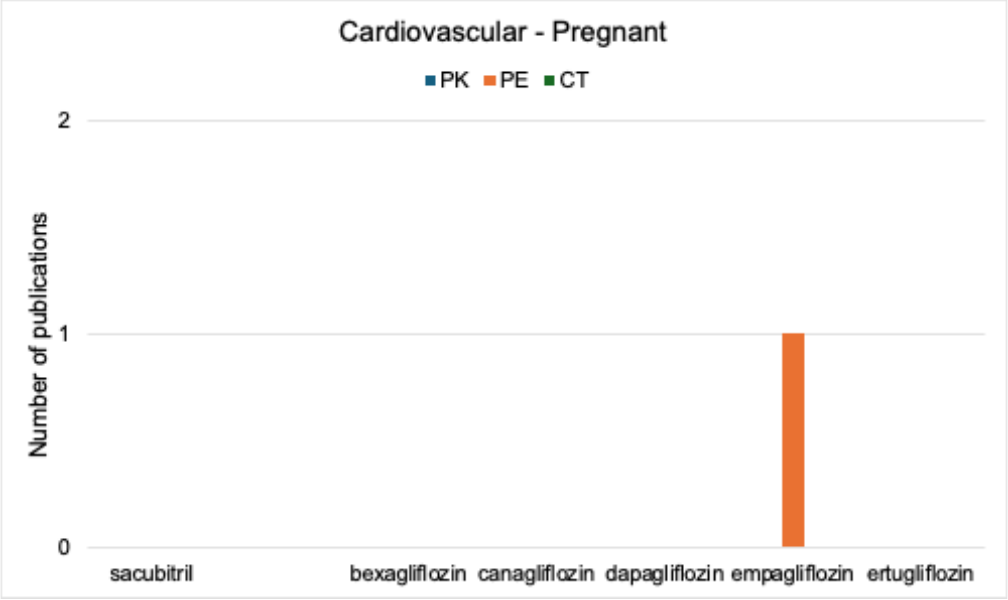
Cardiovascular additional nominations



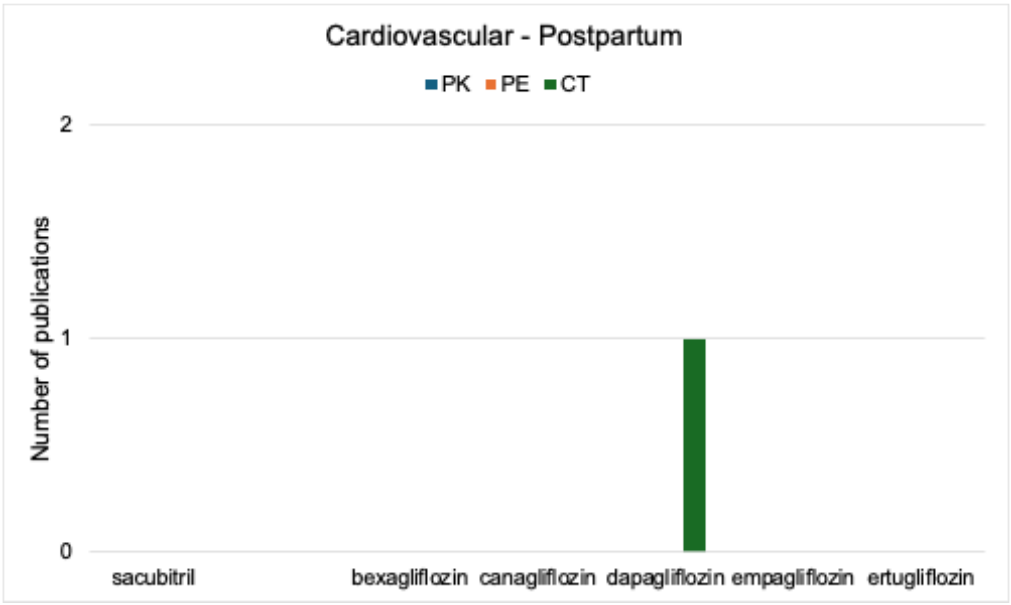
Cardiovascular additional nominations



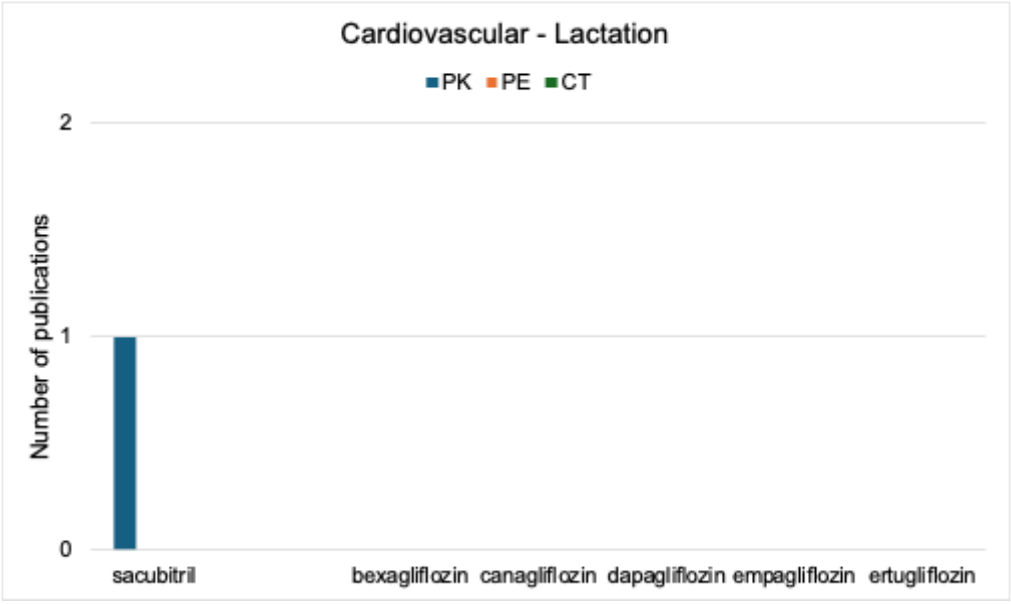
Cardiovascular additional nominations



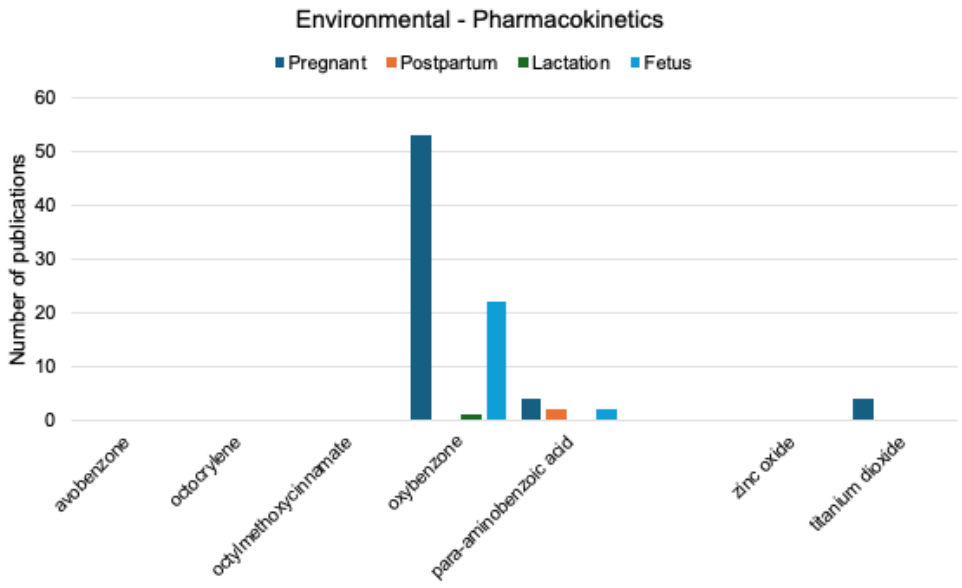
Cardiovascular additional nominations



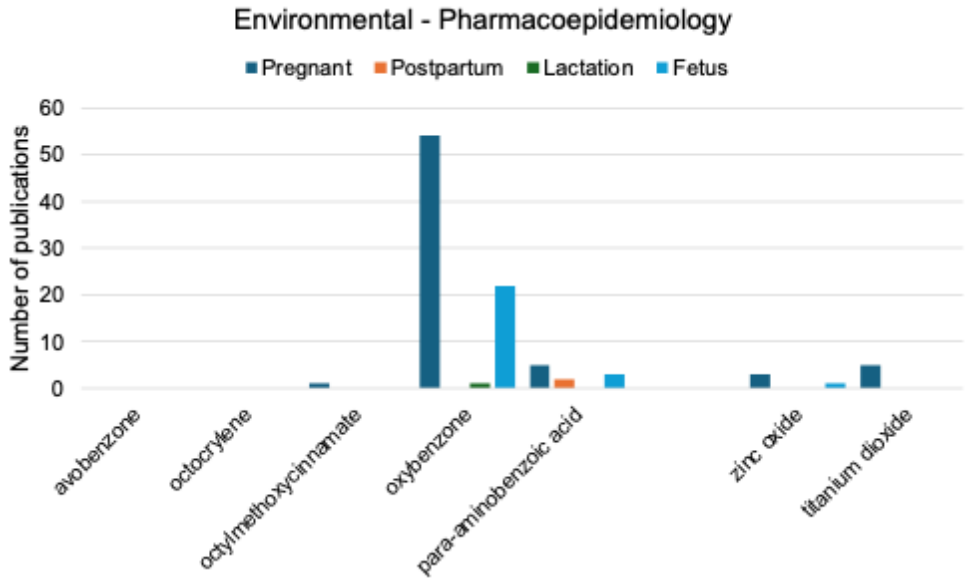
Cardiovascular additional nominations



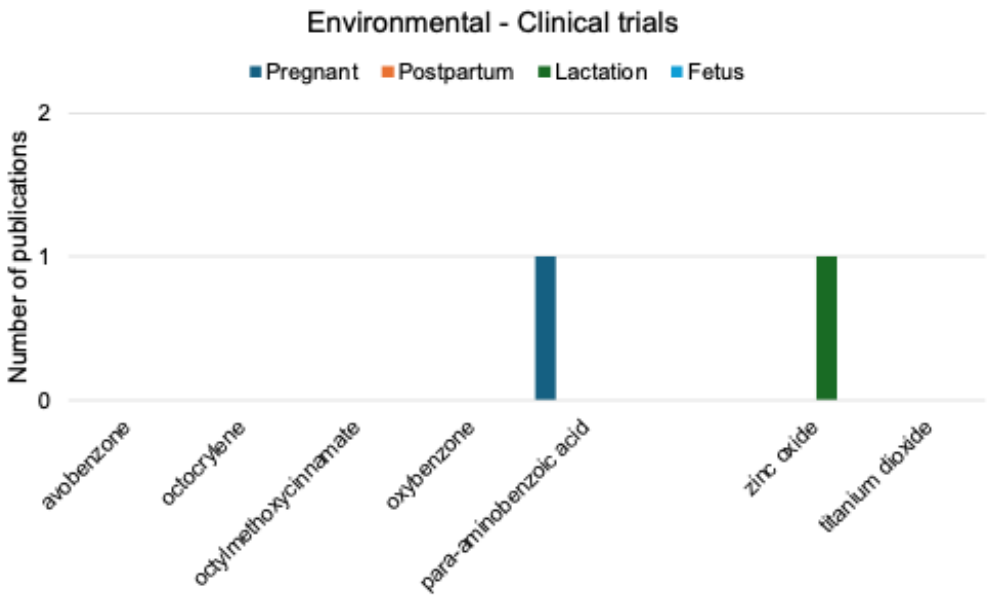
Environmental nominations



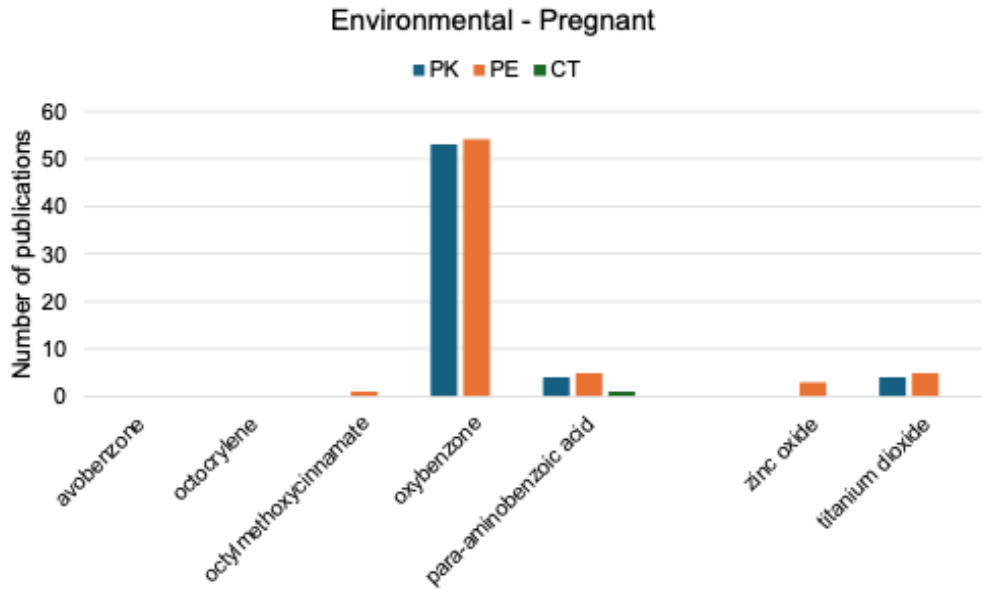
Environmental nominations



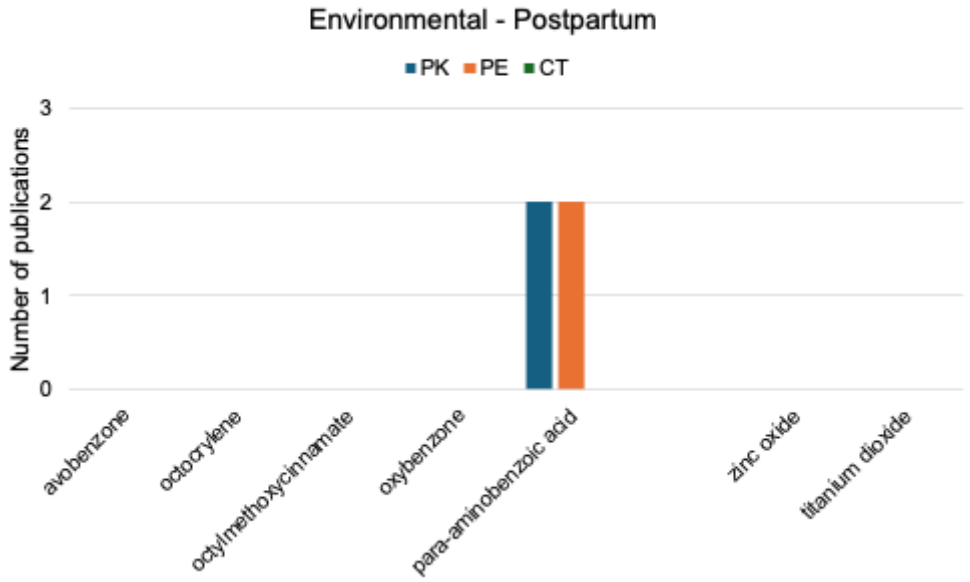
Environmental nominations



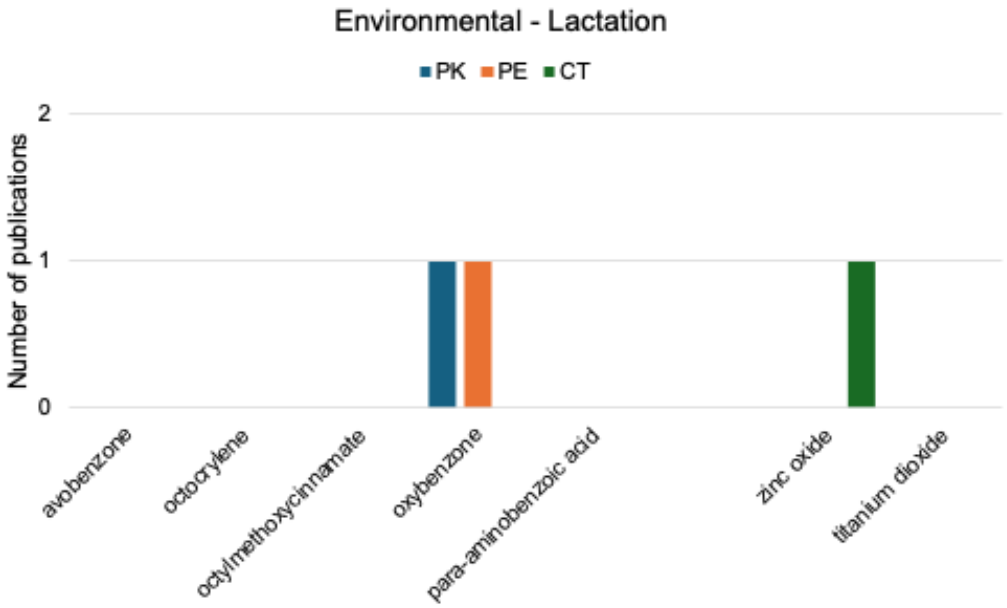
Environmental nominations



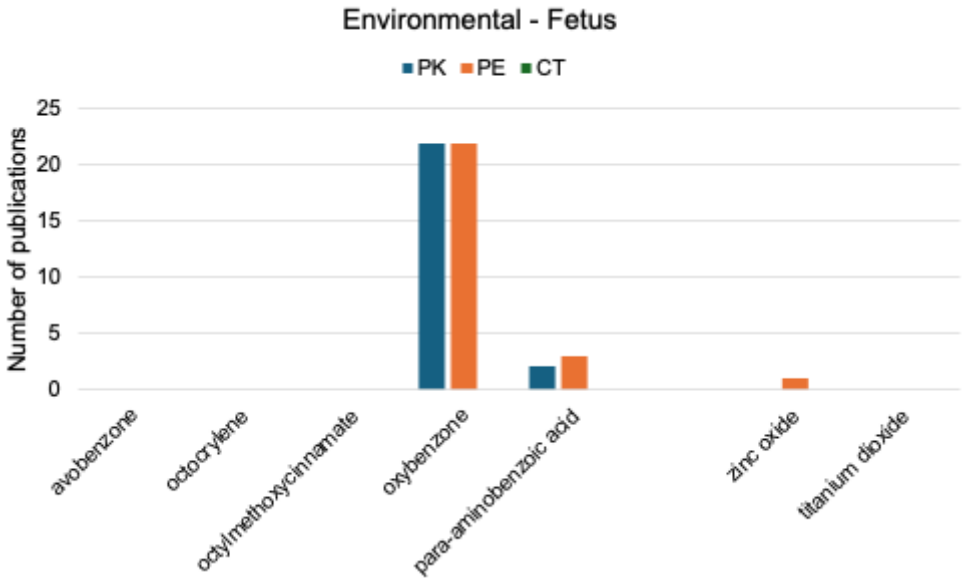
Environmental nominations



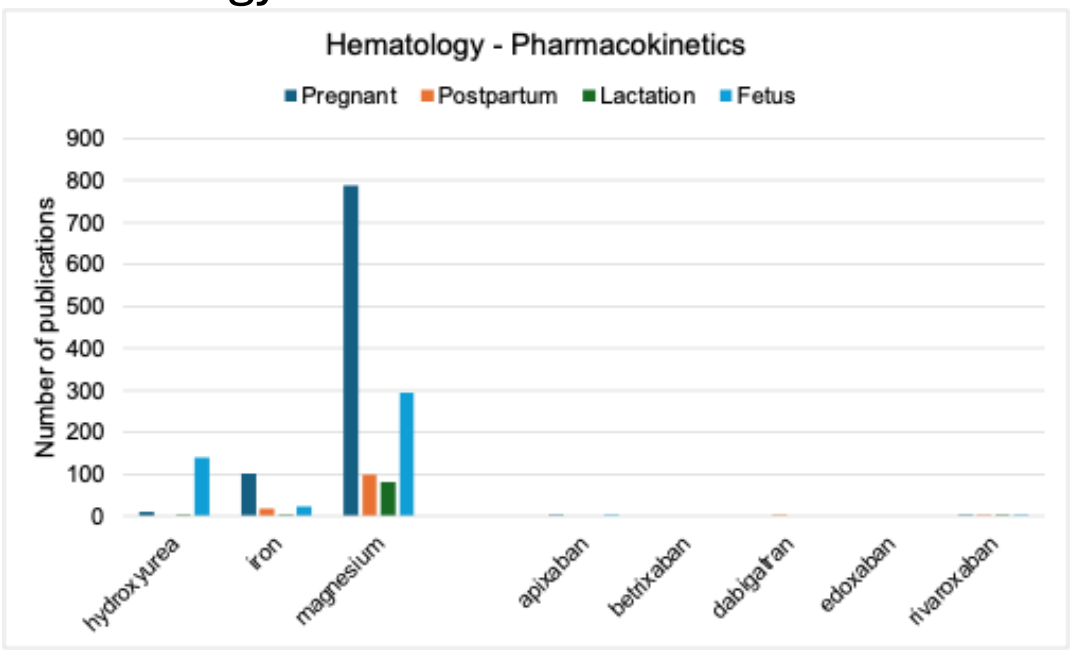
Environmental nominations



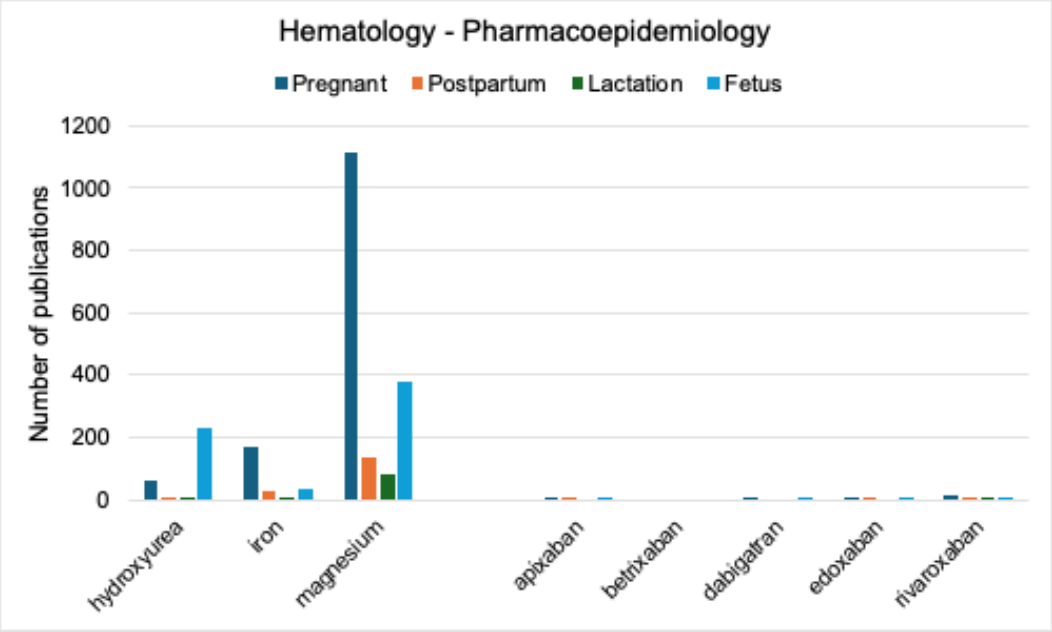
Environmental nominations



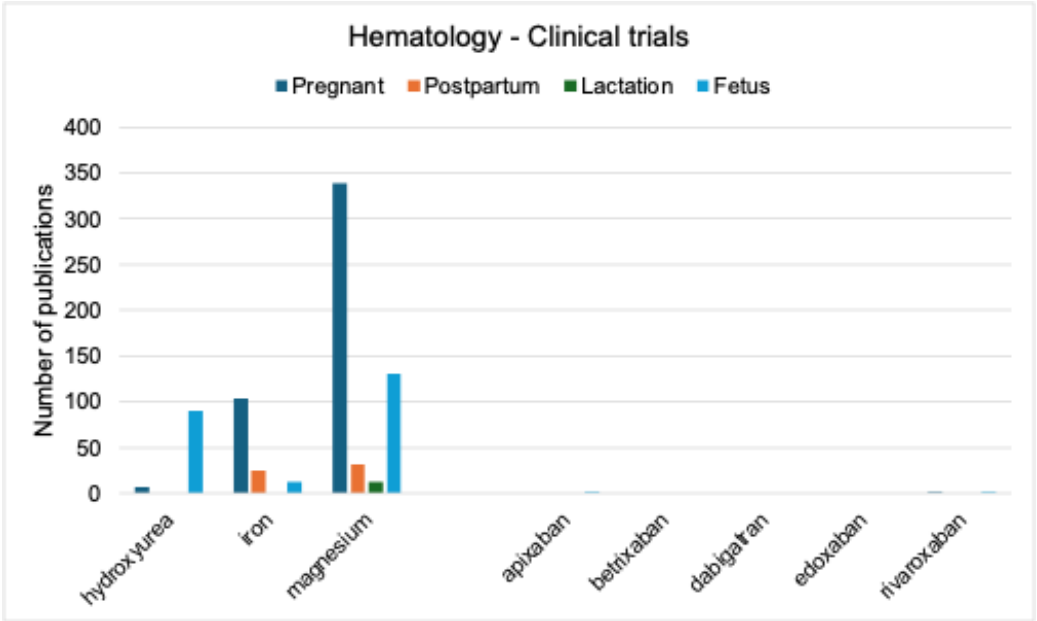
Hematology nominations



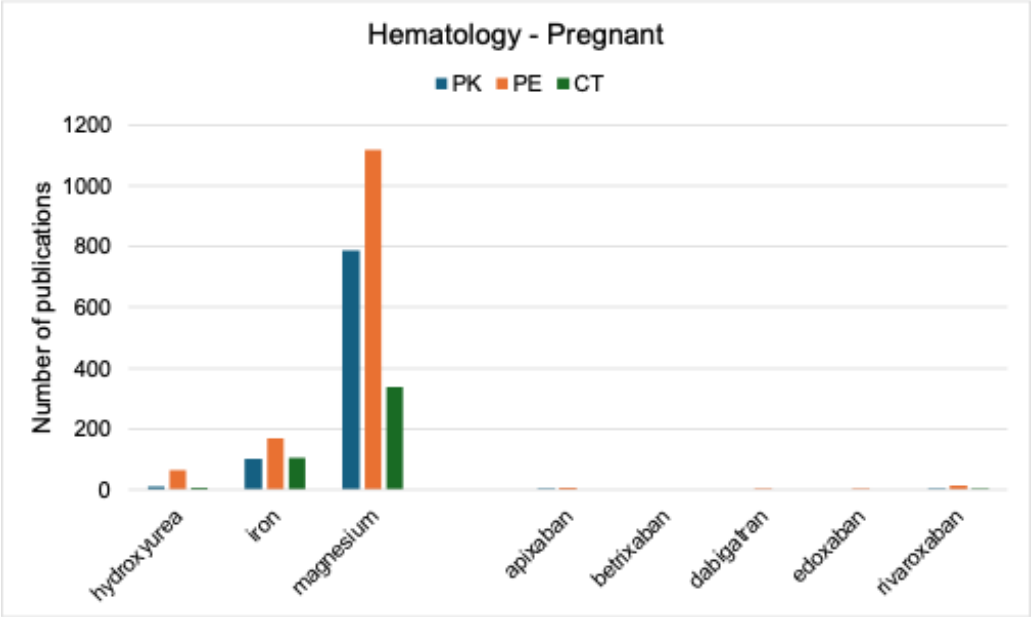
Hematology nominations



Hematology nominations



Hematology nominations



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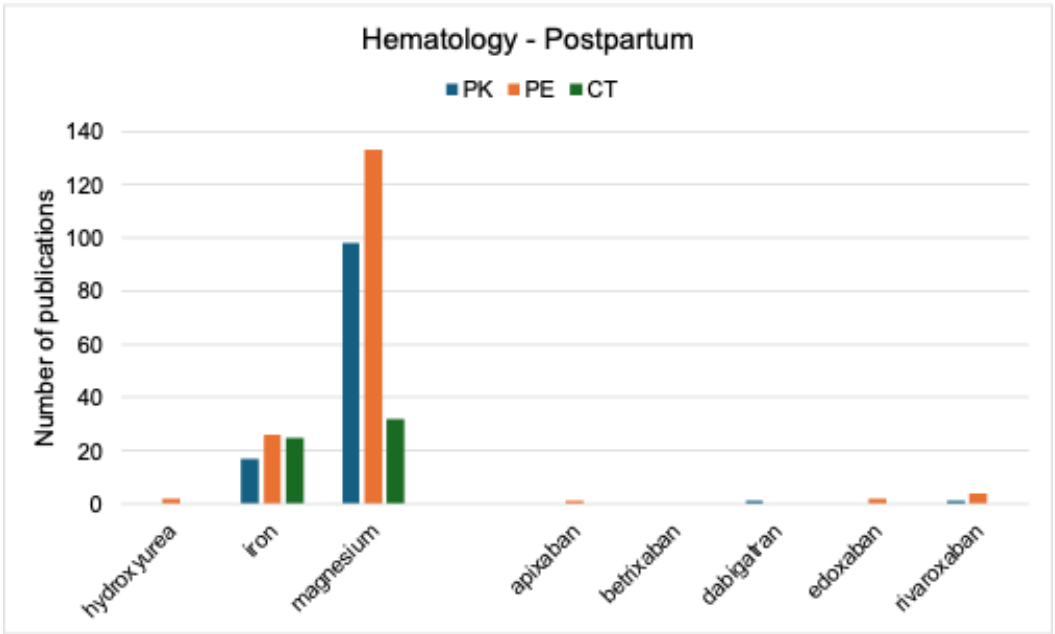

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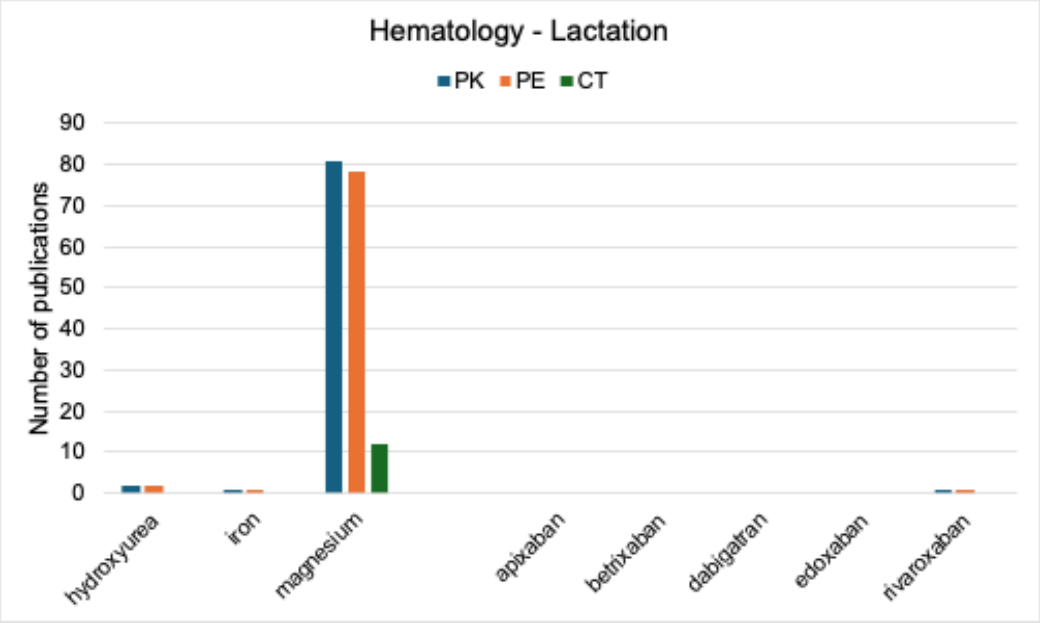
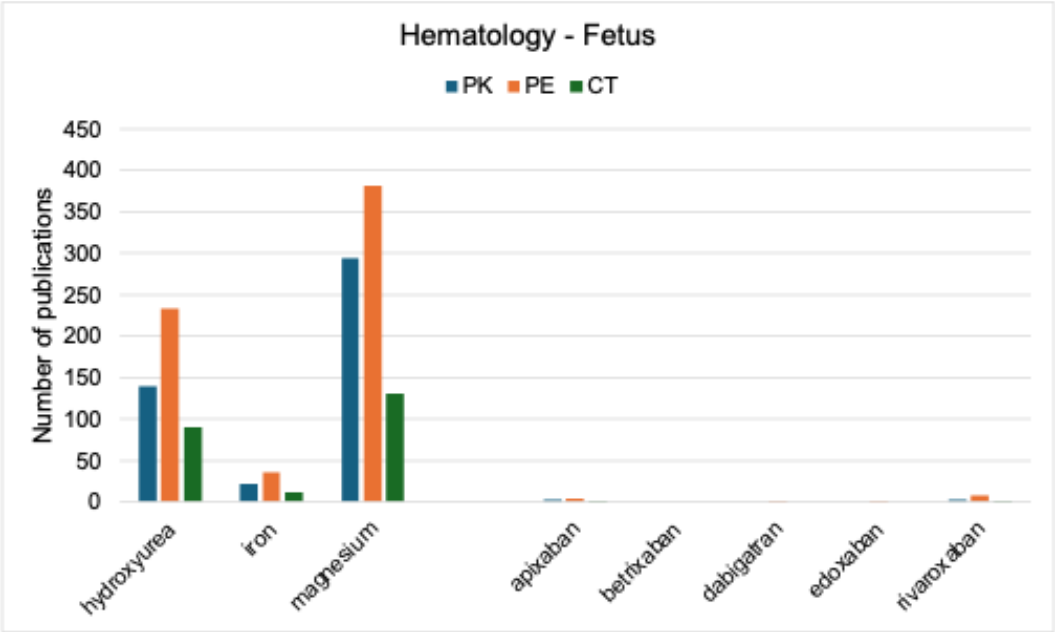
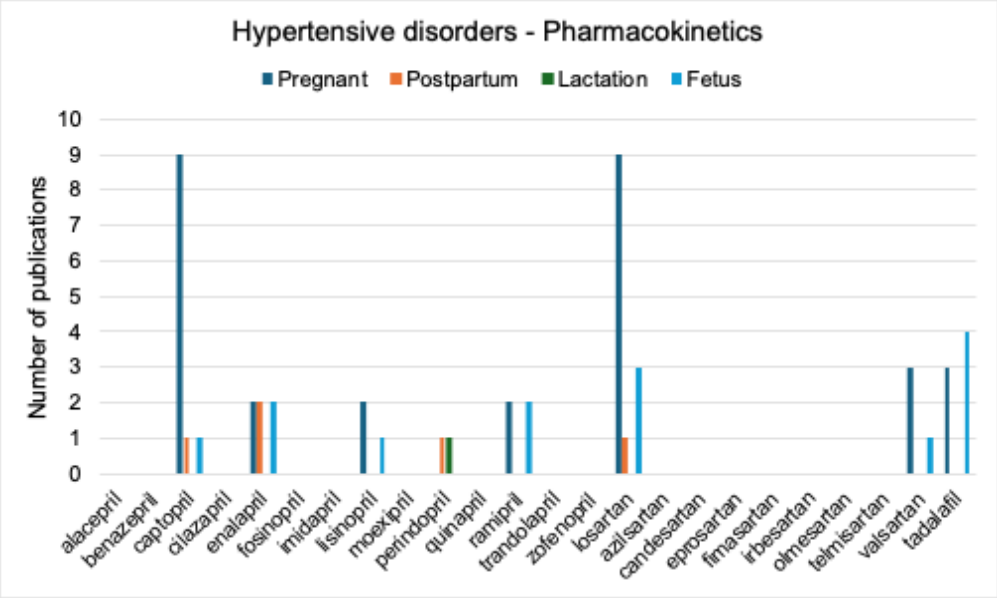


Hematology nominations



Hypertension nominations



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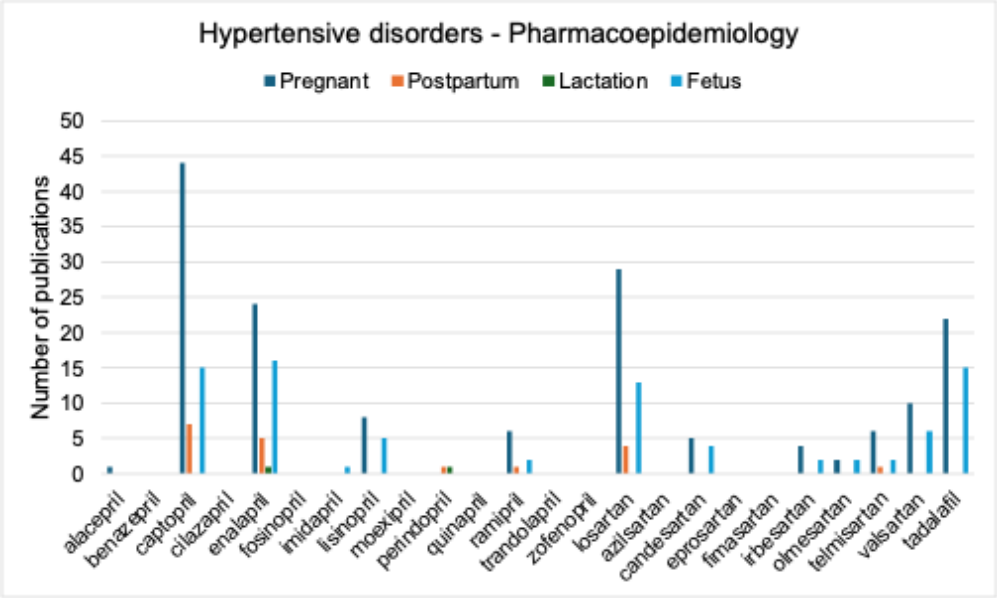

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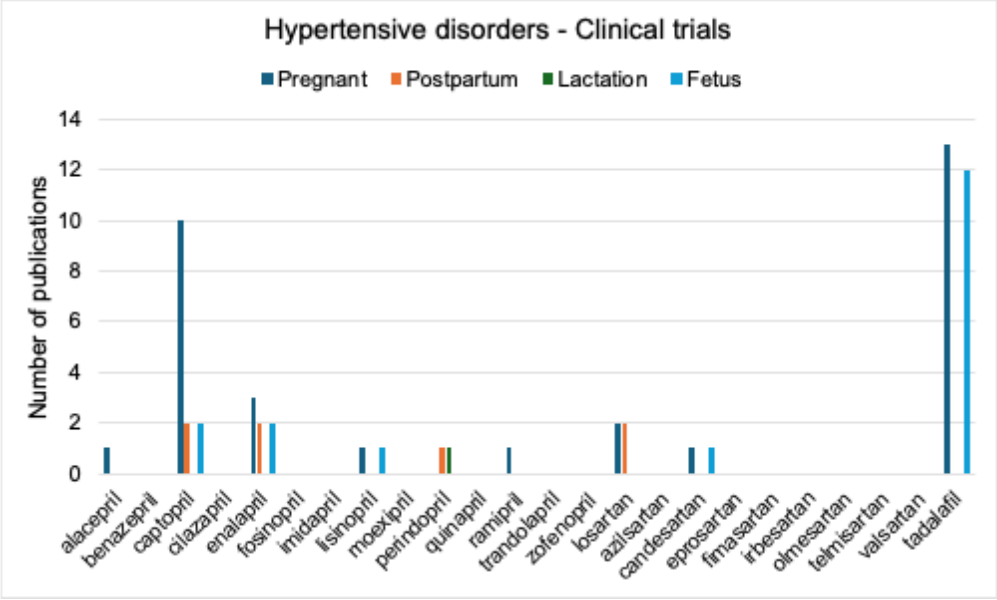

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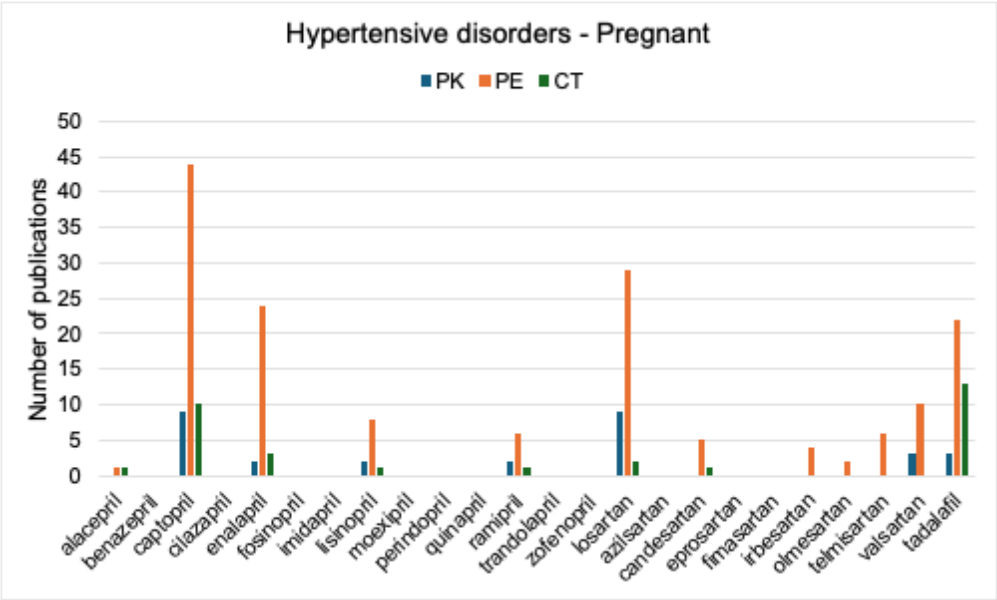

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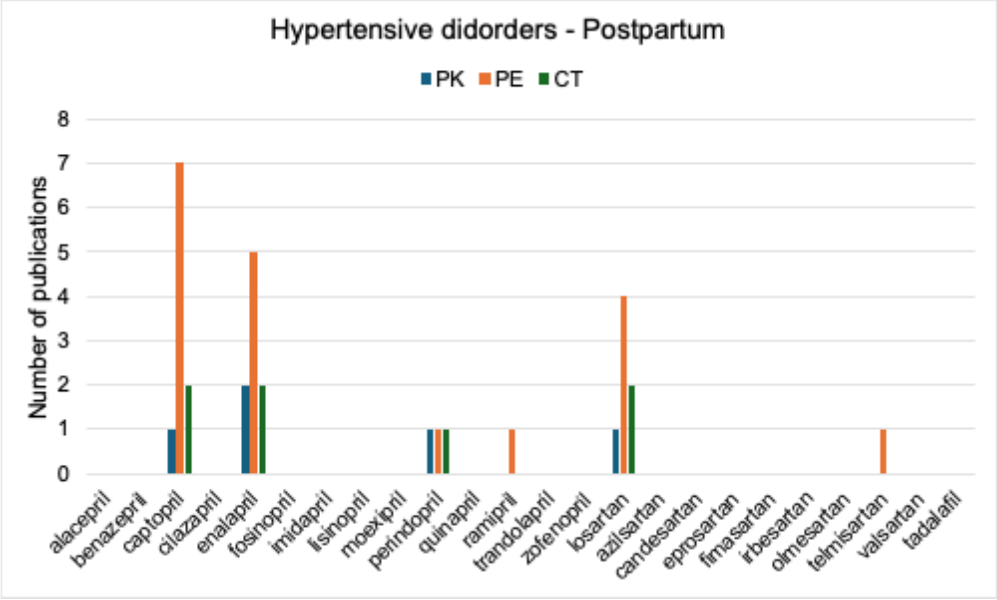

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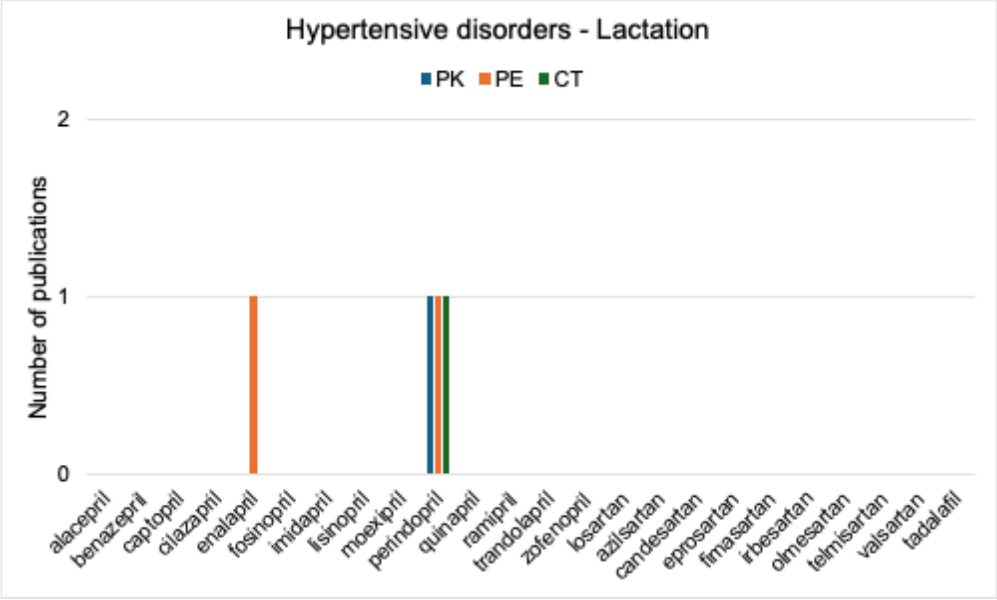
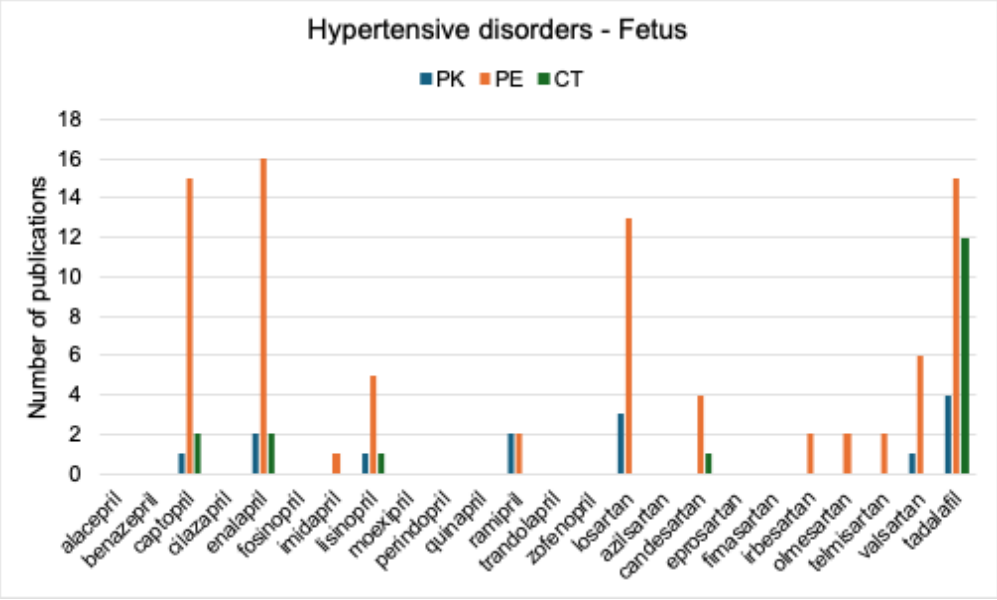
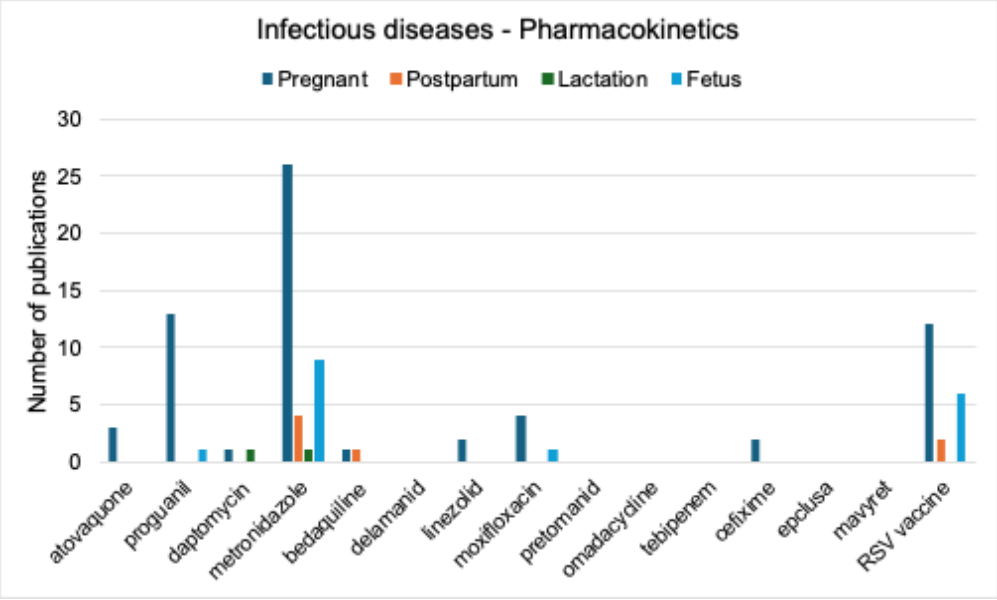


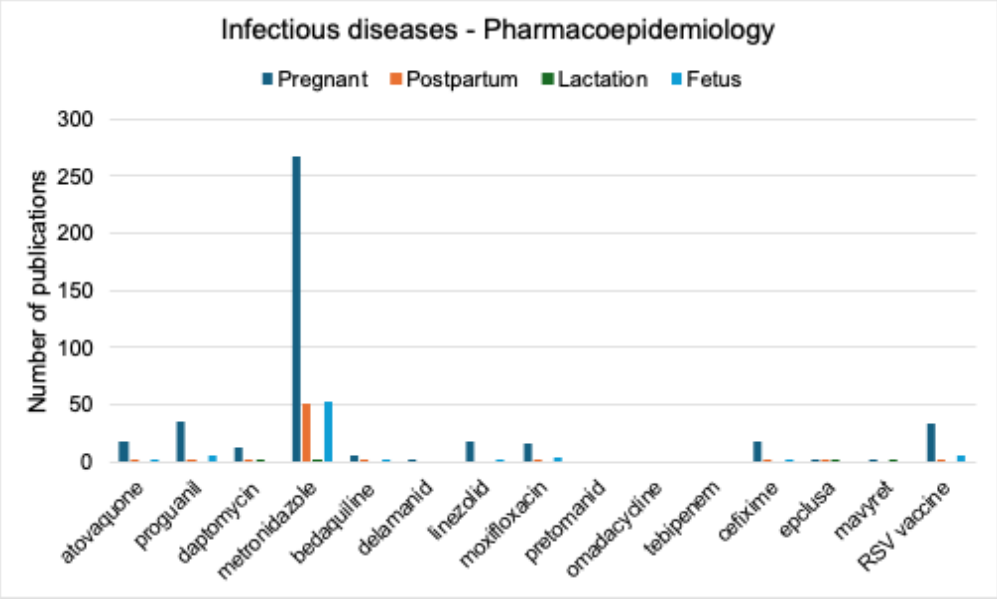
Hypertension nominations



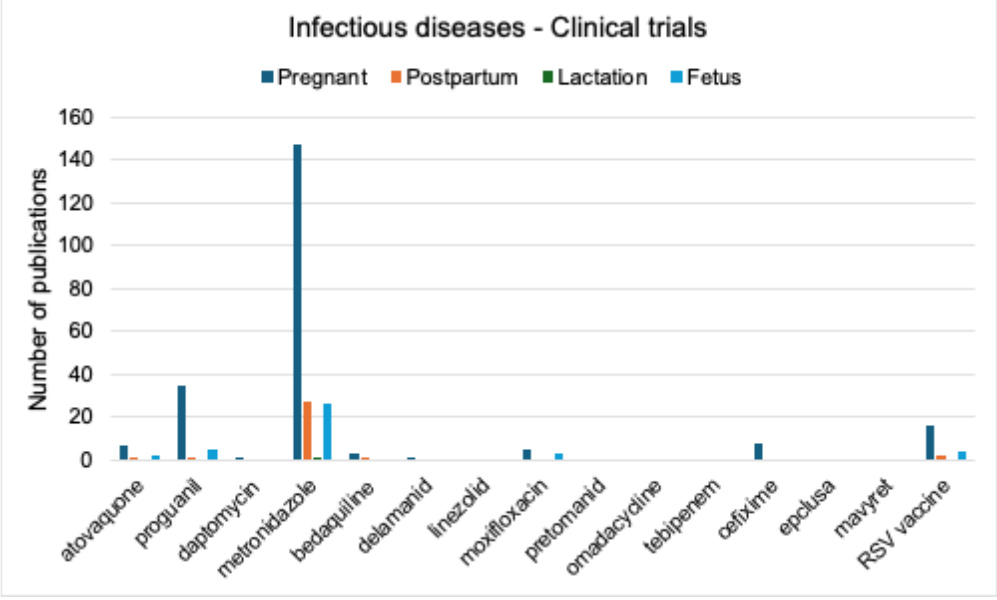
Infectious disease nominations



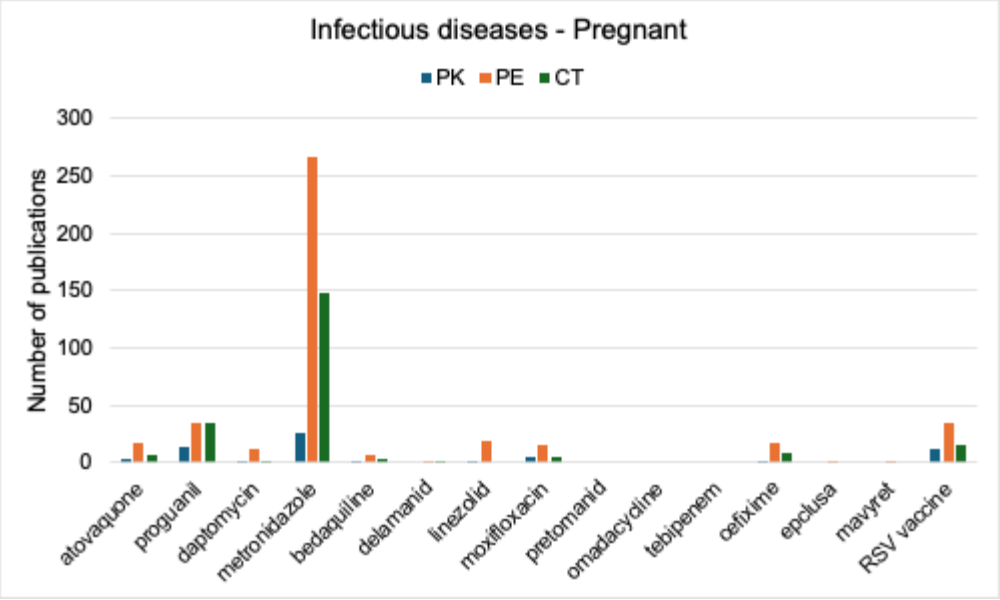
Infectious disease nominations



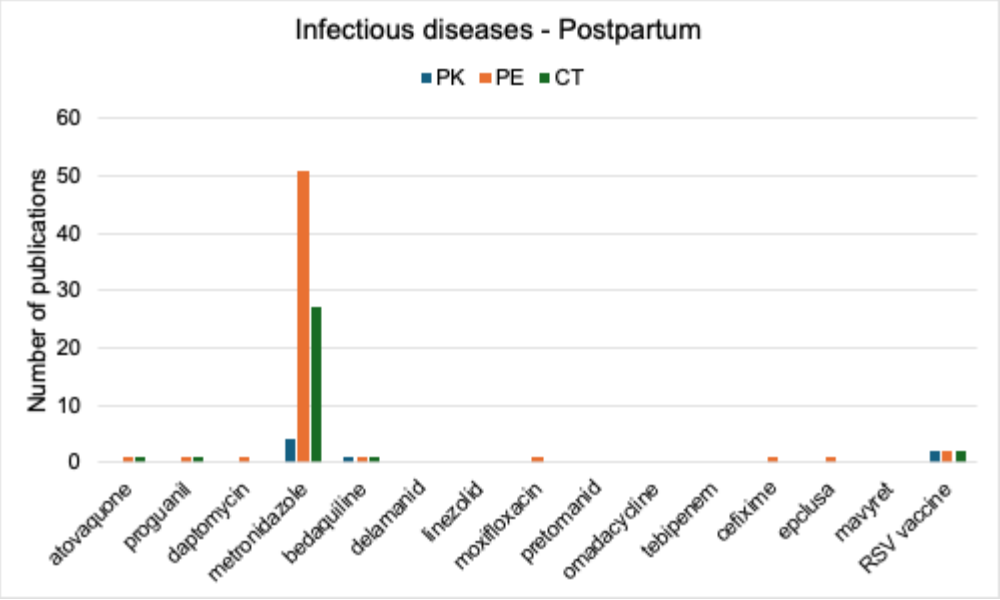
Infectious disease nominations



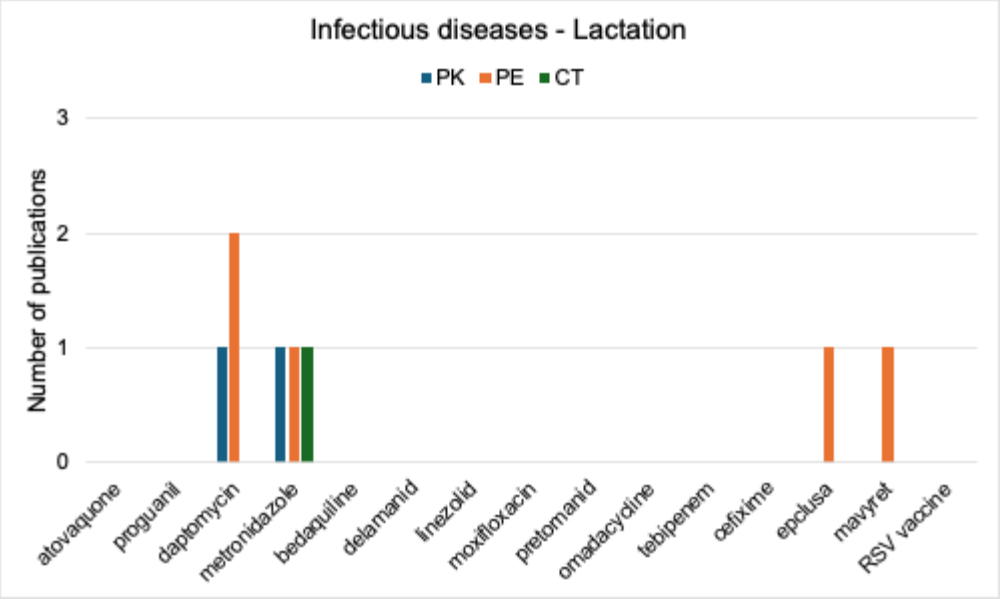
Infectious disease nominations



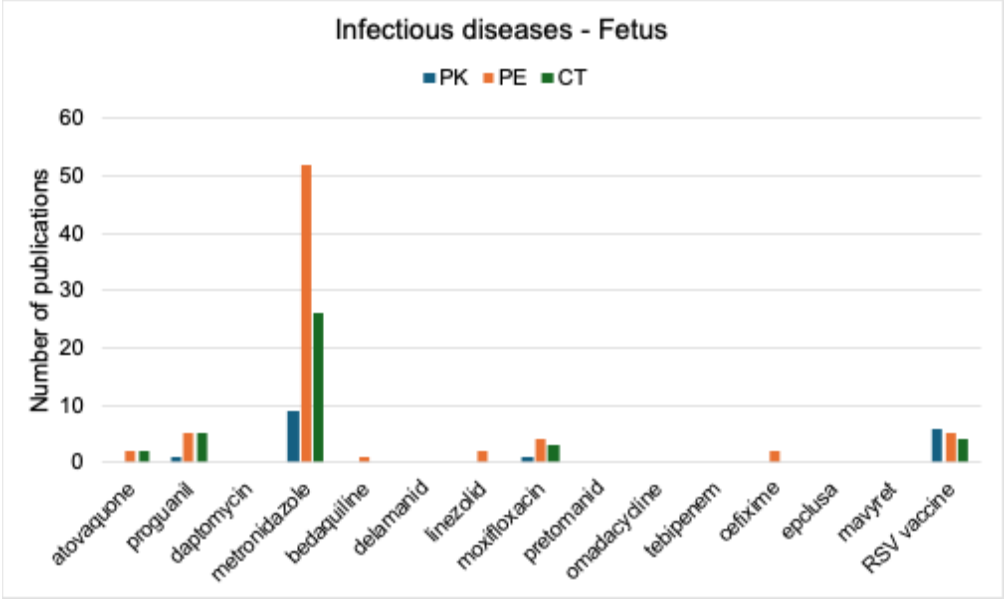
Infectious disease nominations



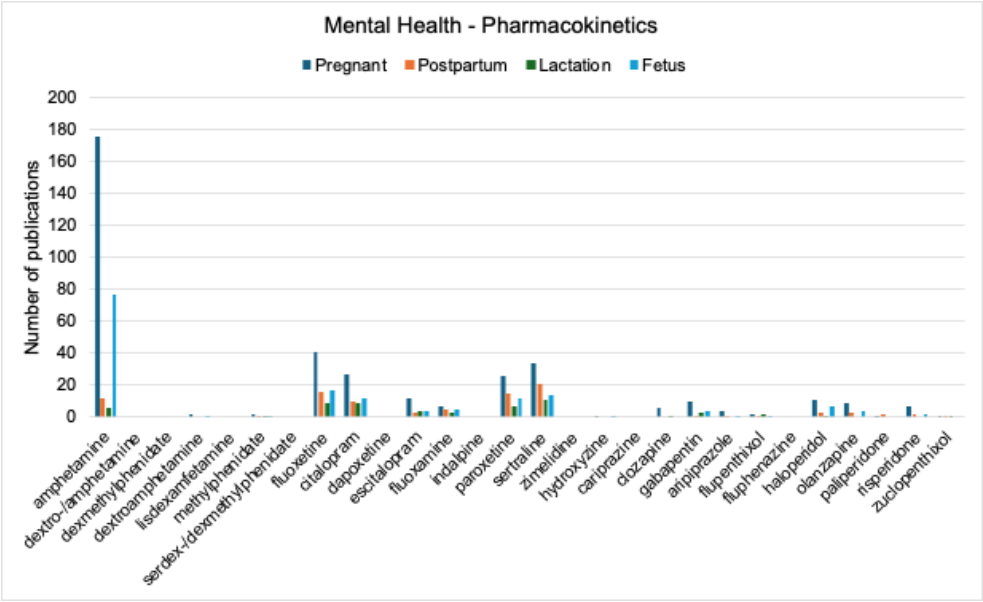
Infectious disease nominations



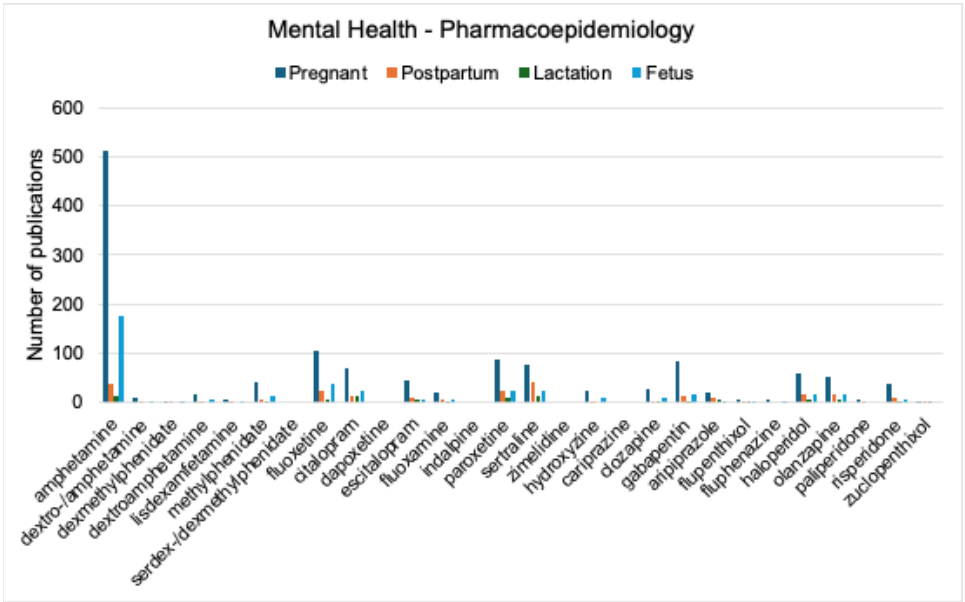
Infectious disease nominations



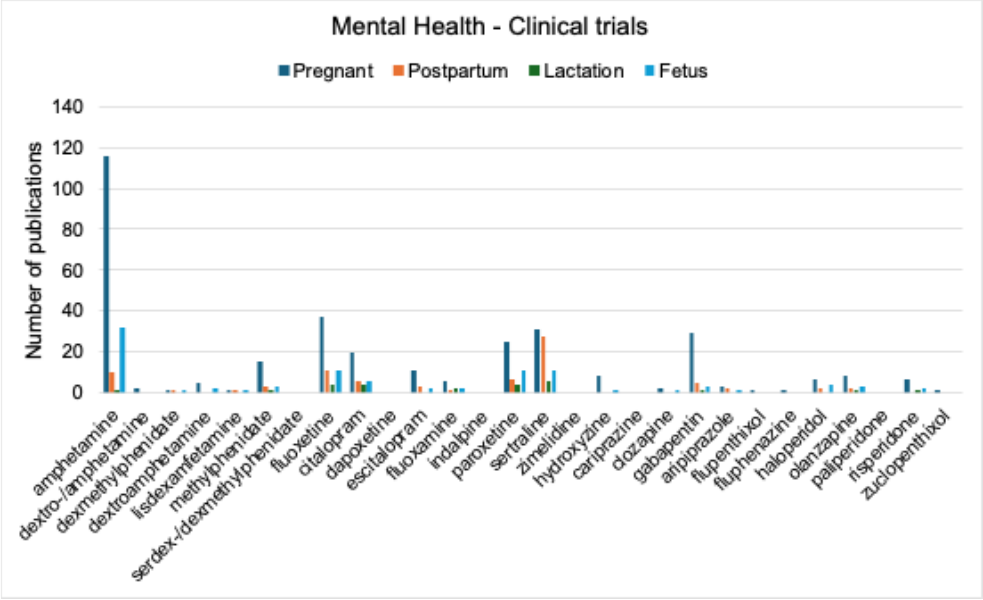
Mental health nominations



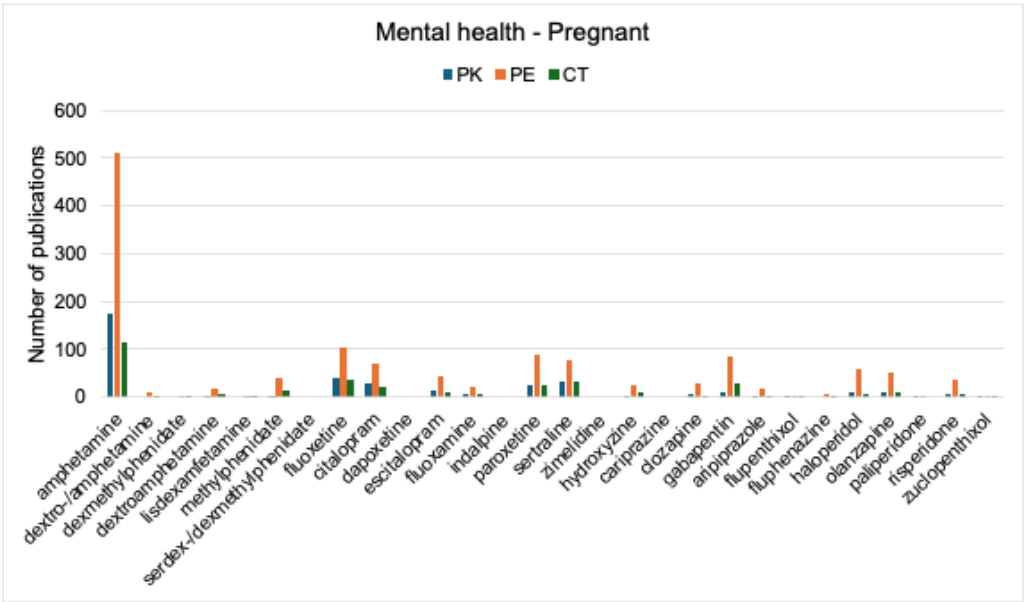
Mental health nominations



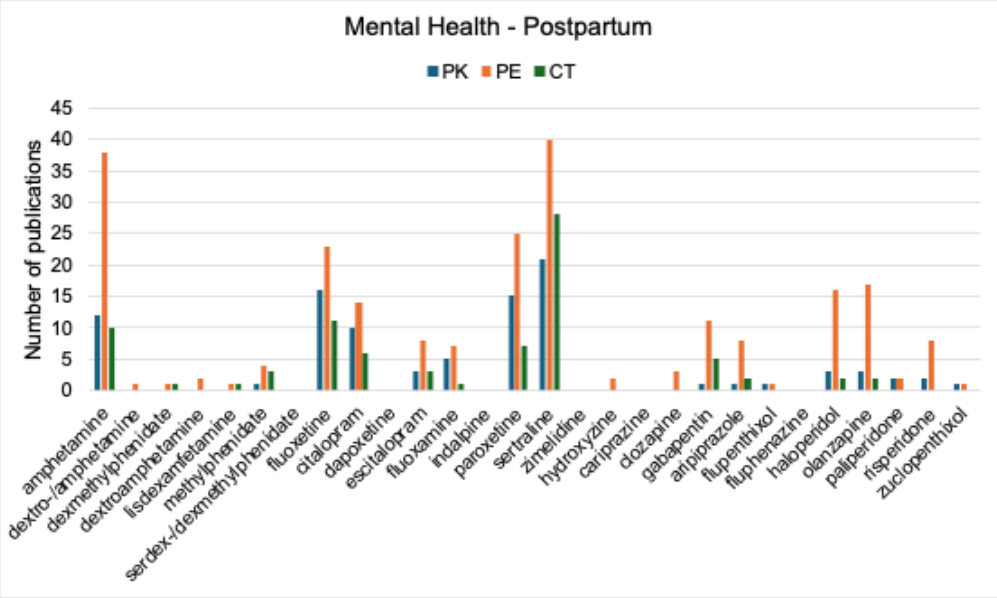
Mental health nominations



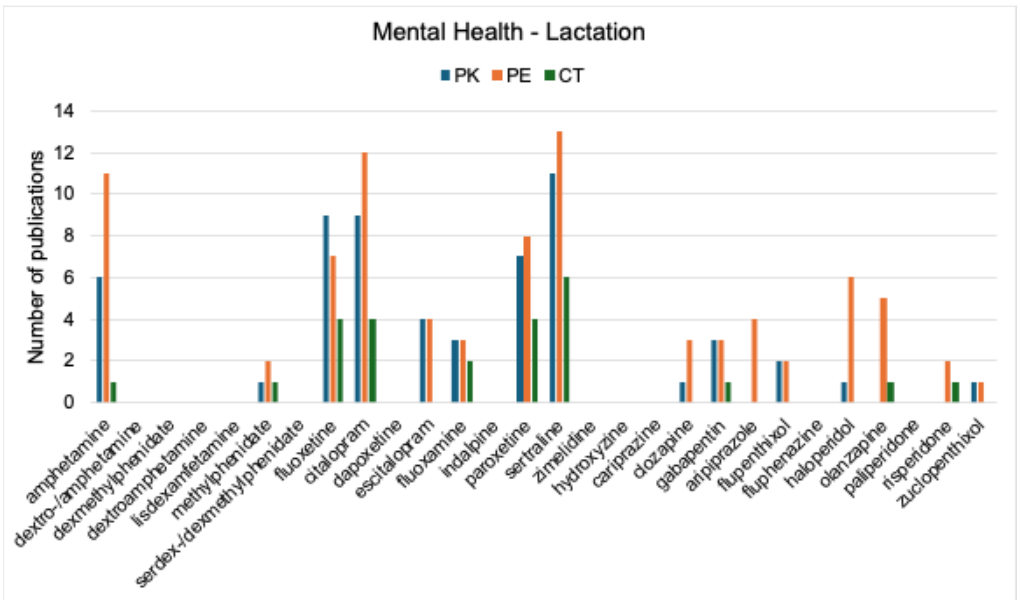
Mental health nominations



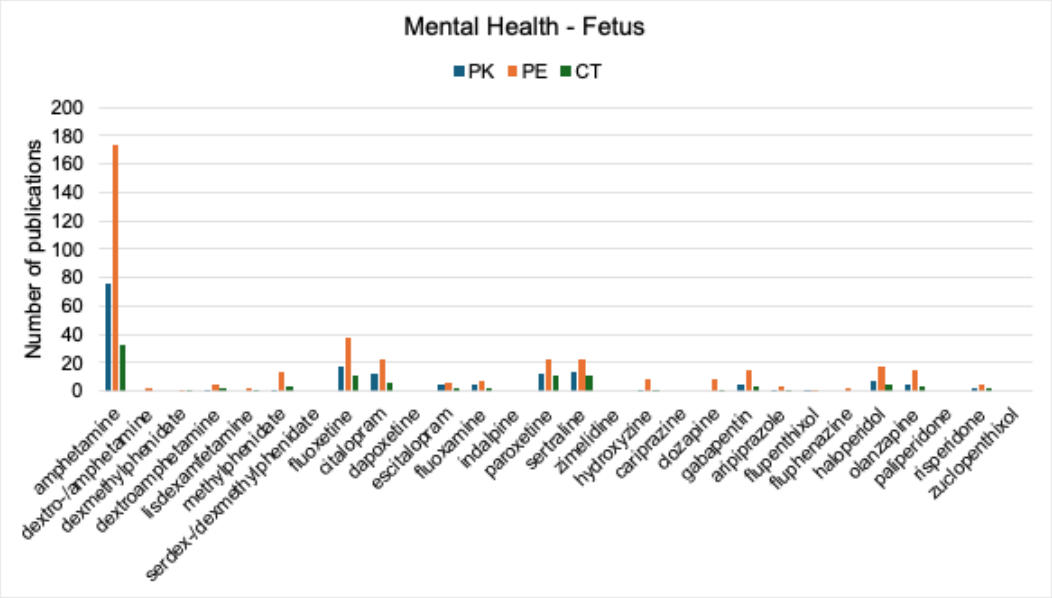
Mental health nominations



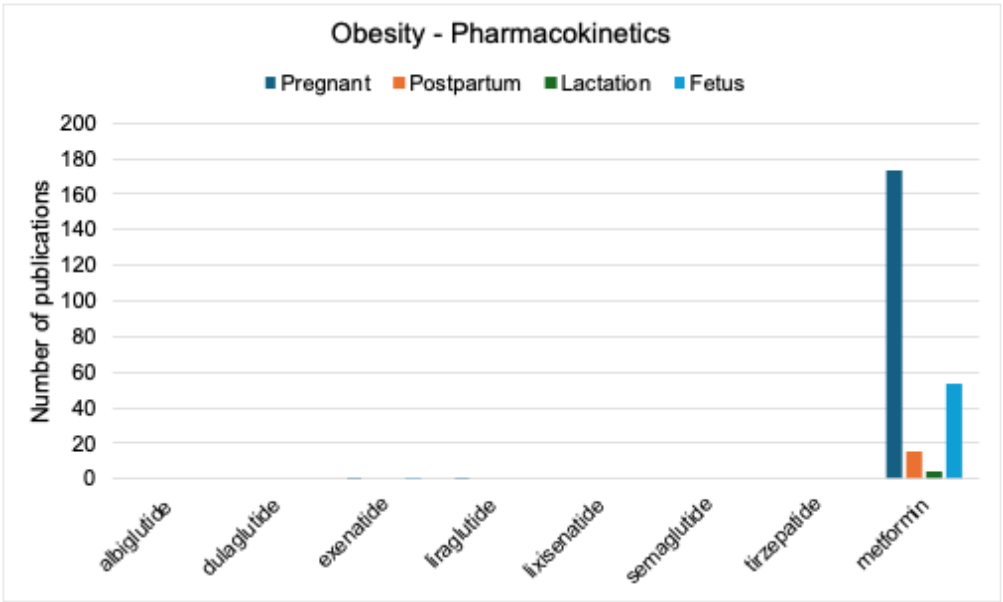
Mental health nominations



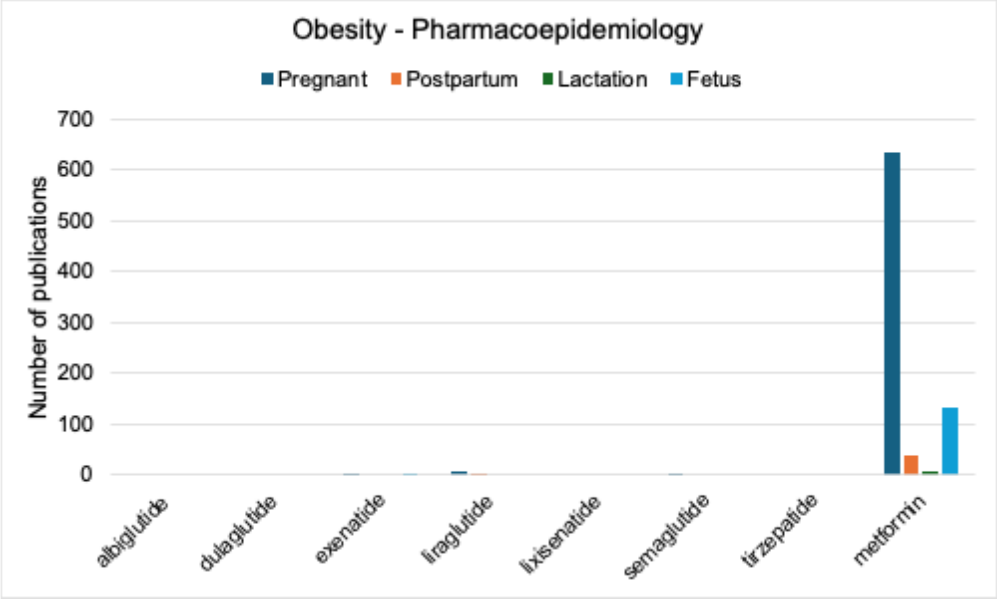
Mental health nominations



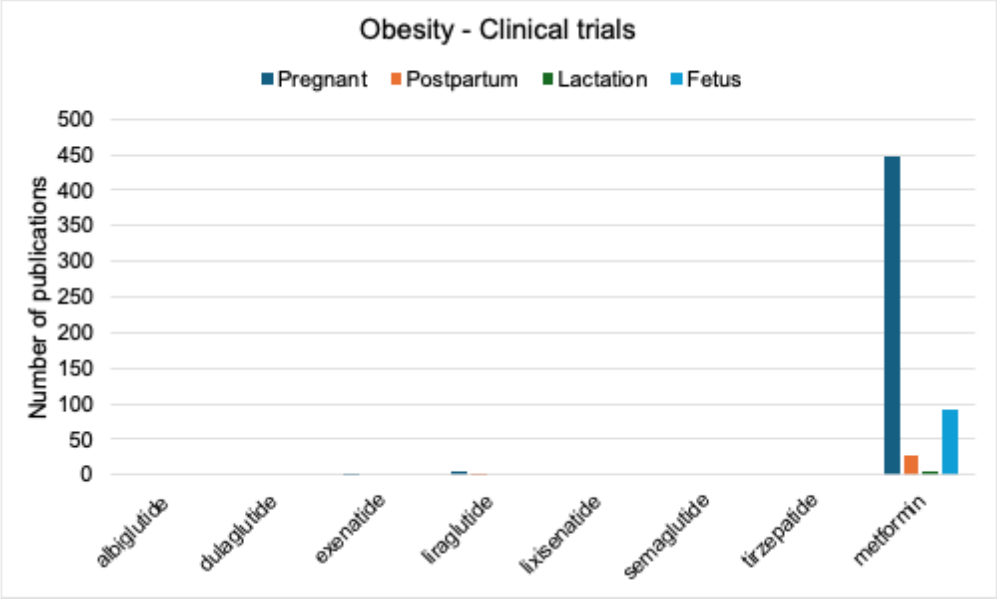
Obesity nominations



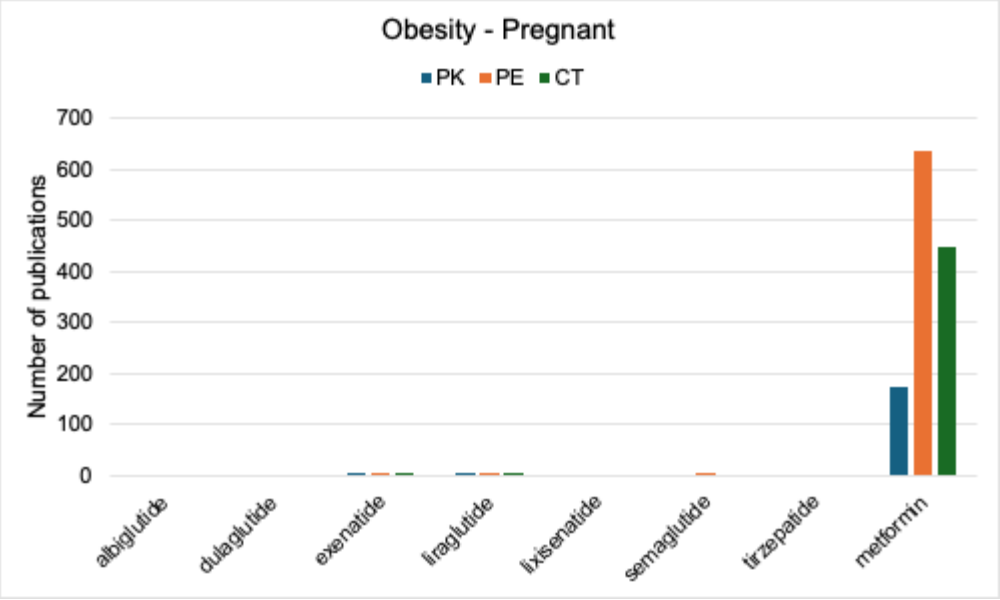
Obesity nominations



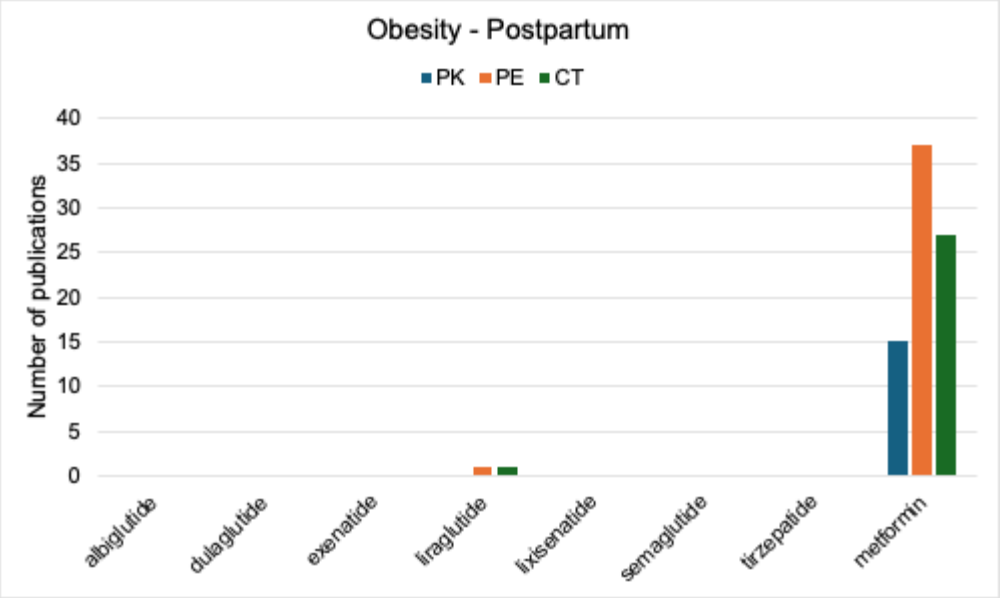
Obesity nominations



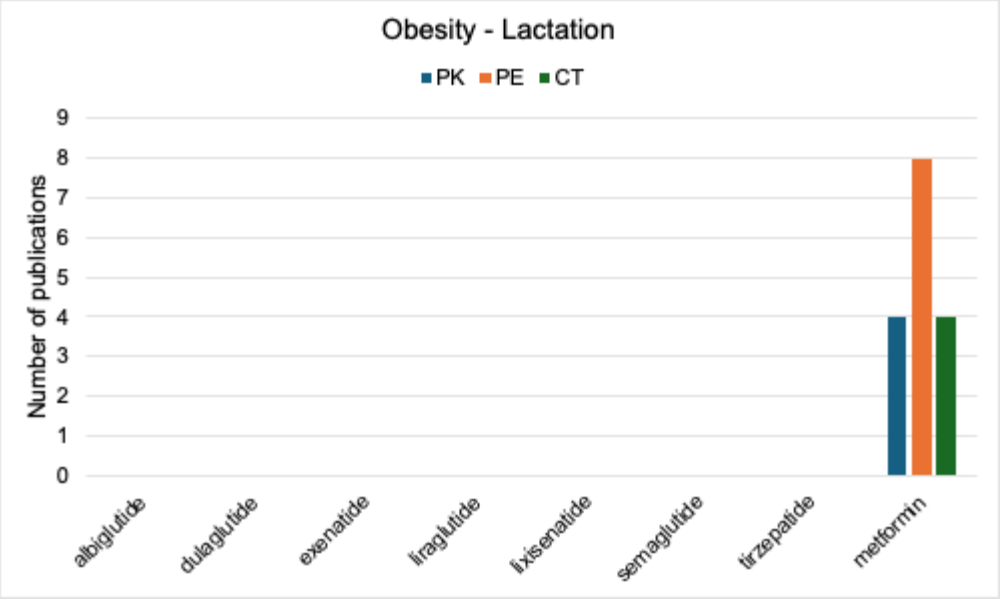
Obesity nominations



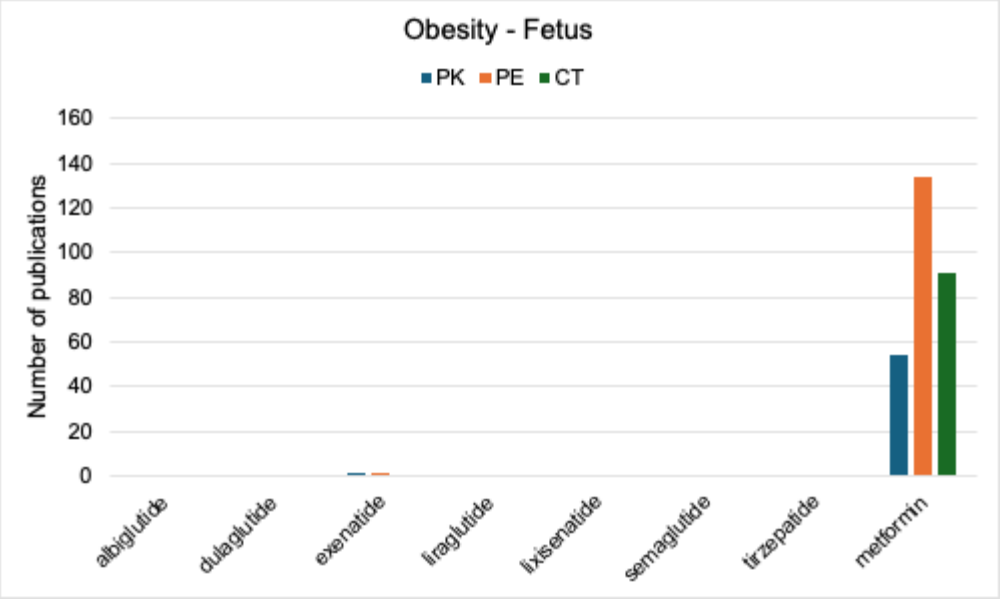
Obesity nominations



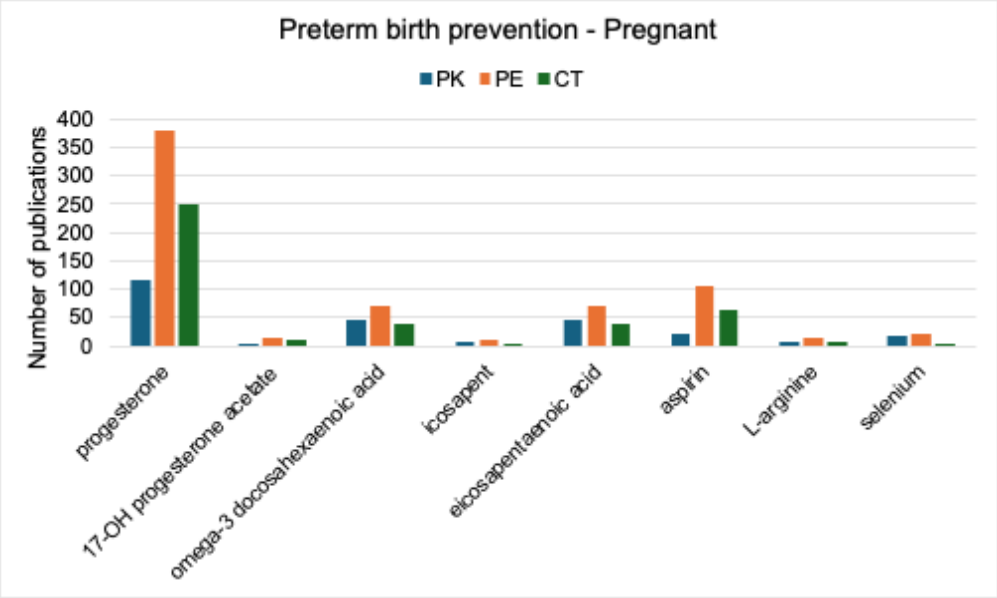
Obesity nominations



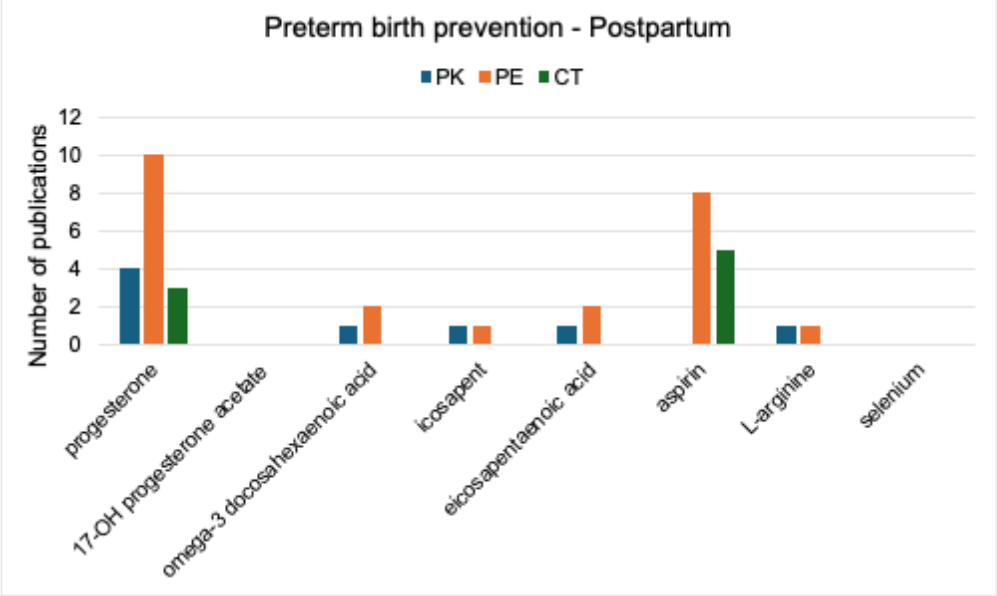
Obesity nominations



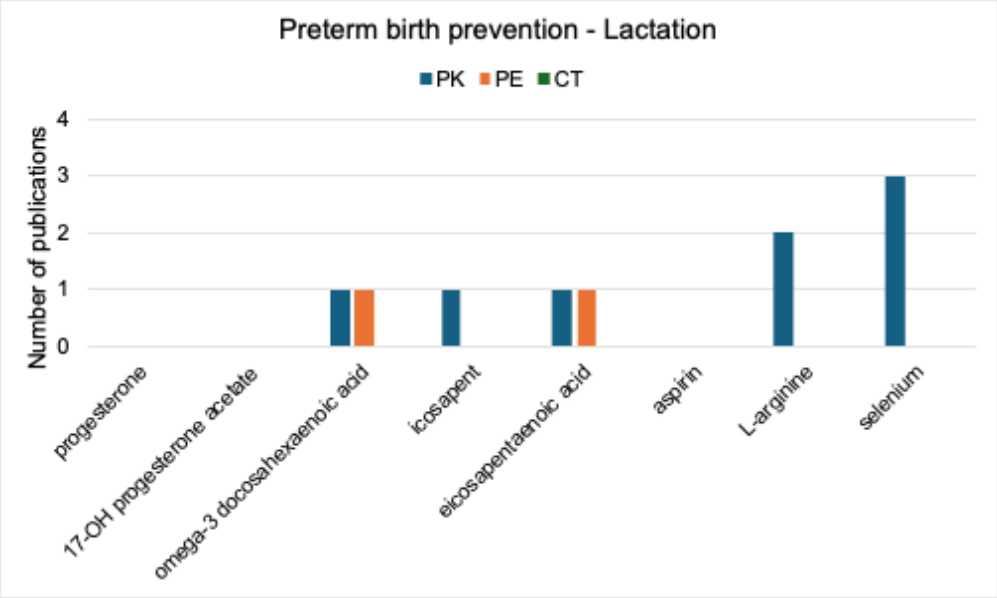
Preterm birth prevention nominations



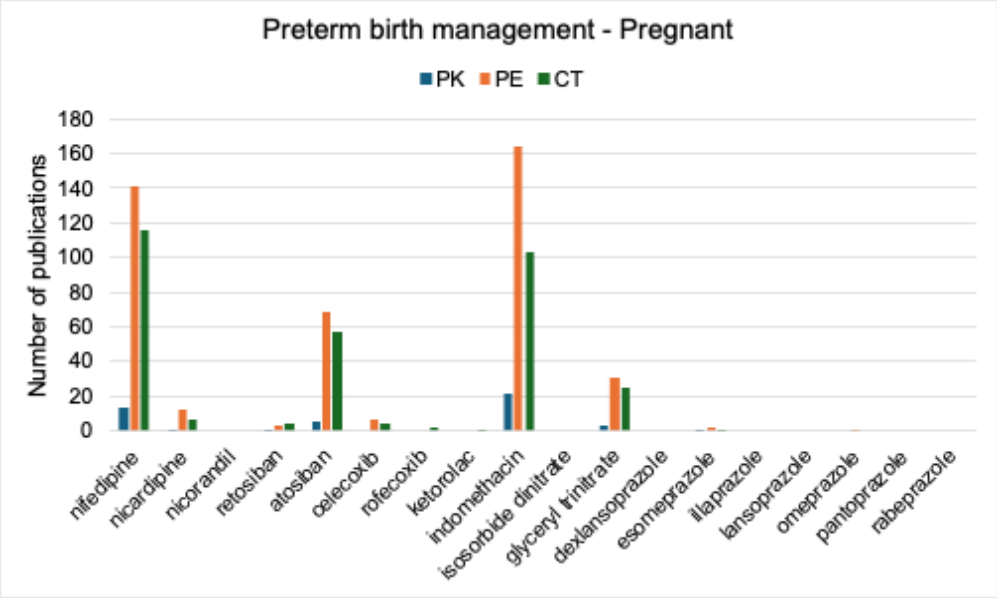
Preterm birth prevention nominations



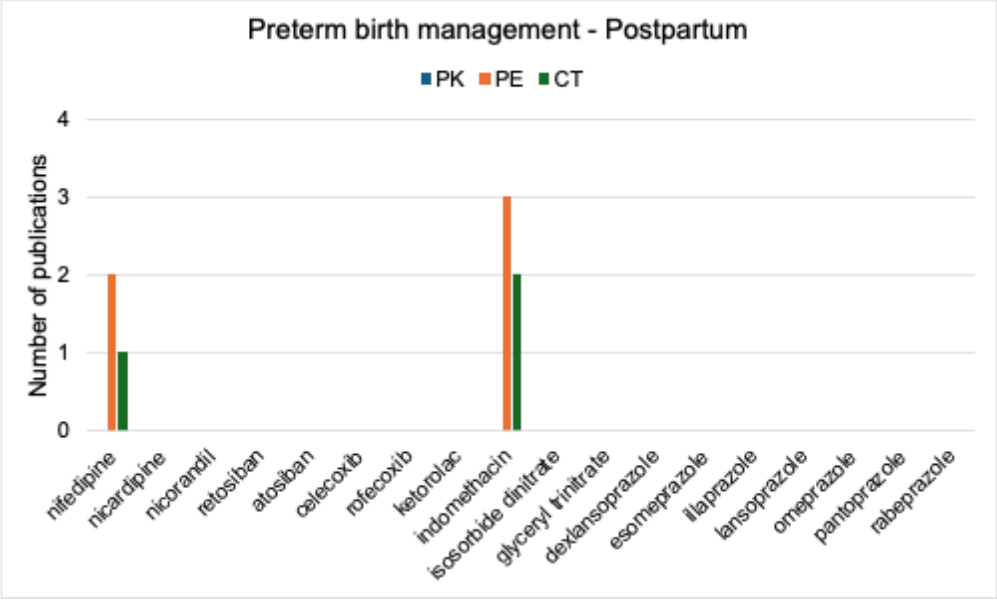
Preterm birth prevention nominations



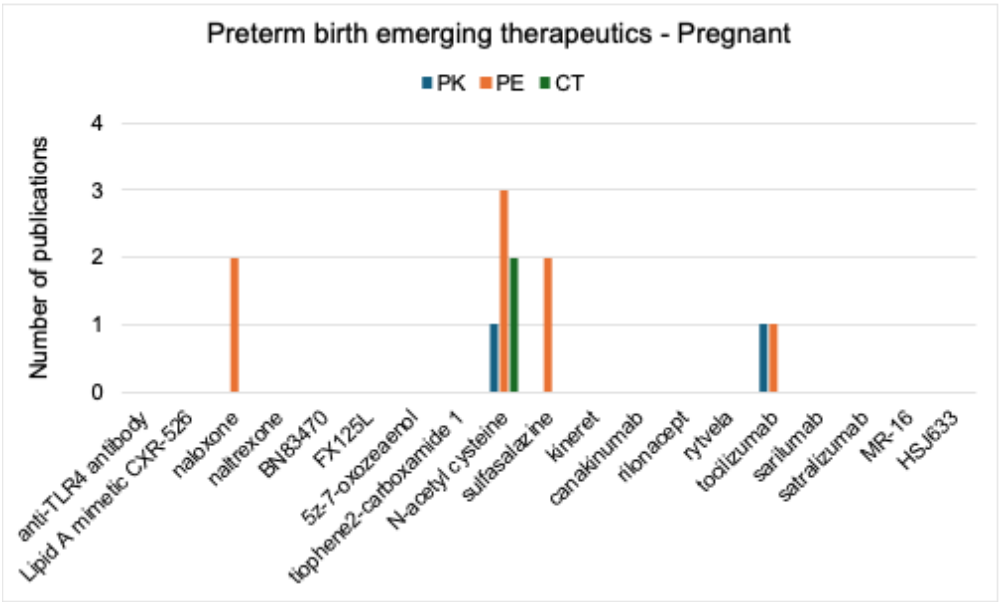
Preterm birth management nominations



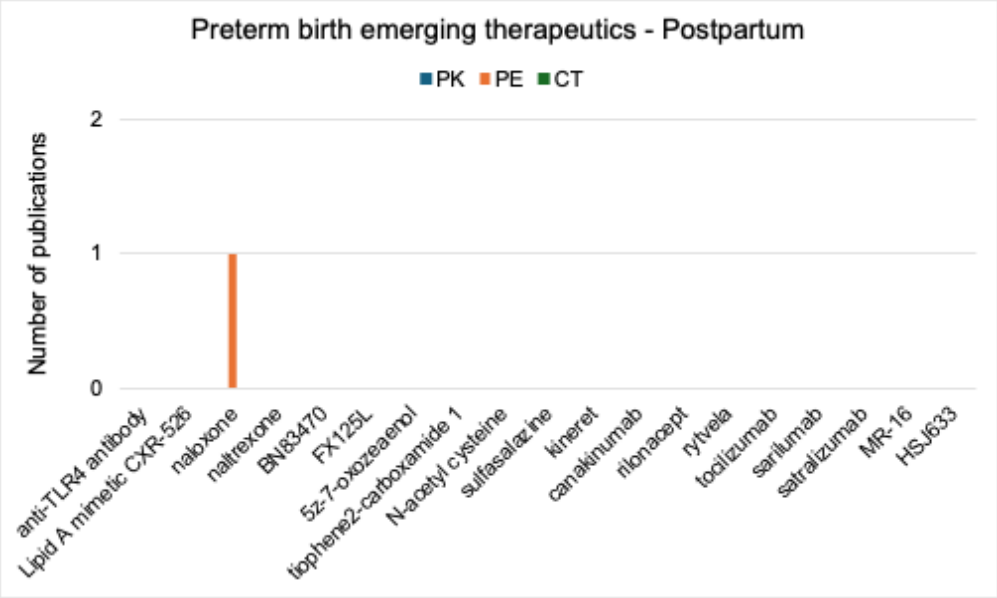
Preterm birth management nominations



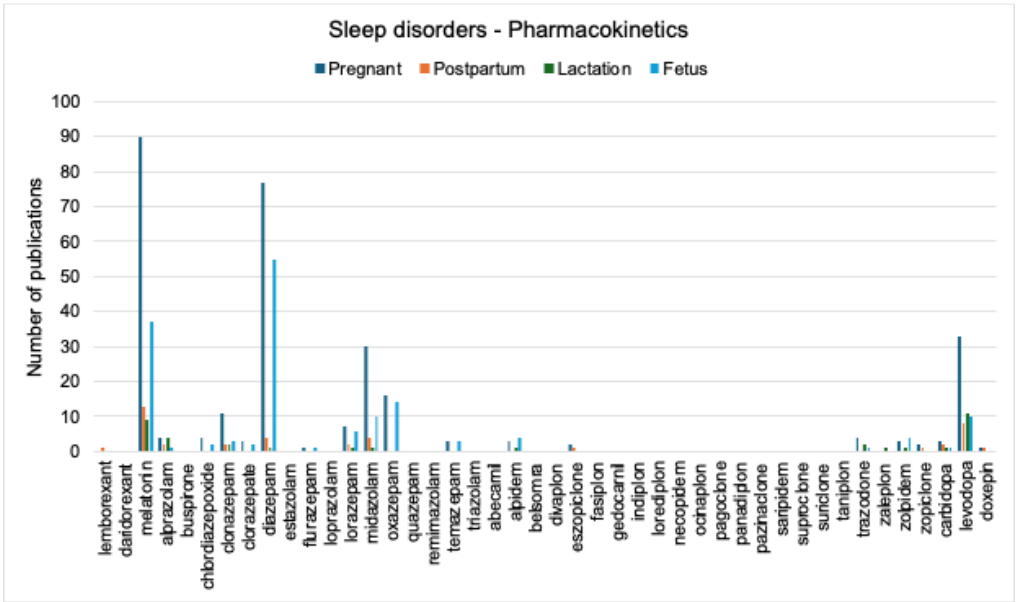
Preterm birth emerging therapeutics nominations



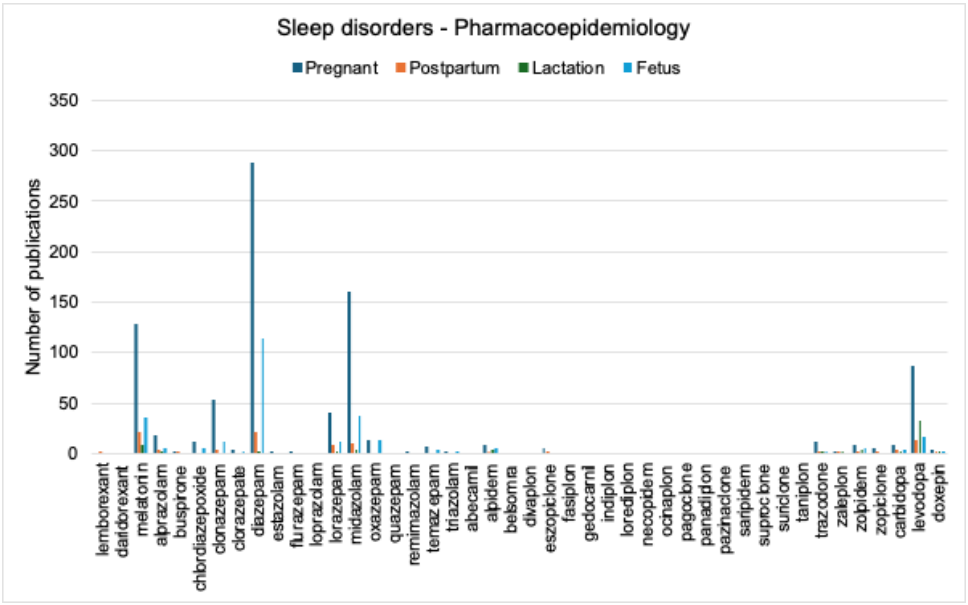
Preterm birth emerging therapeutics nominations



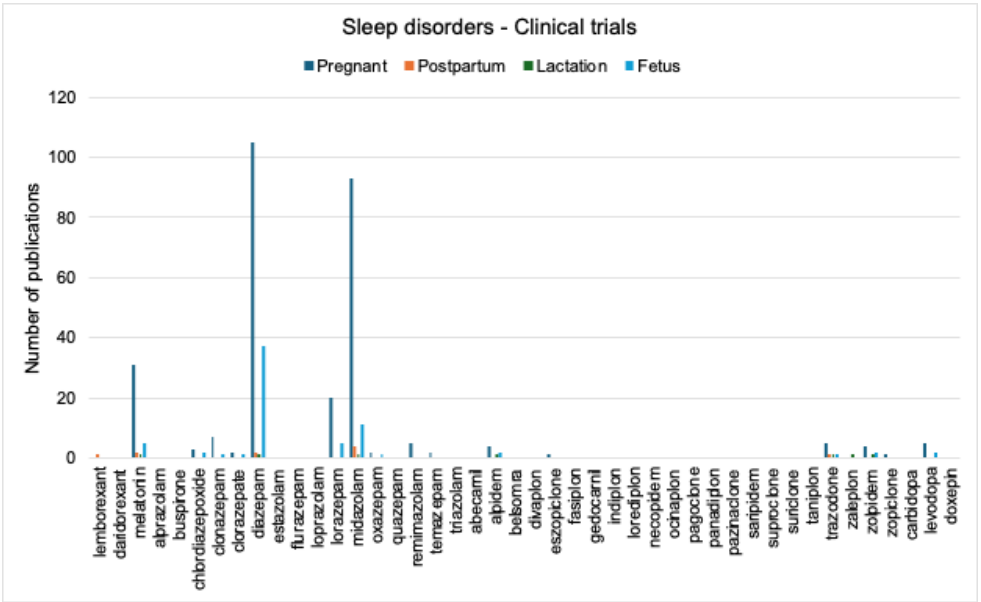
Sleep/Circadian disorders (SCD) nominations



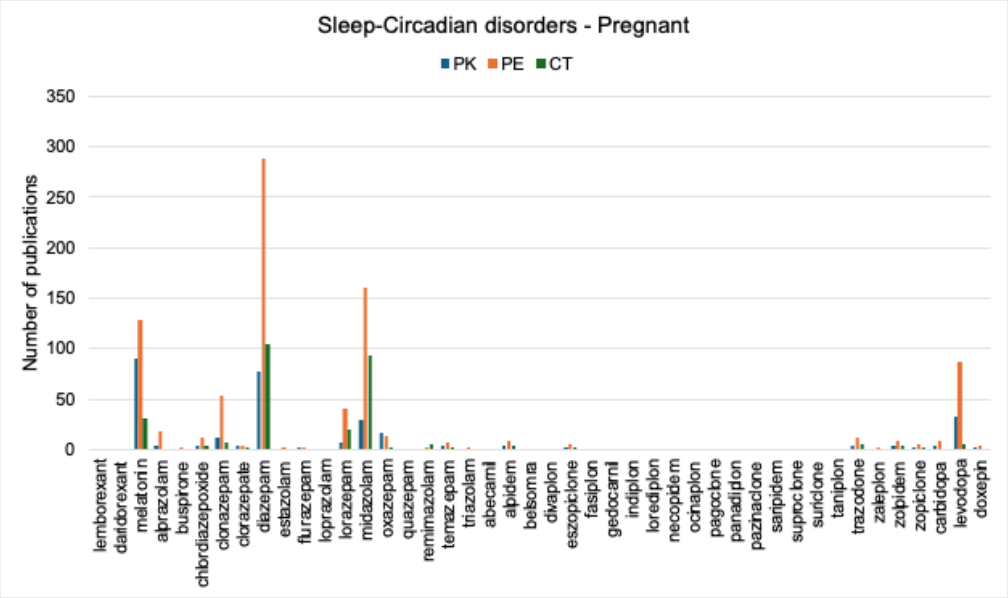
Sleep/Circadian disorders (SCD) nominations



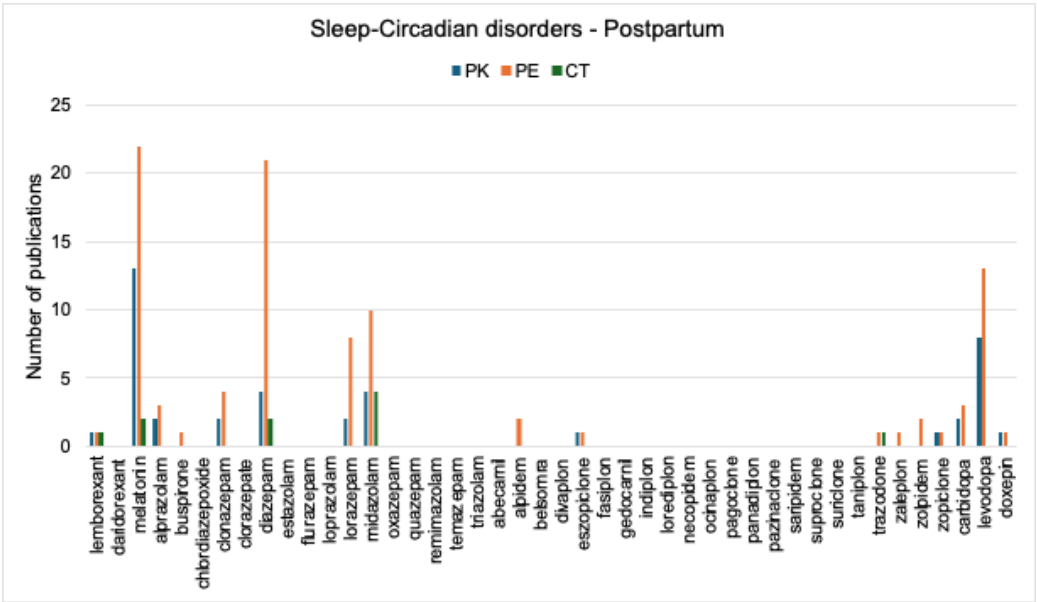
Sleep/Circadian disorders (SCD) nominations



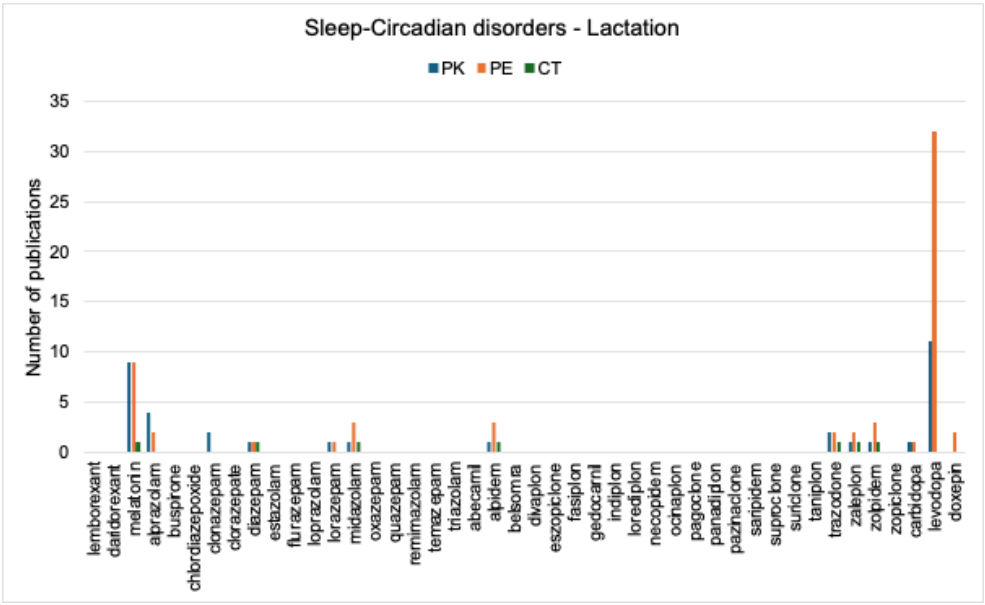
Sleep/Circadian disorders (SCD) nominations



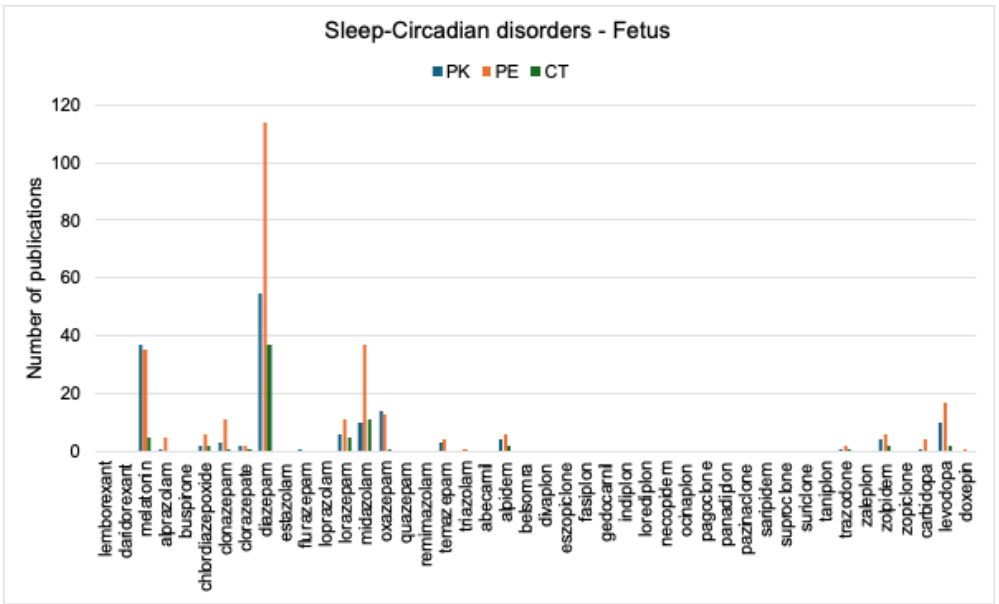
Sleep/Circadian disorders (SCD) nominations



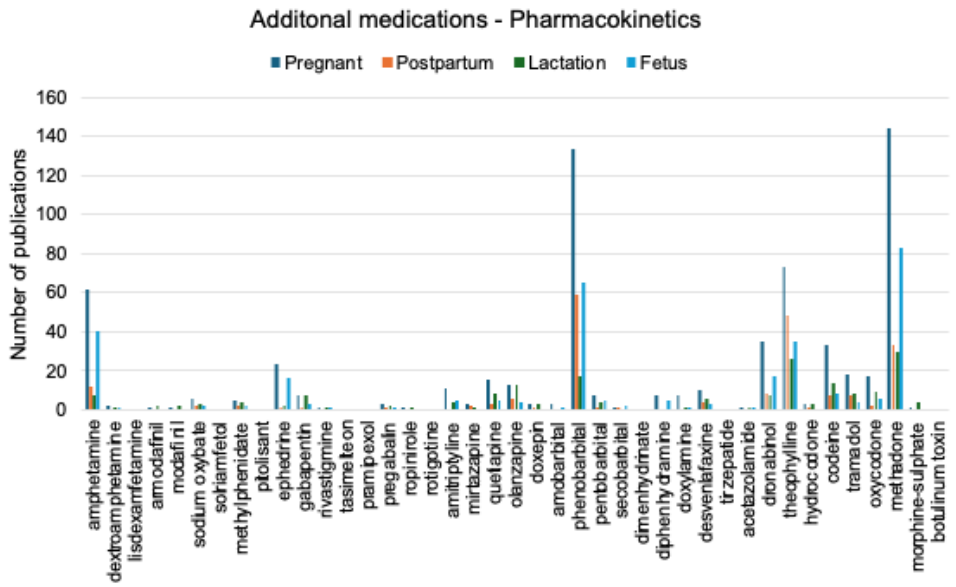
Sleep/Circadian disorders (SCD) nominations



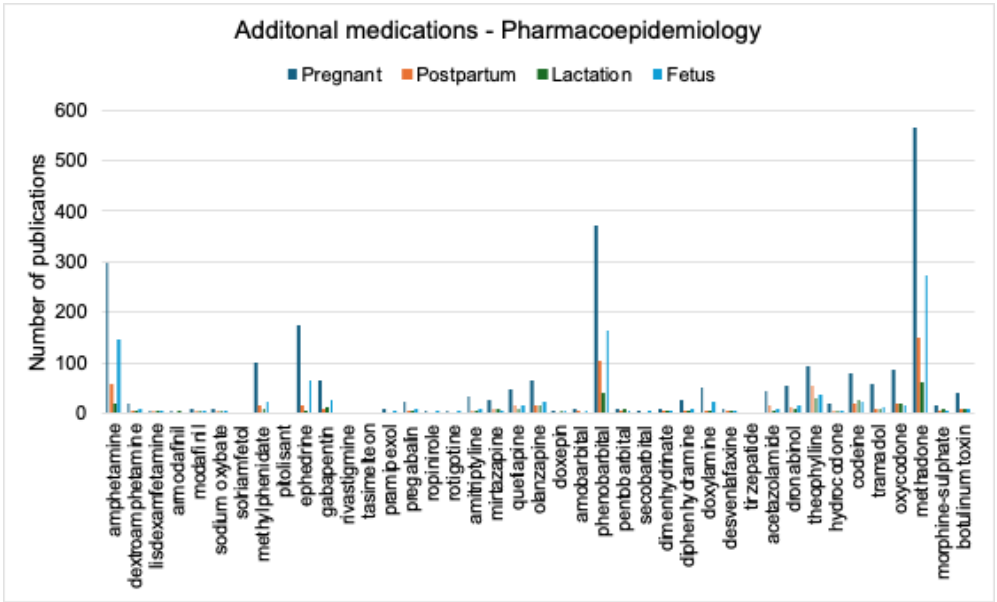
Sleep/Circadian disorders (SCD) nominations



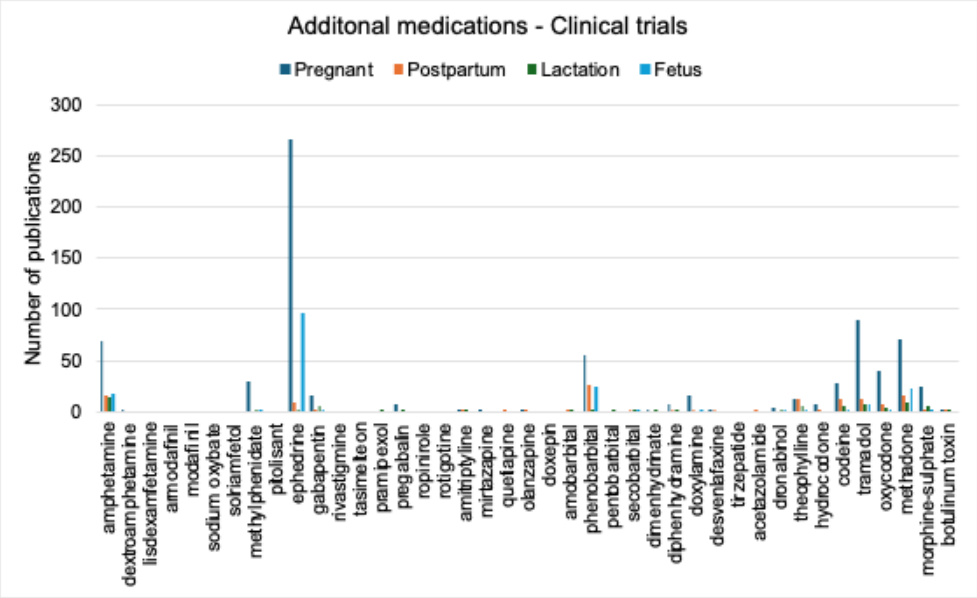
SCD additional nominations



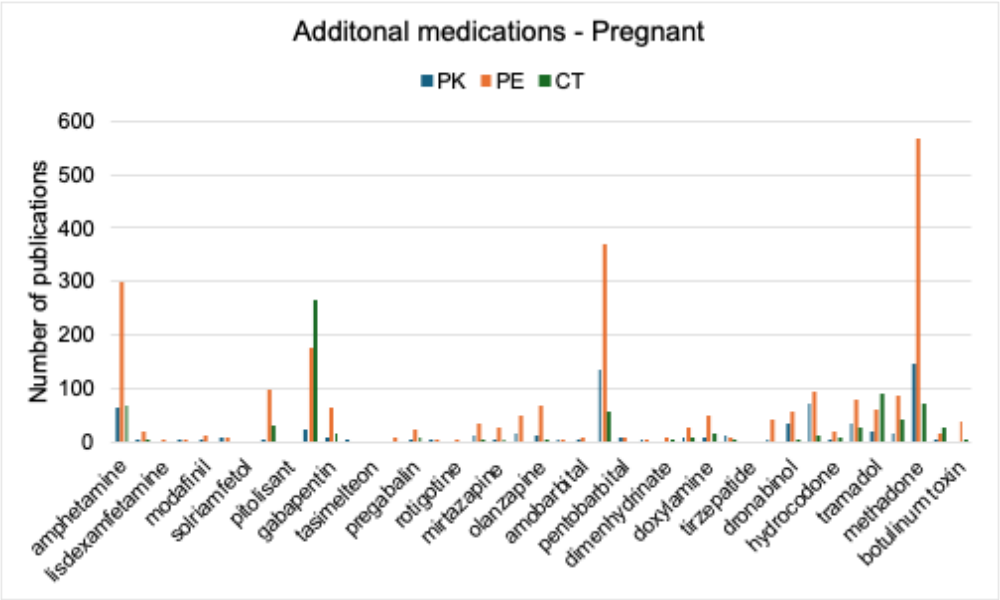
SCD additional nominations



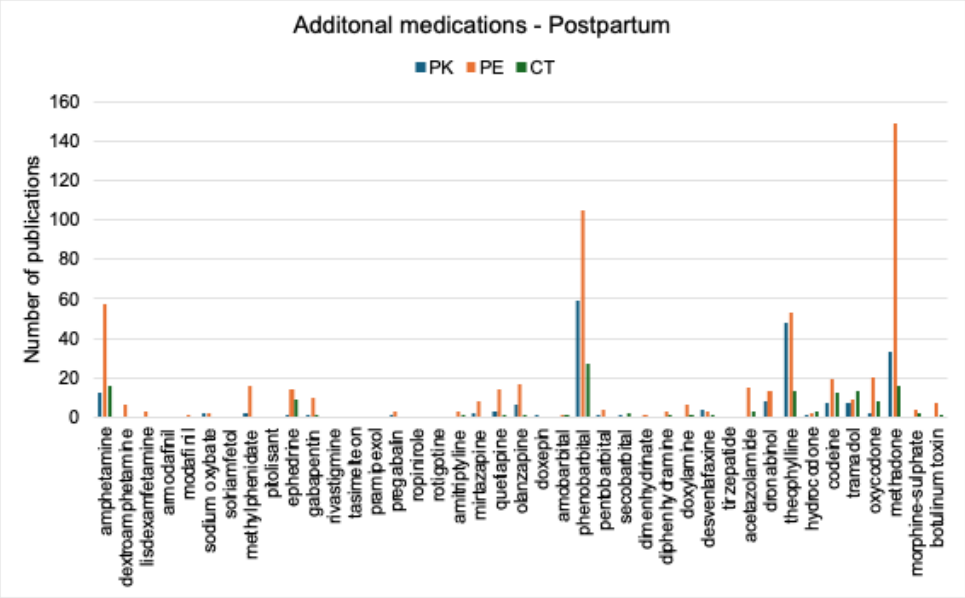
SCD additional nominations



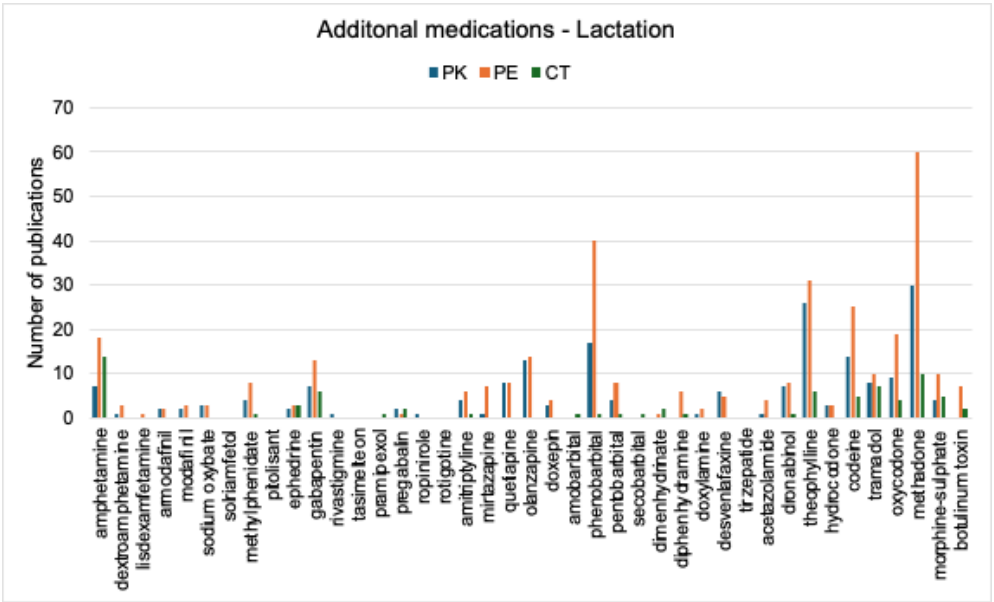
SCD additional nominations



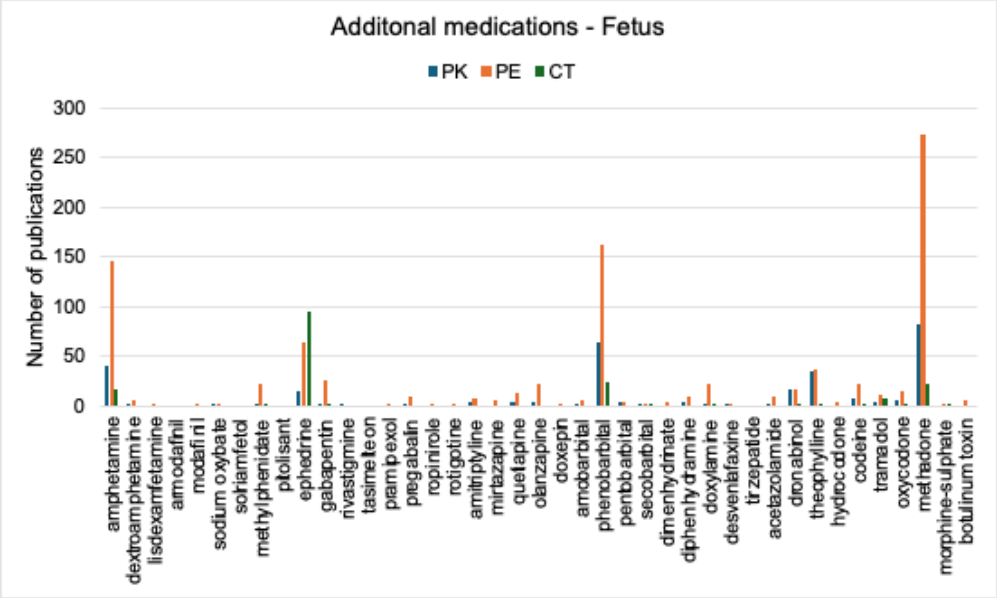
SCD additional nominations



SCD additional nominations

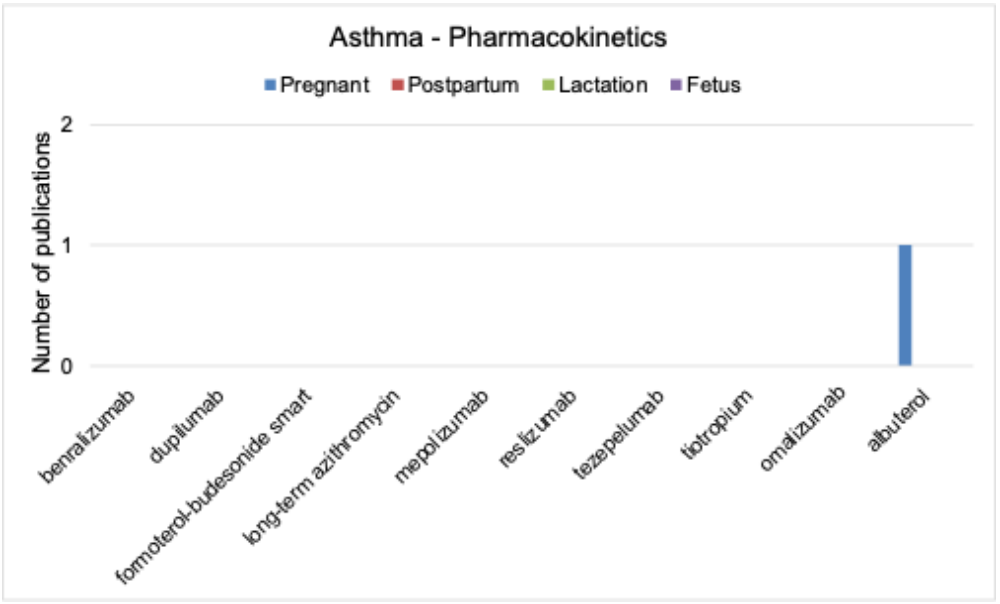


SCD additional nominations

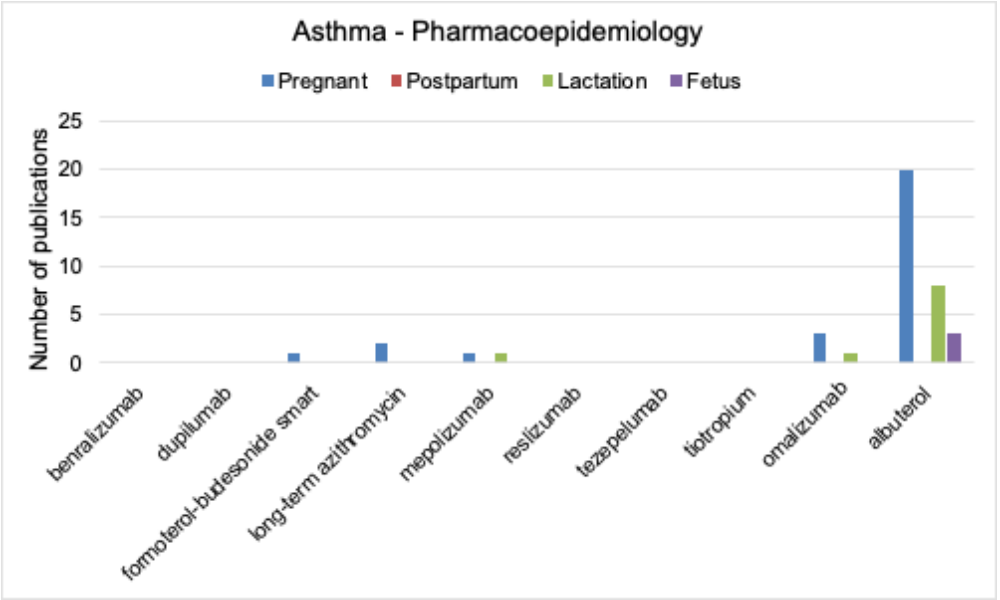


2025 Landscape analysis for nominations not discussed

Asthma nominations



Asthma nominations



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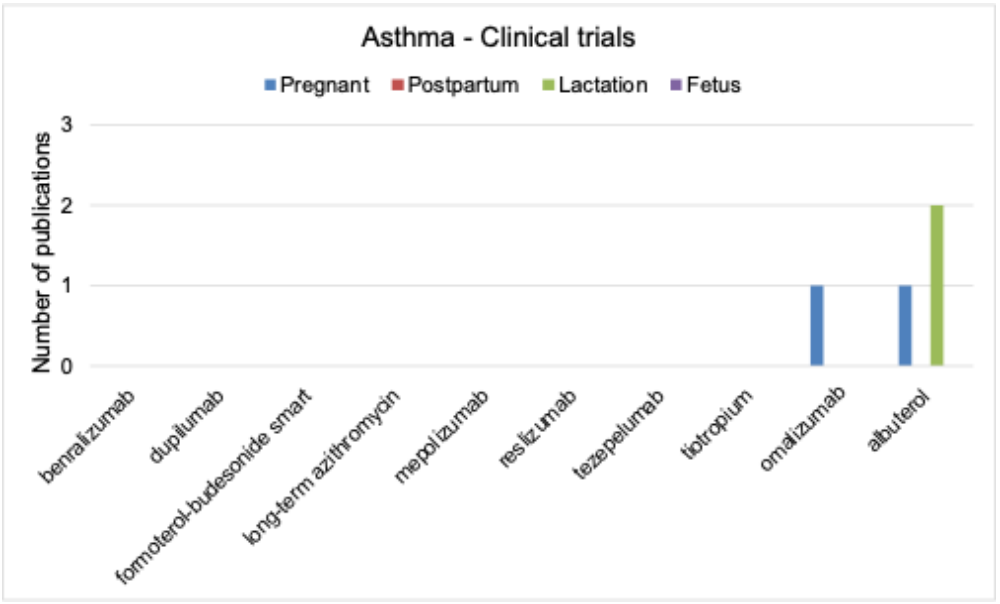

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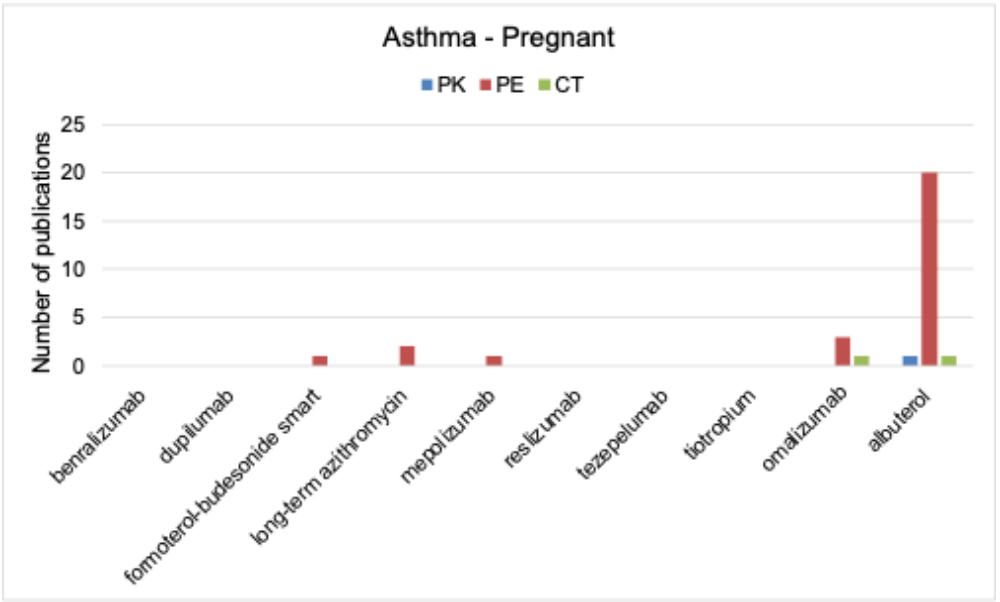

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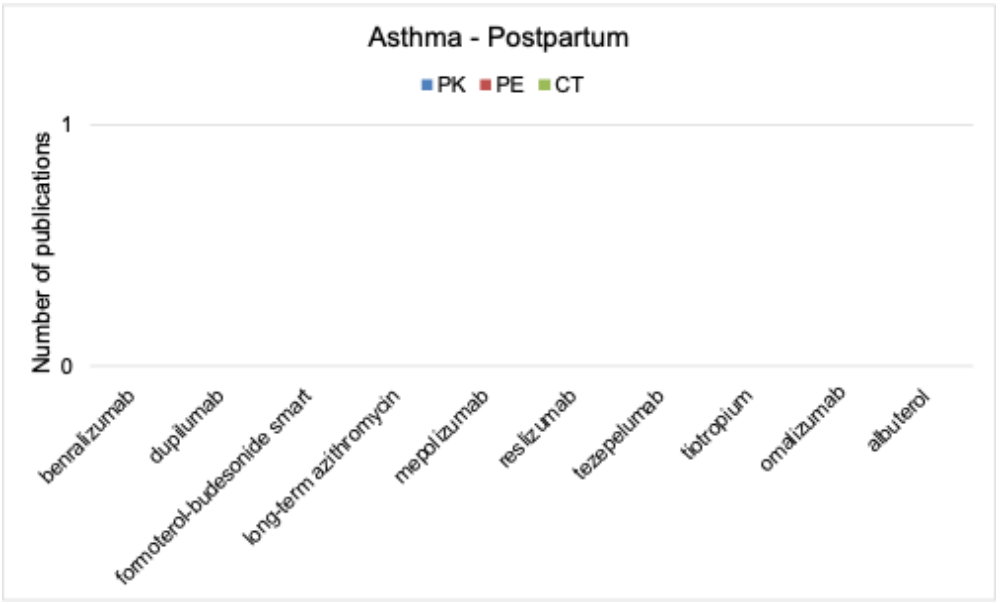

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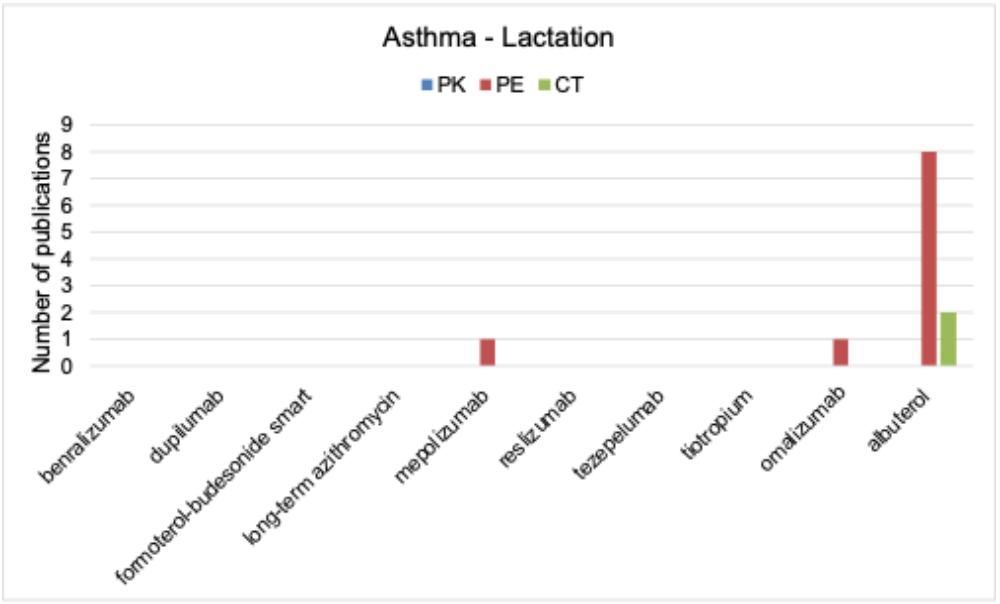

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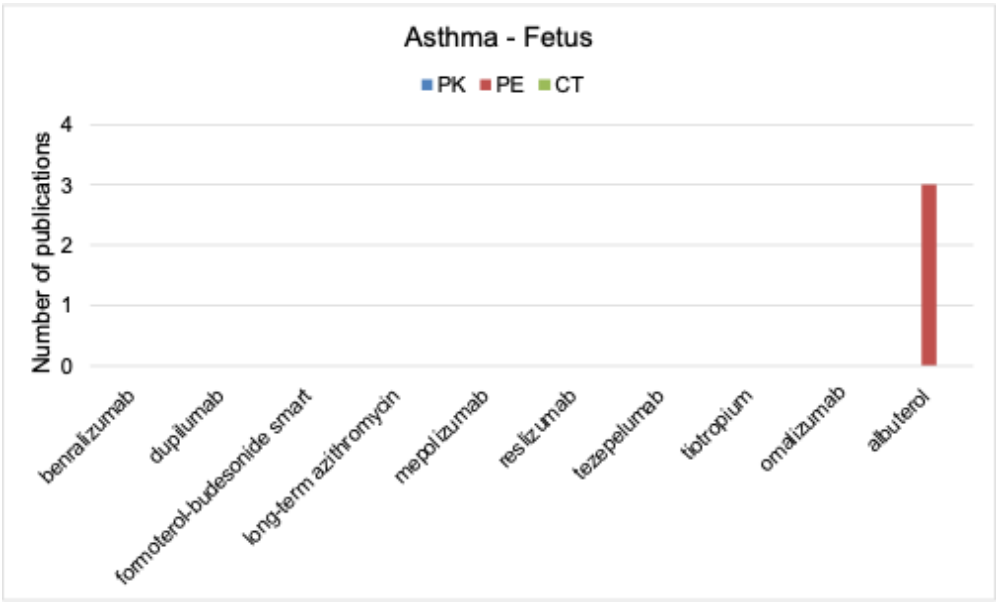

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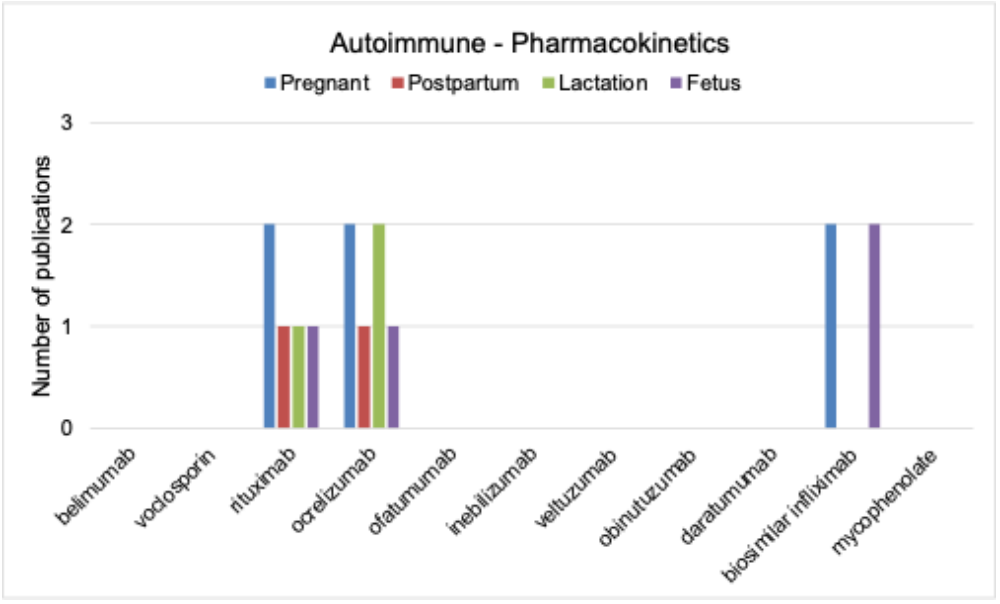

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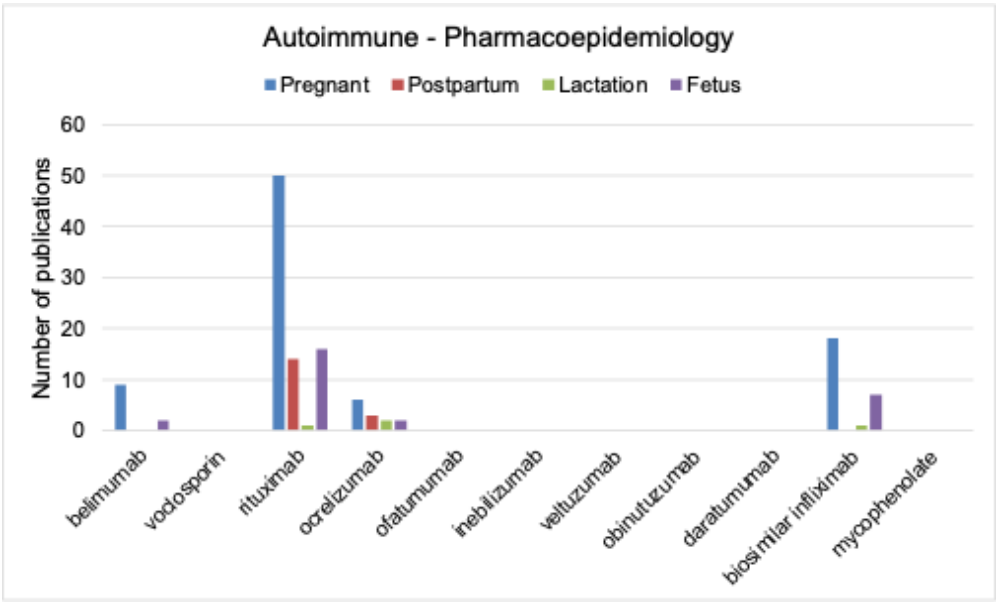

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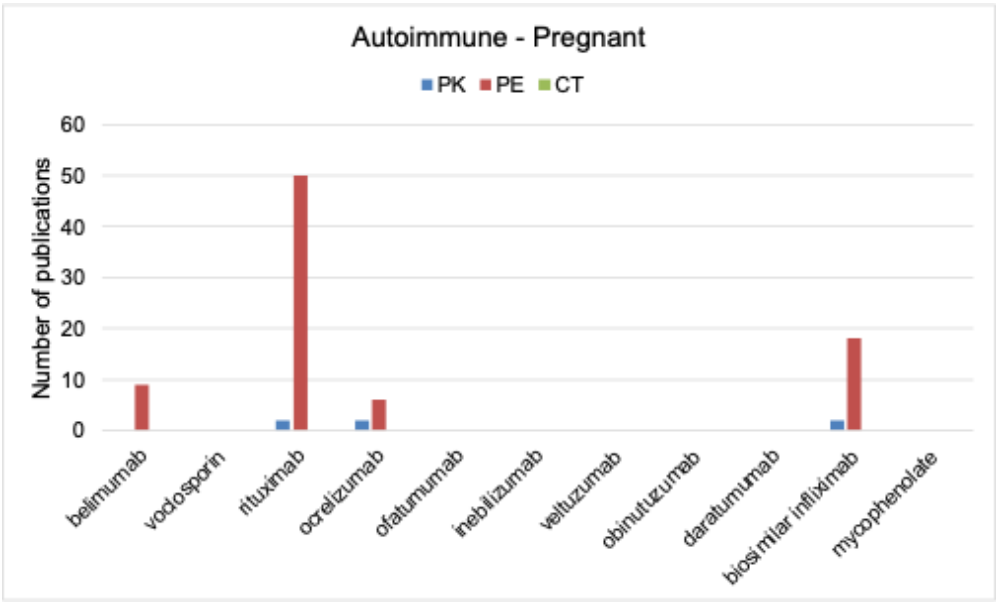

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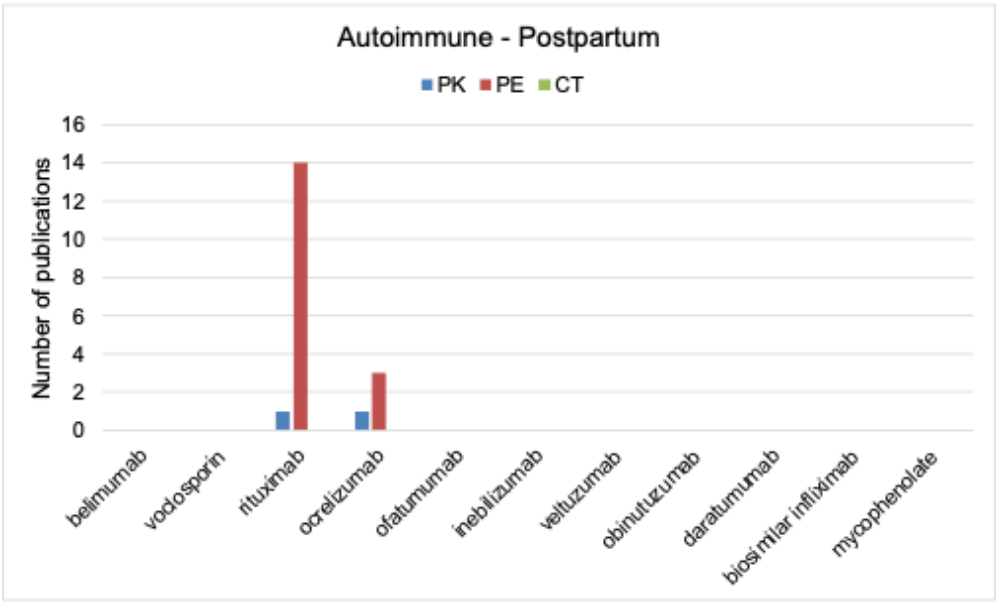

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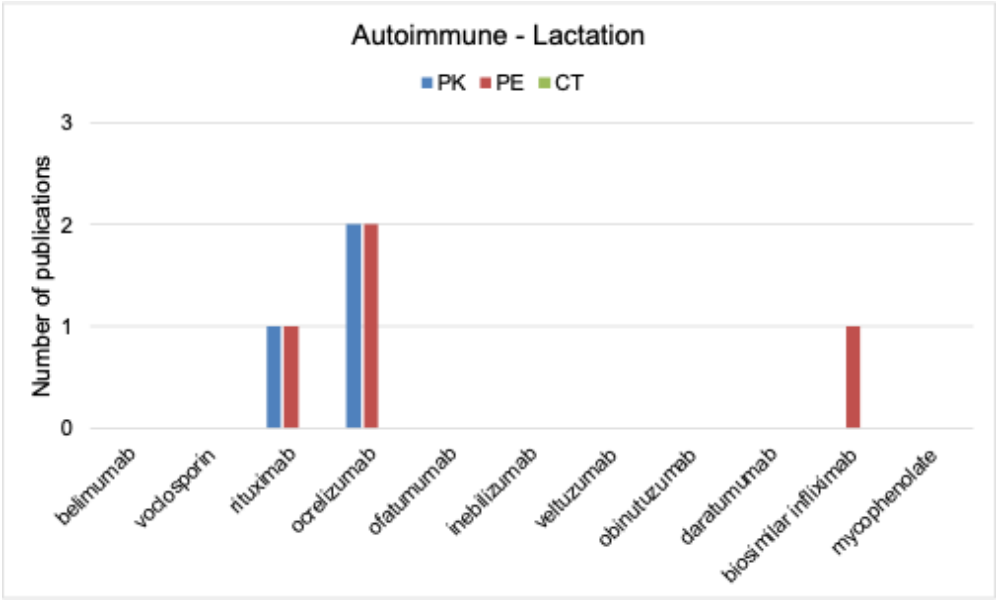

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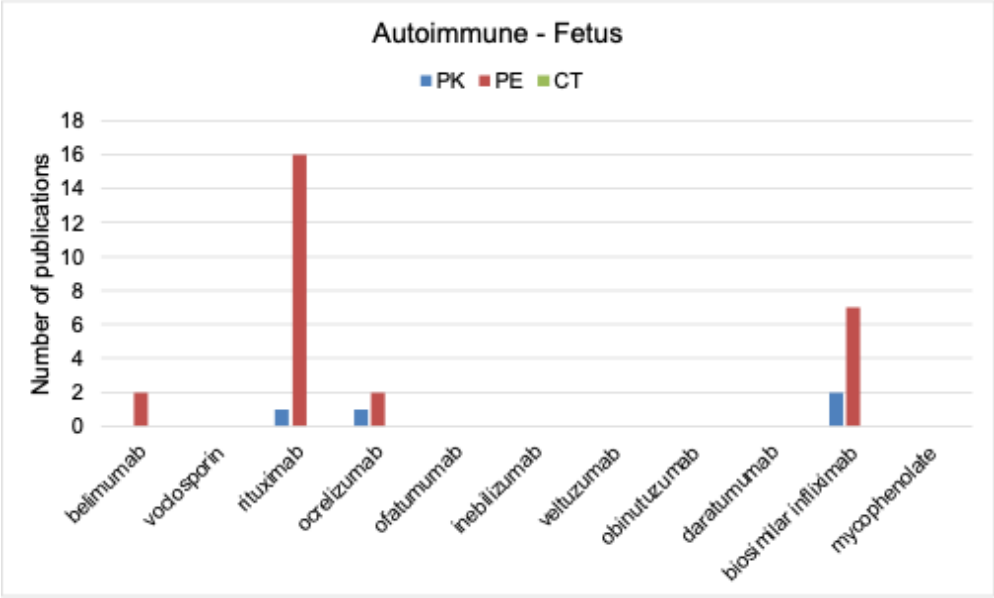
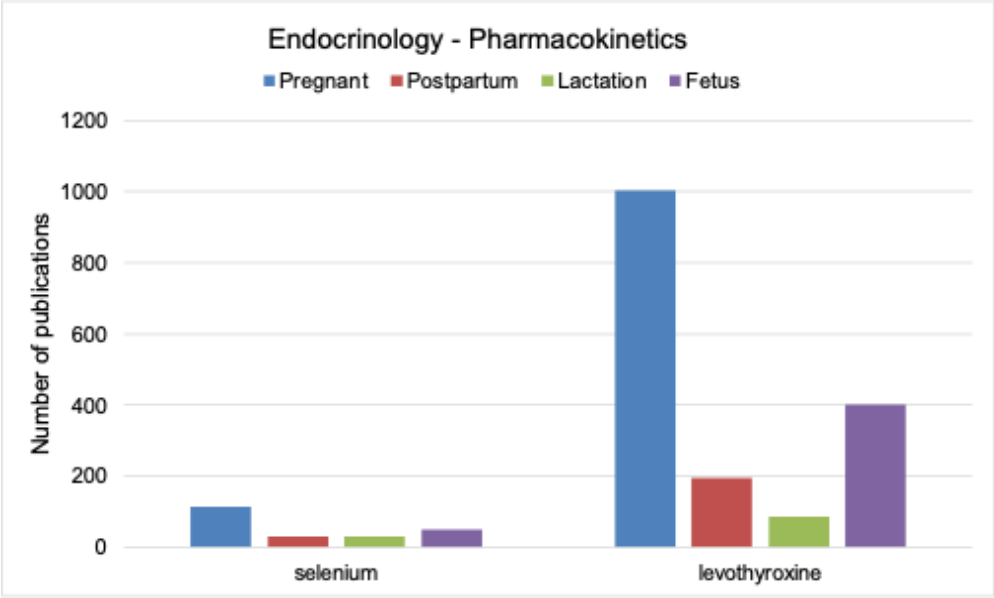


Endocrinology nominations



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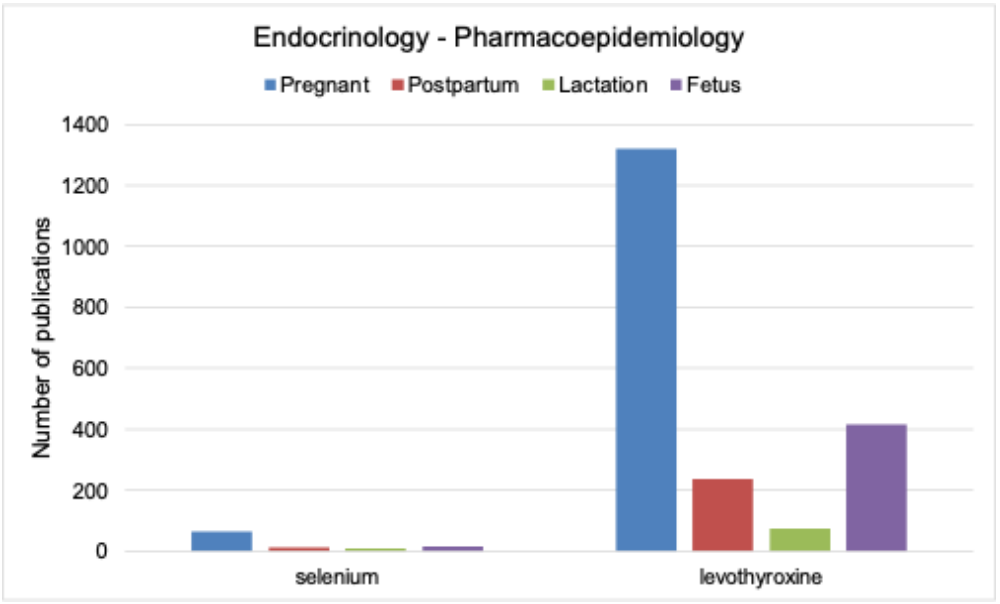

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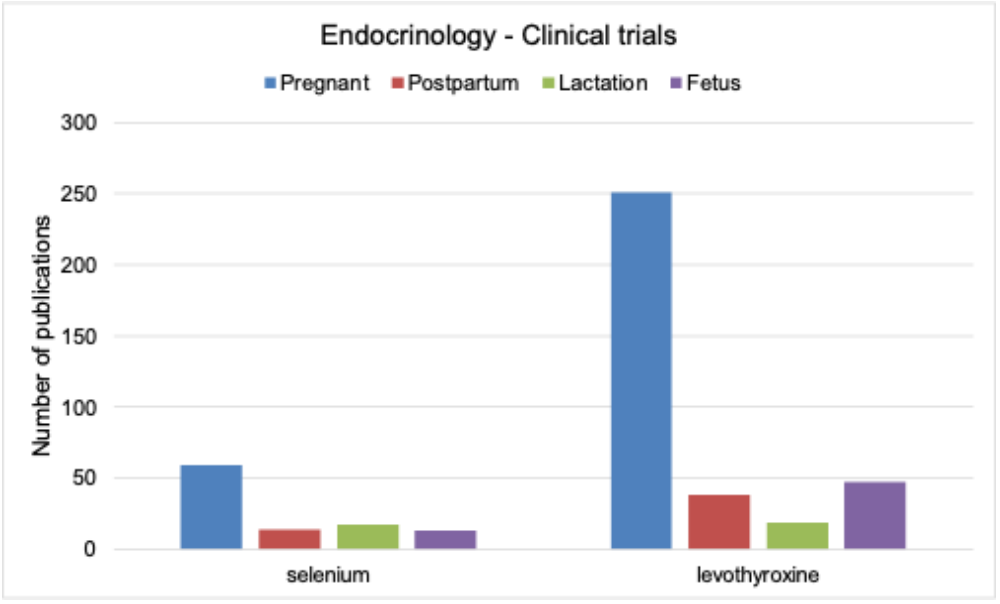

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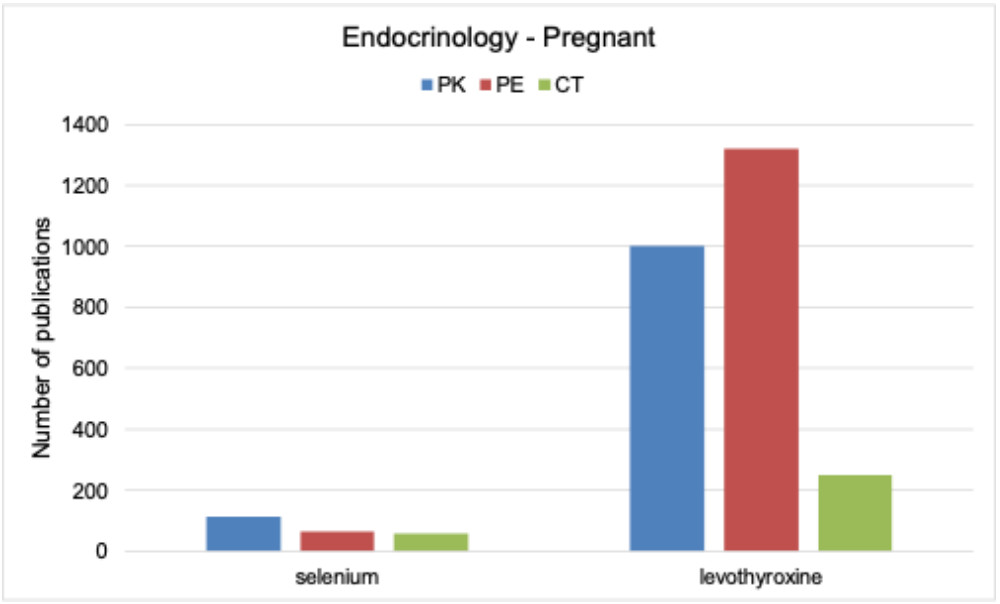

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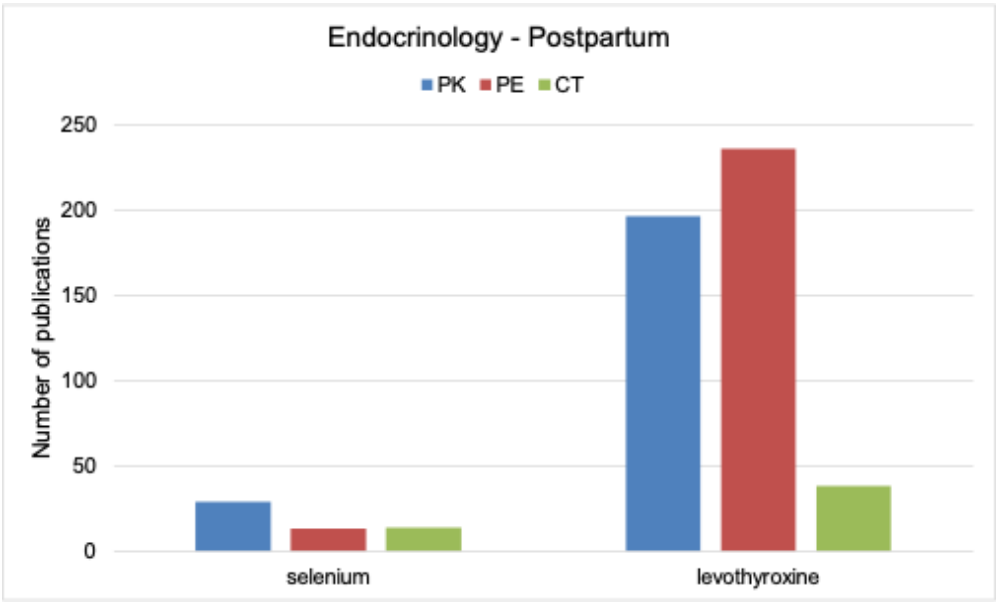

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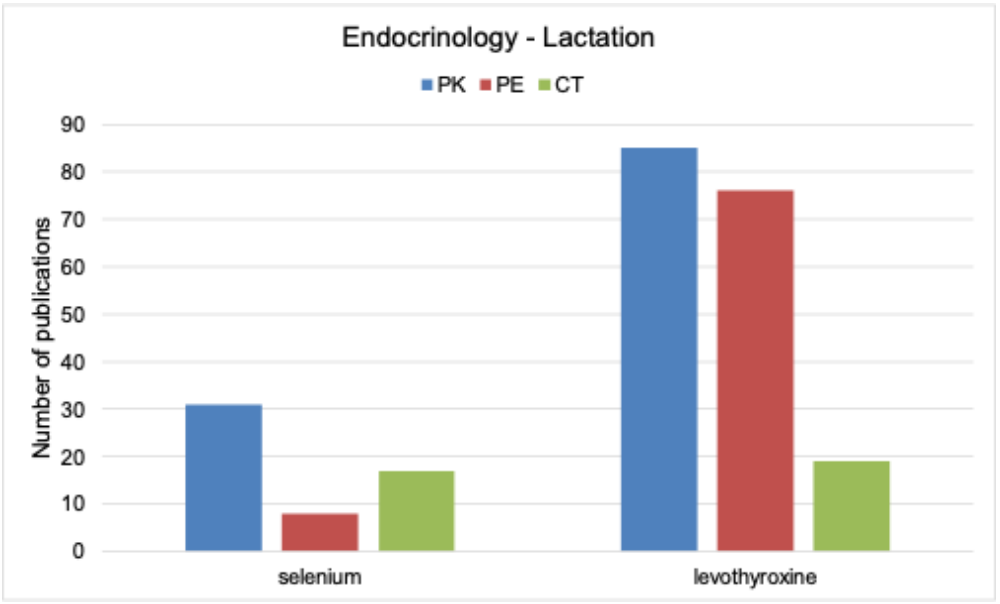

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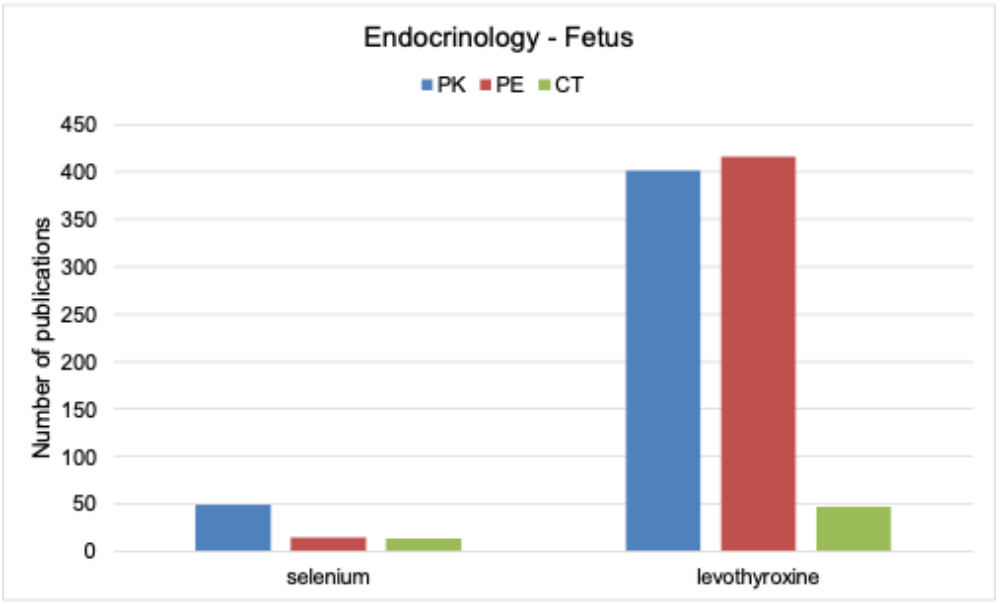

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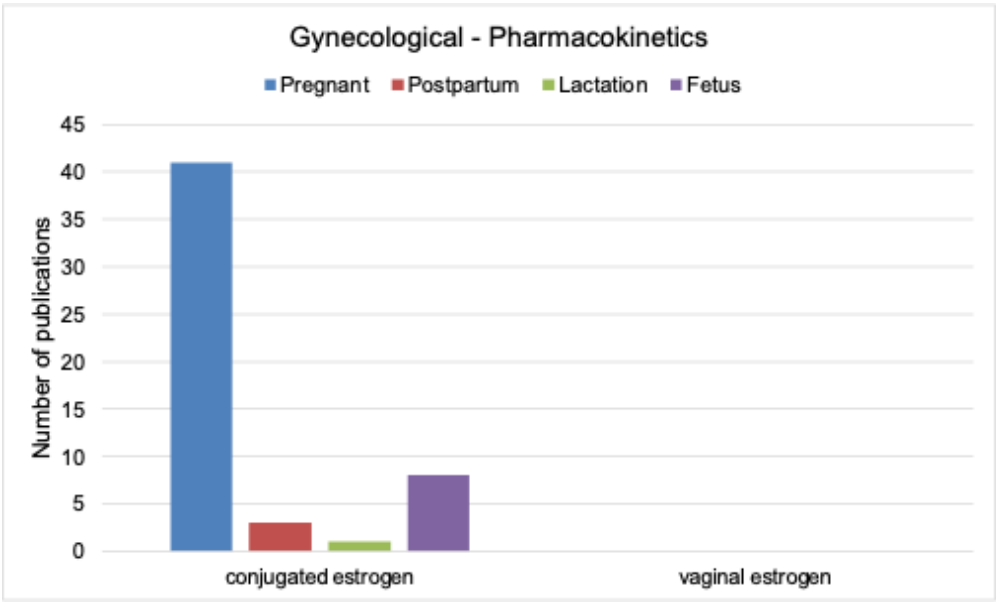

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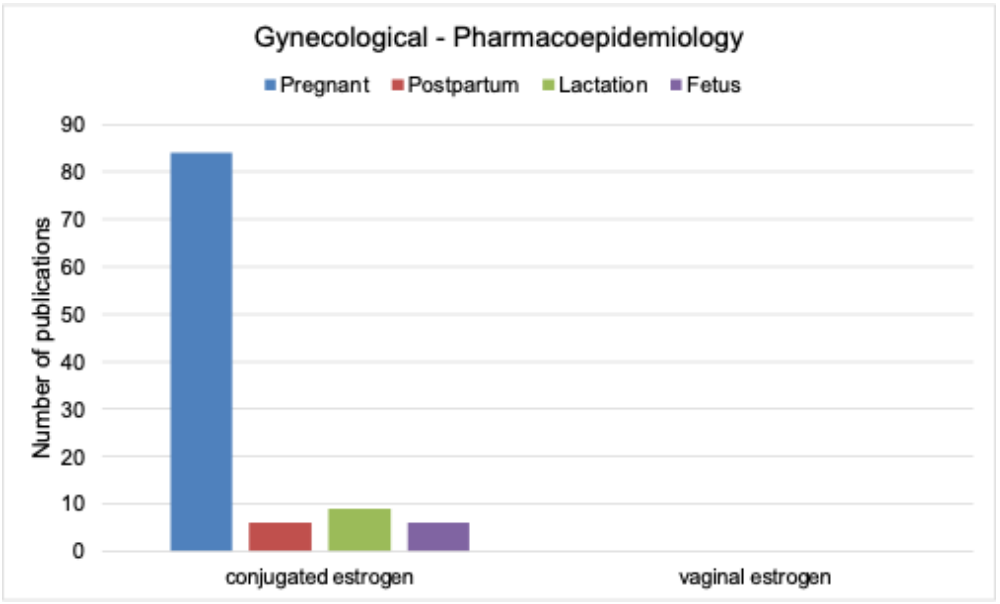

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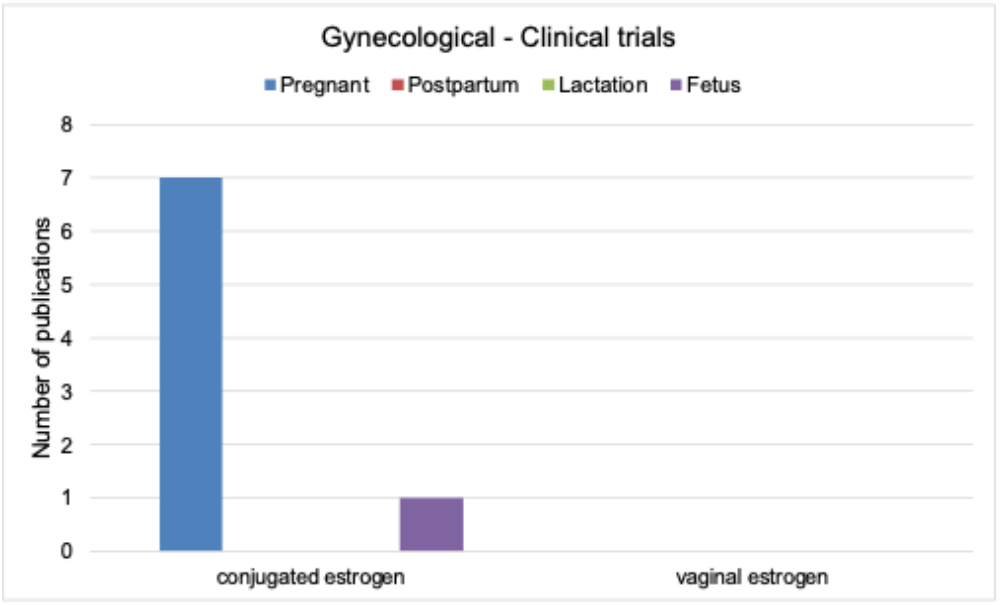

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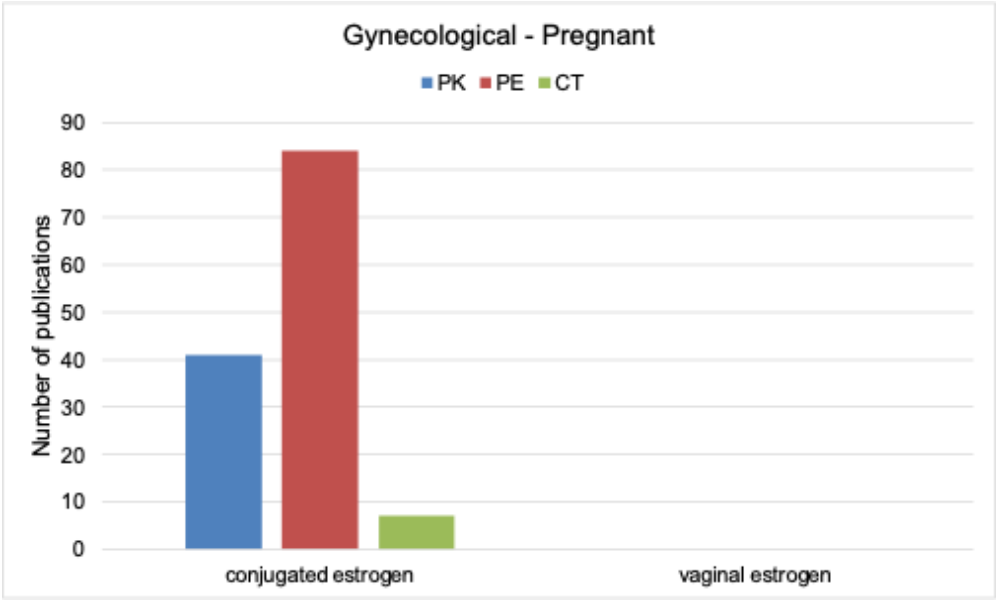

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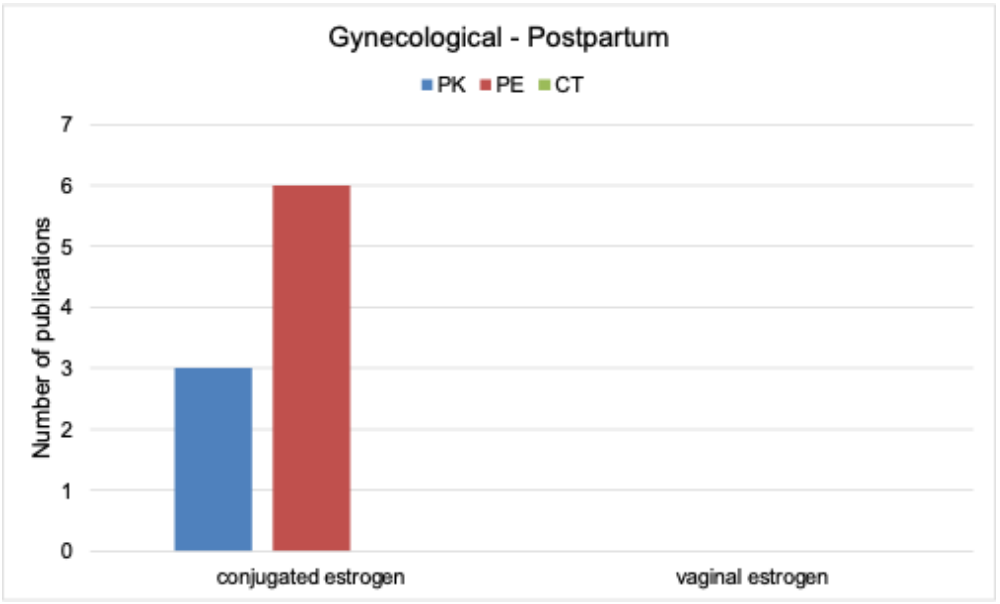

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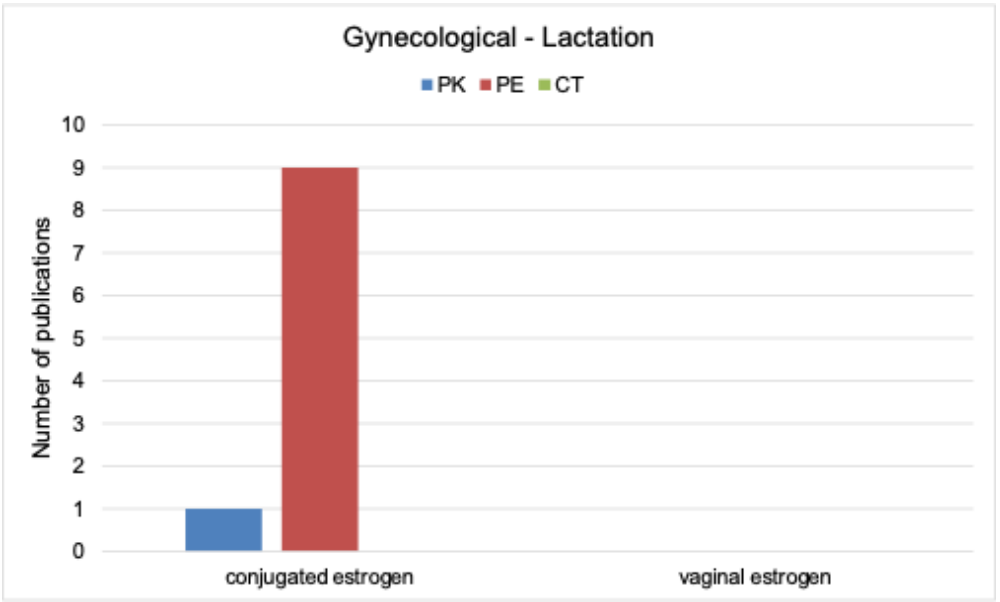

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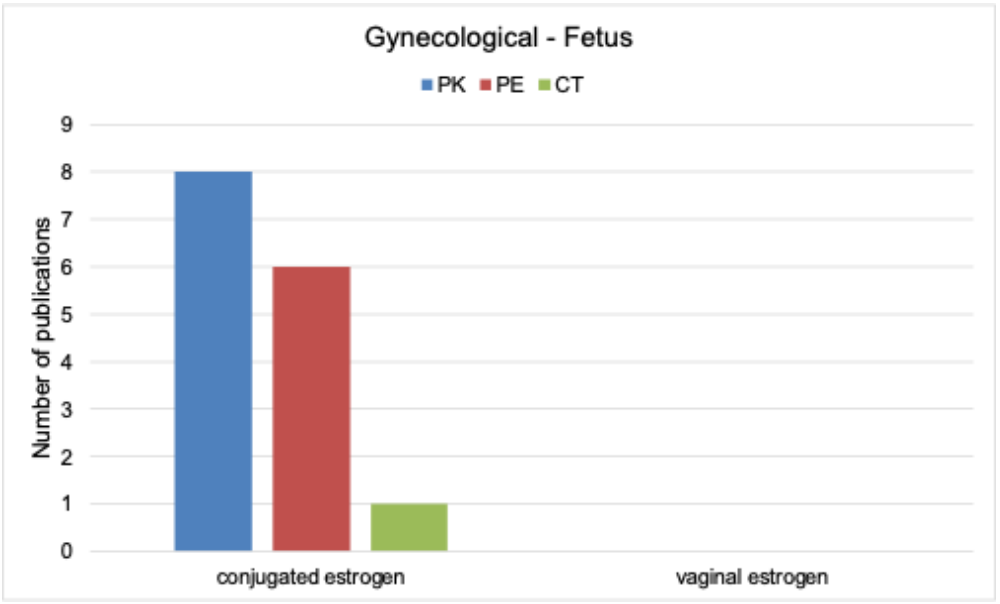
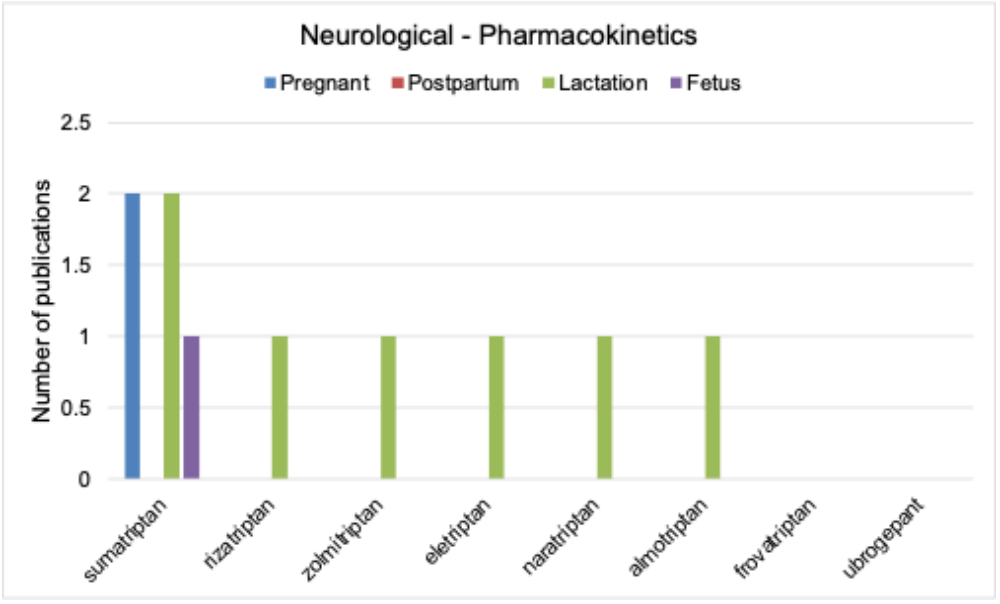


Neurological nominations



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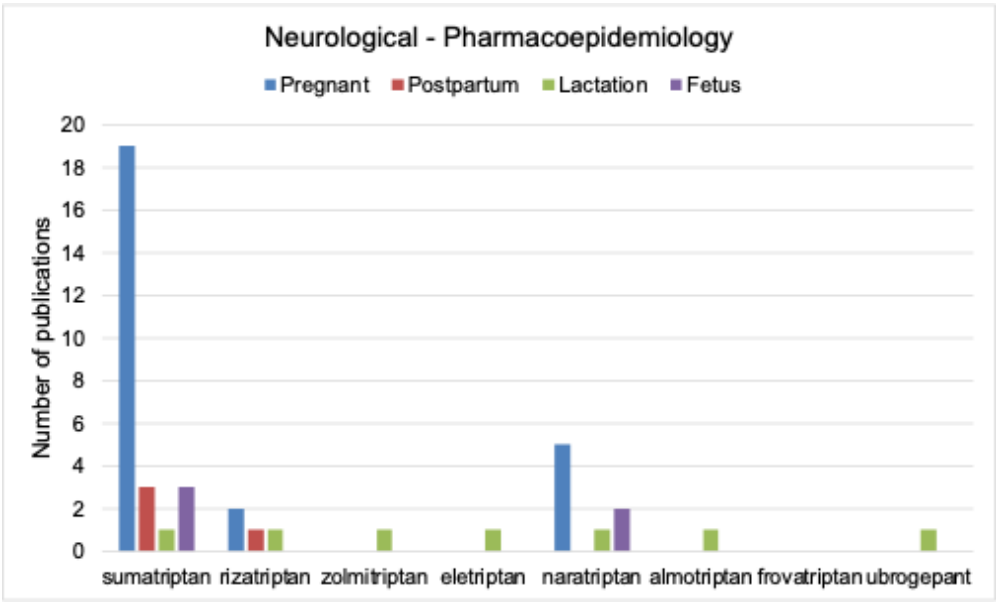

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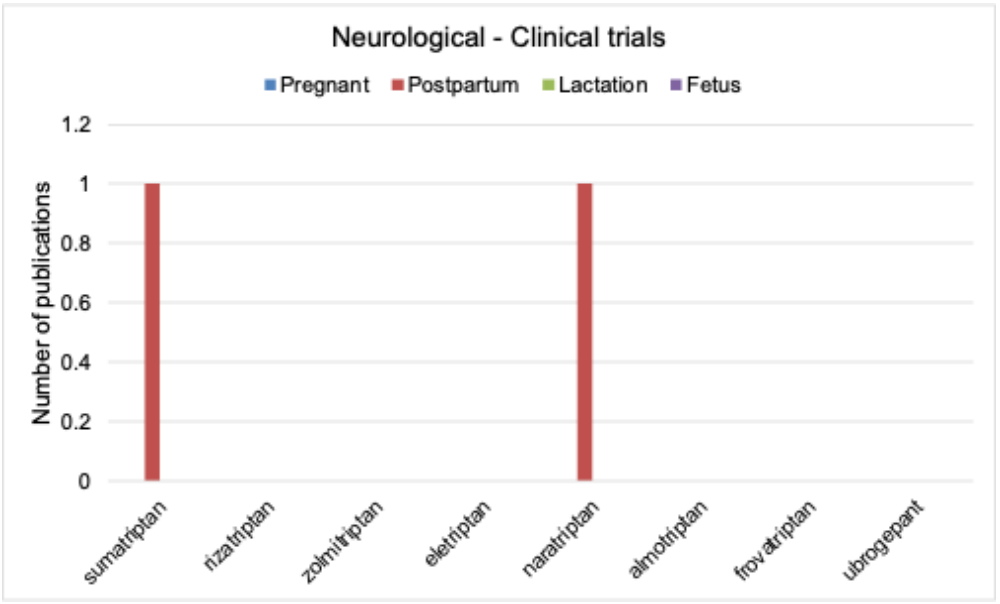

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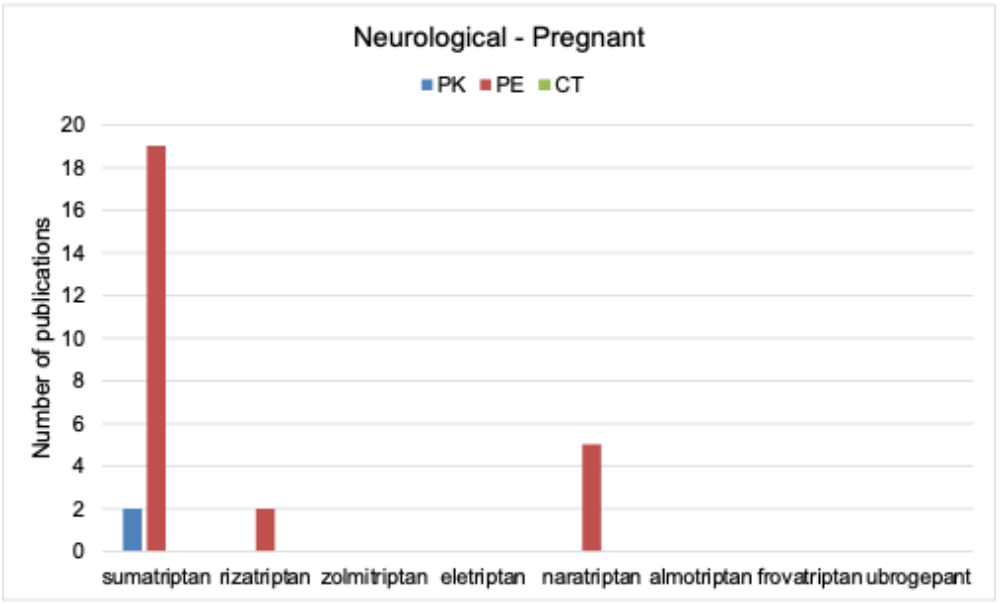

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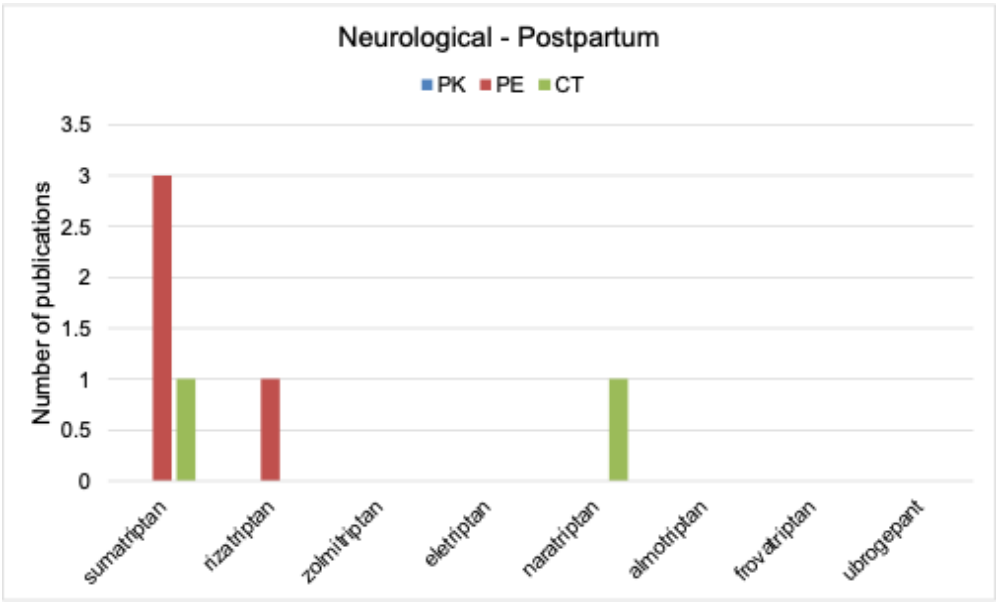

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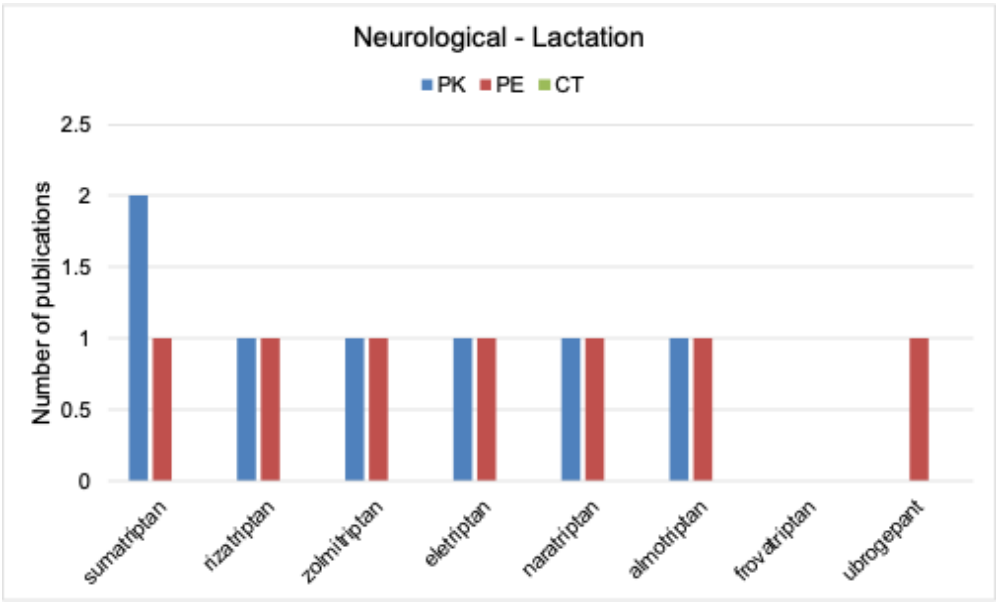

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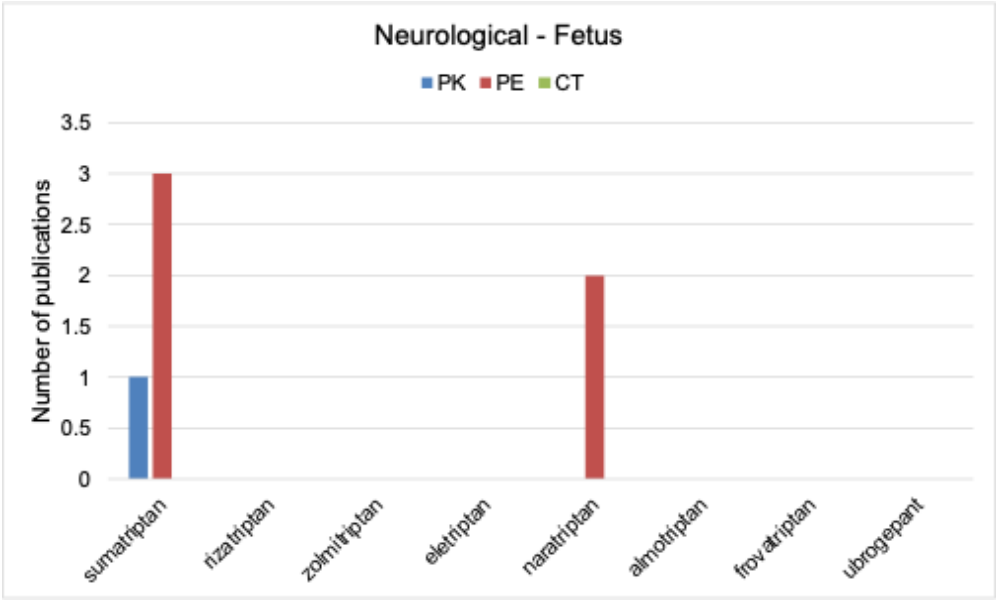
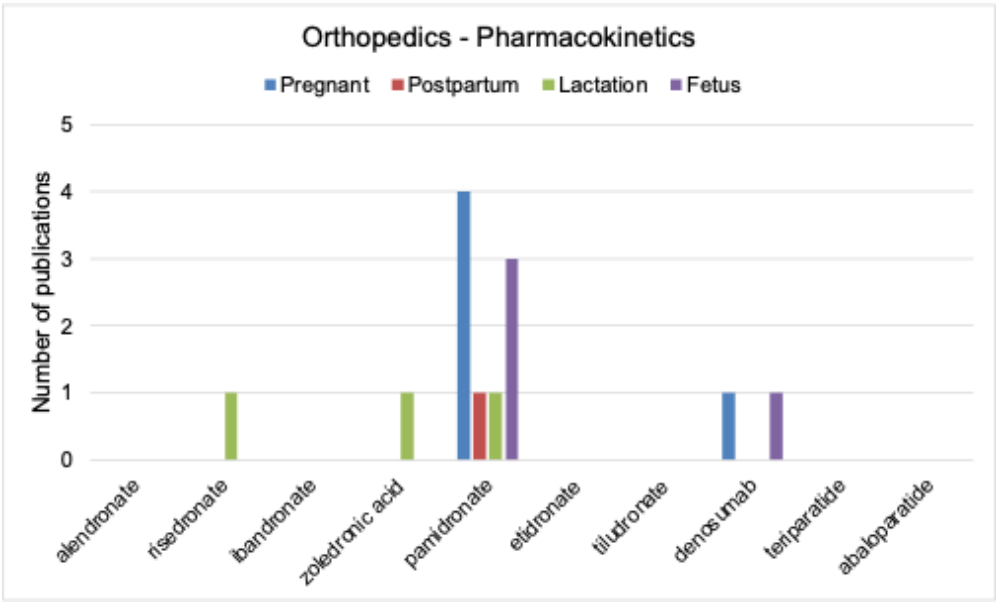
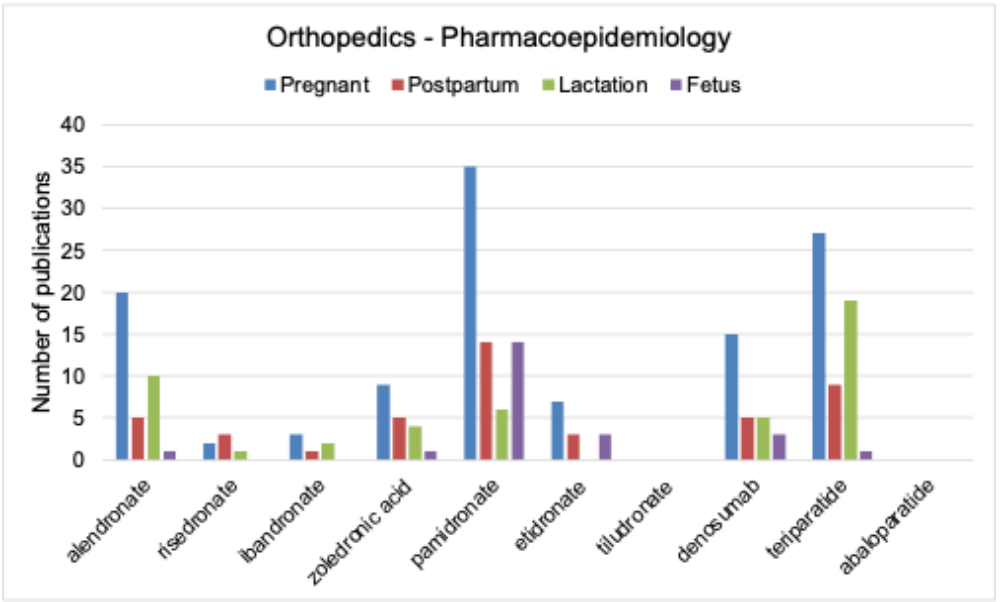


Orthopedics nominations



Orthopedics nominations



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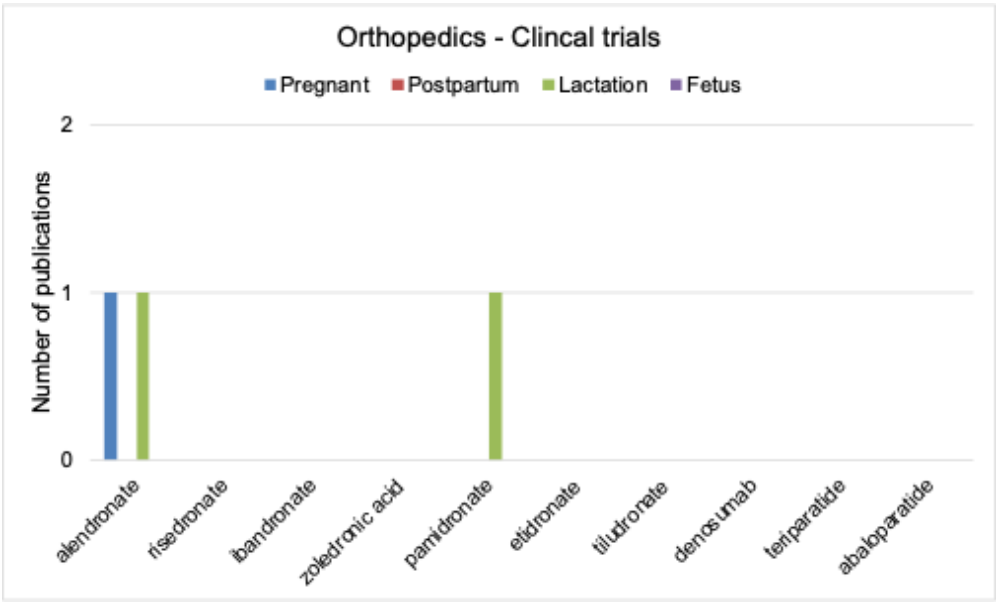

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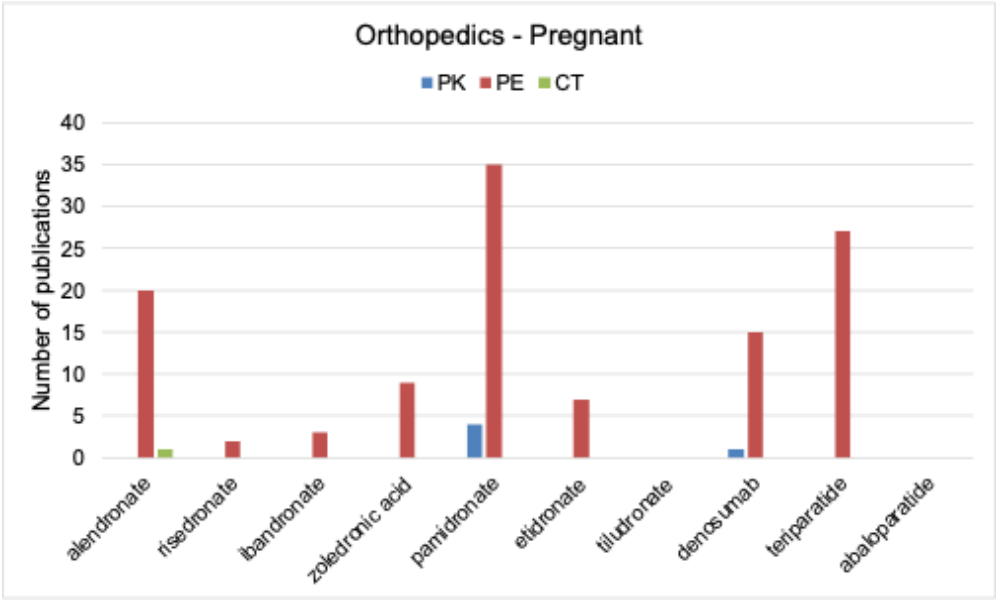

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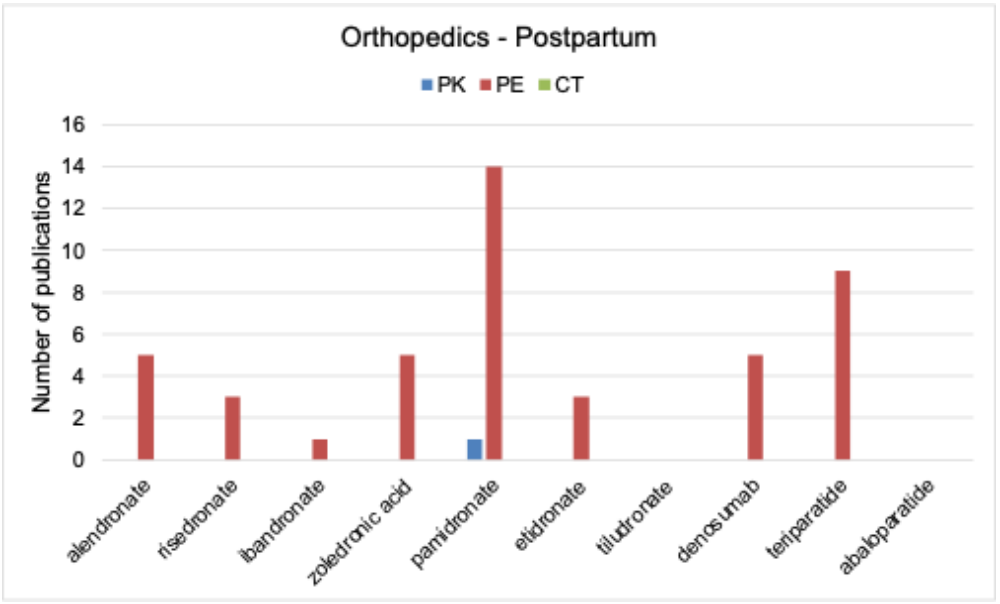

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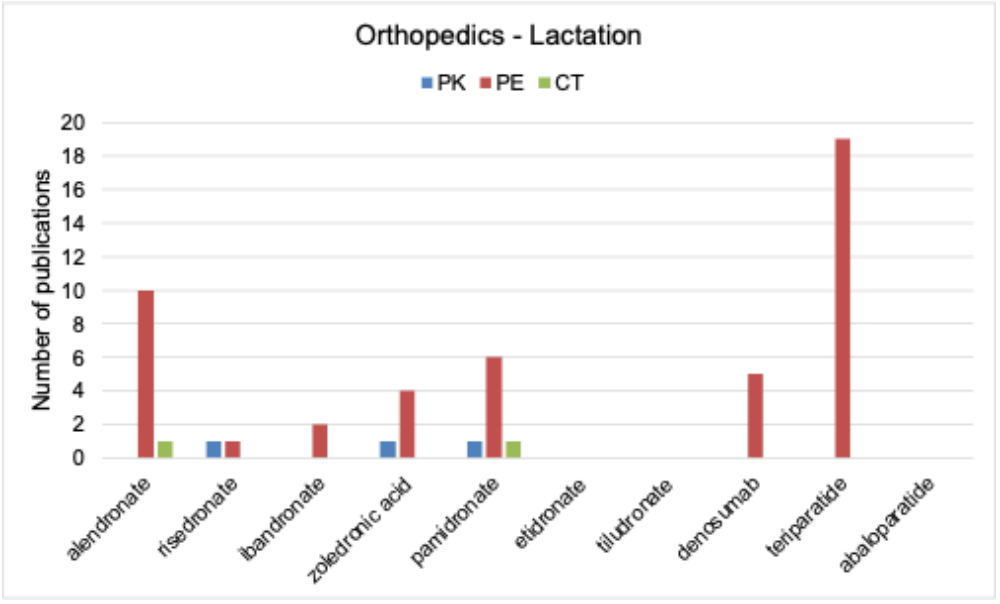

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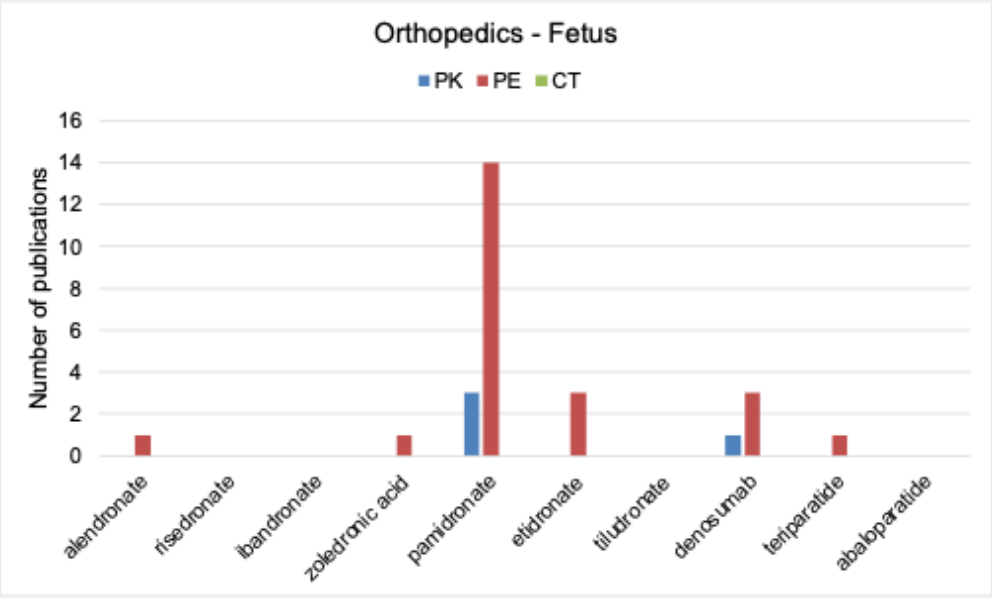
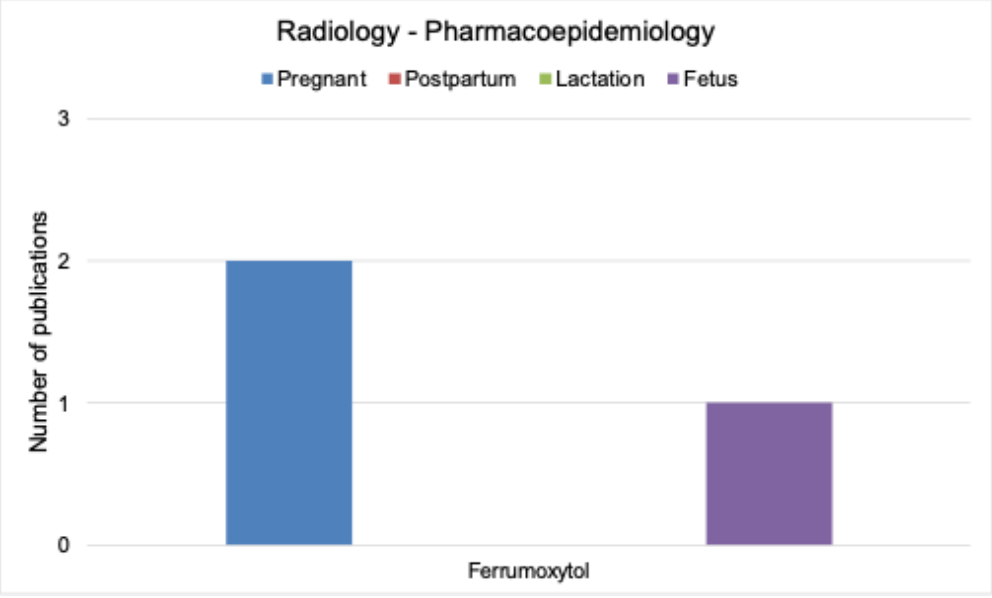
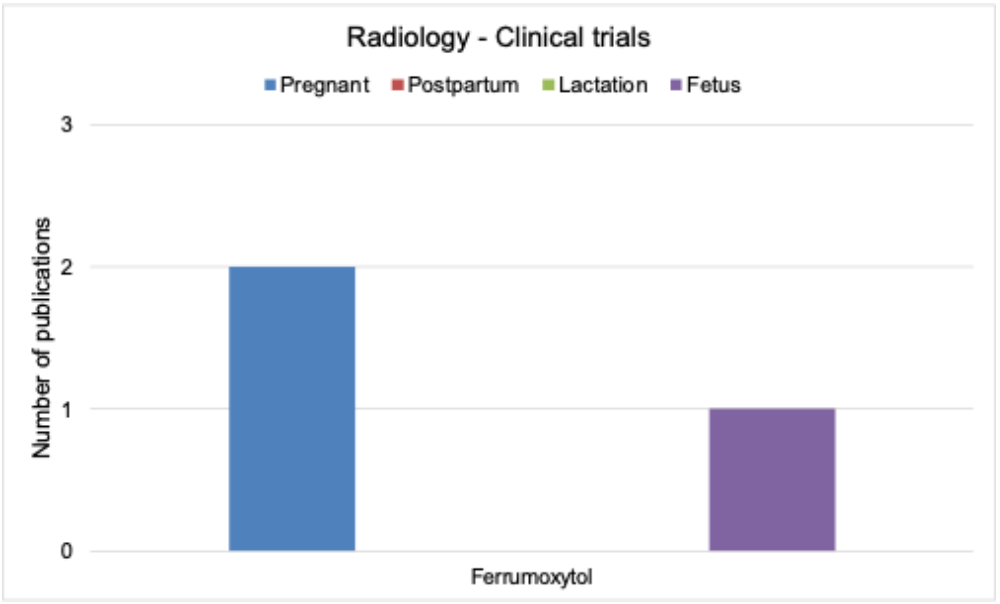


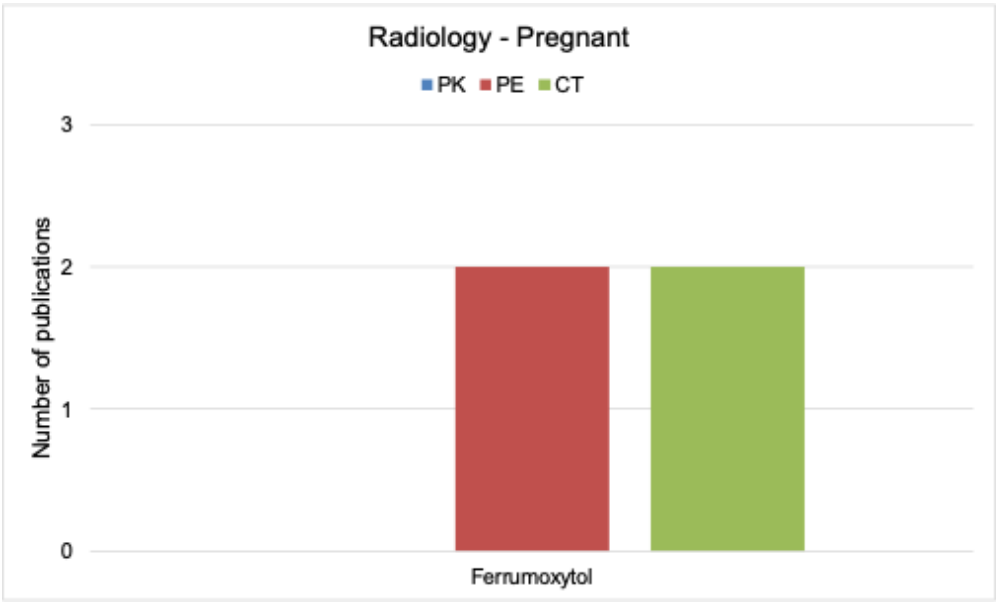
Radiology nominations



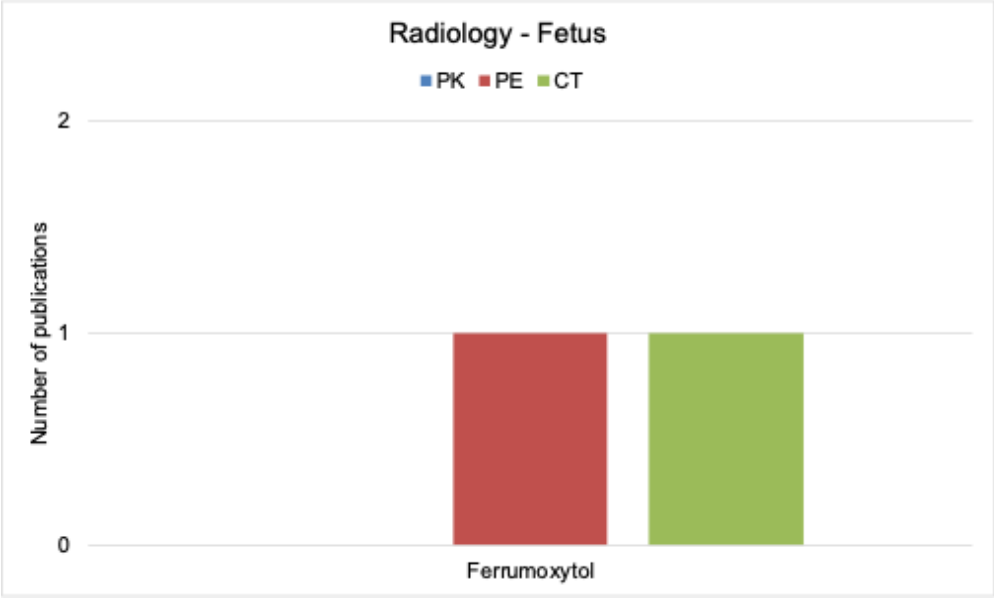
Radiology nominations



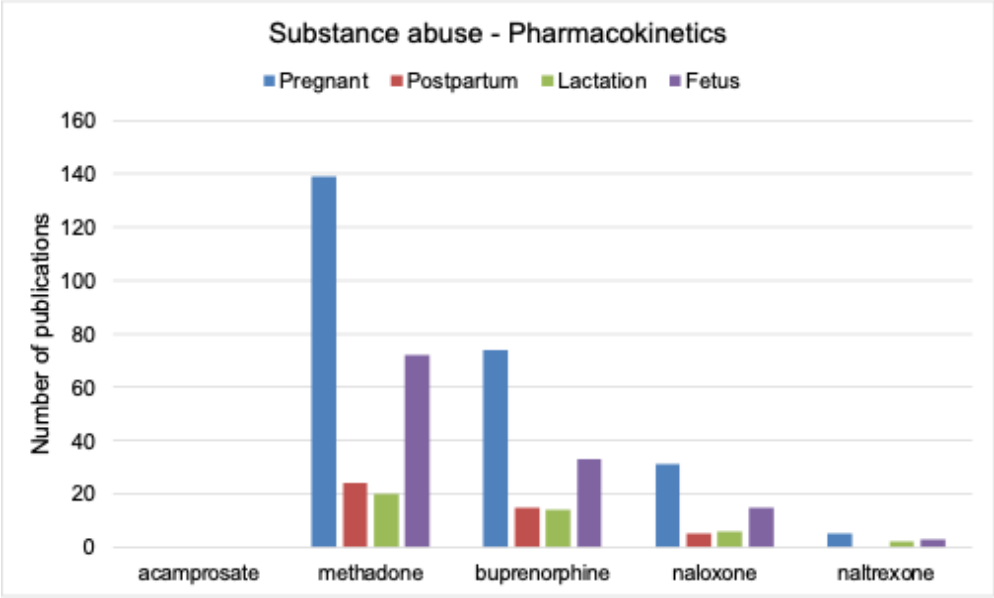
Radiology nominations



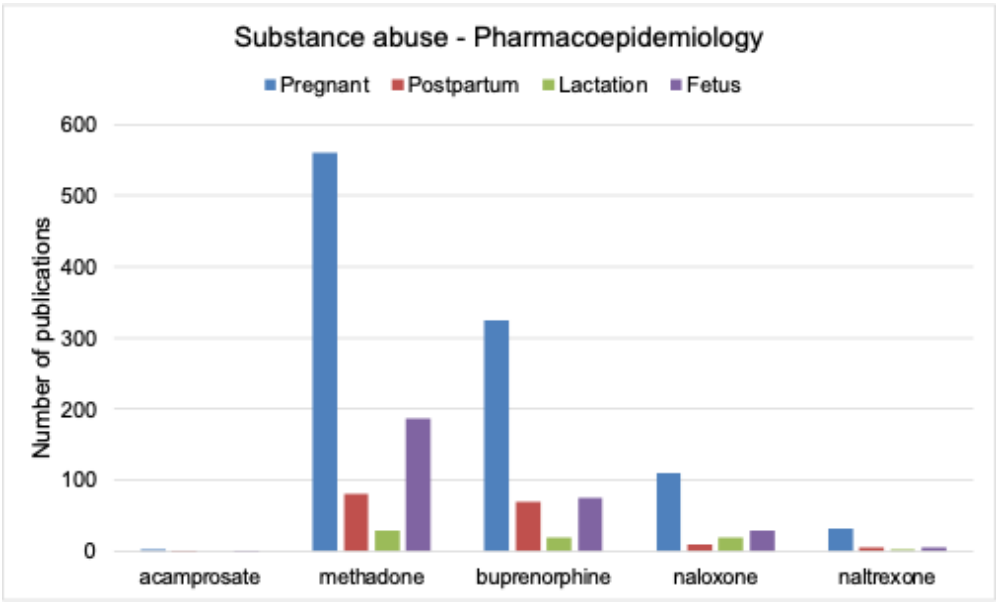
Radiology nominations



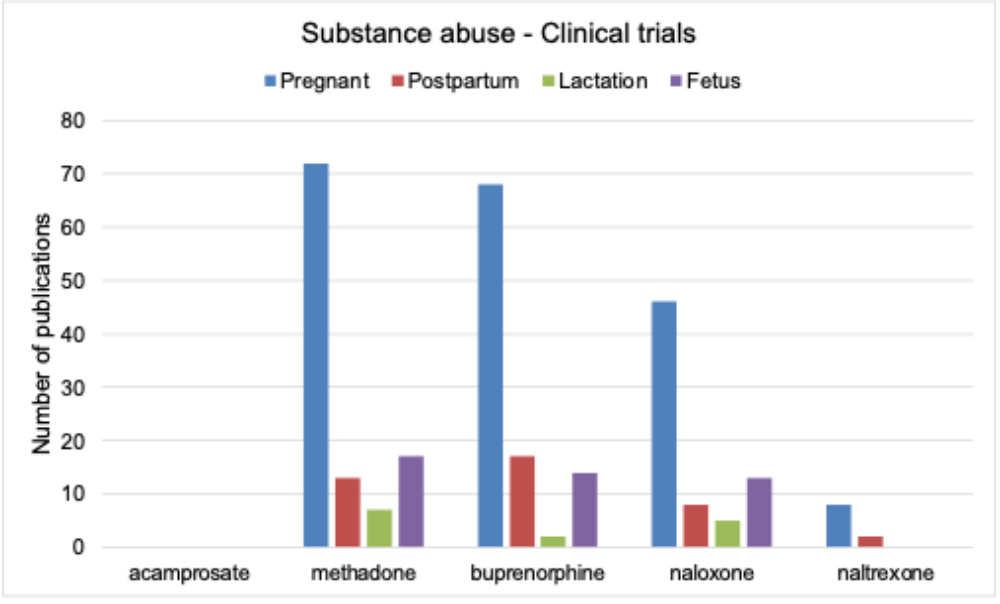
Substance abuse nominations



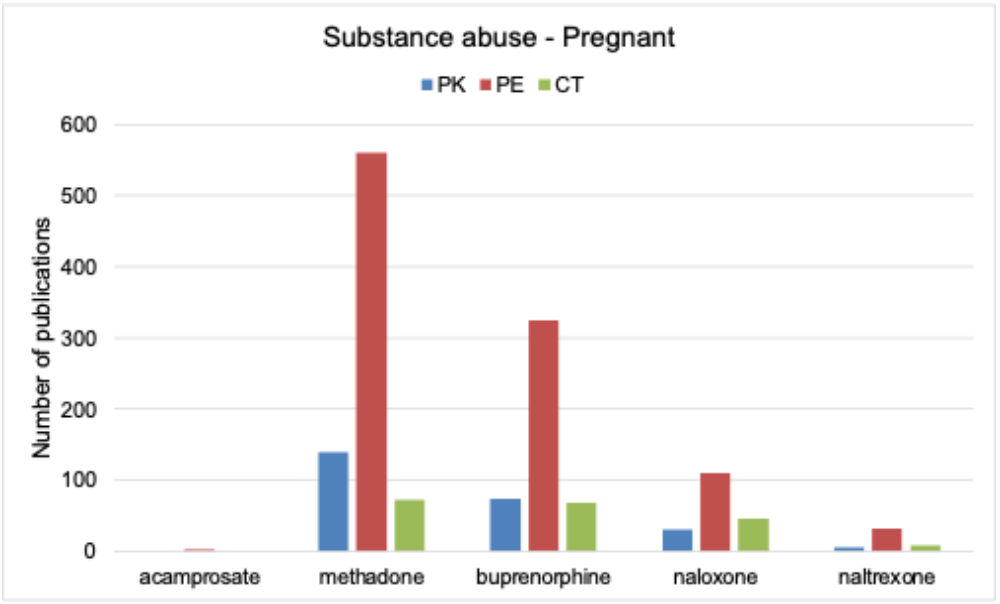
Substance abuse nominations



Substance abuse nominations



Substance abuse nominations



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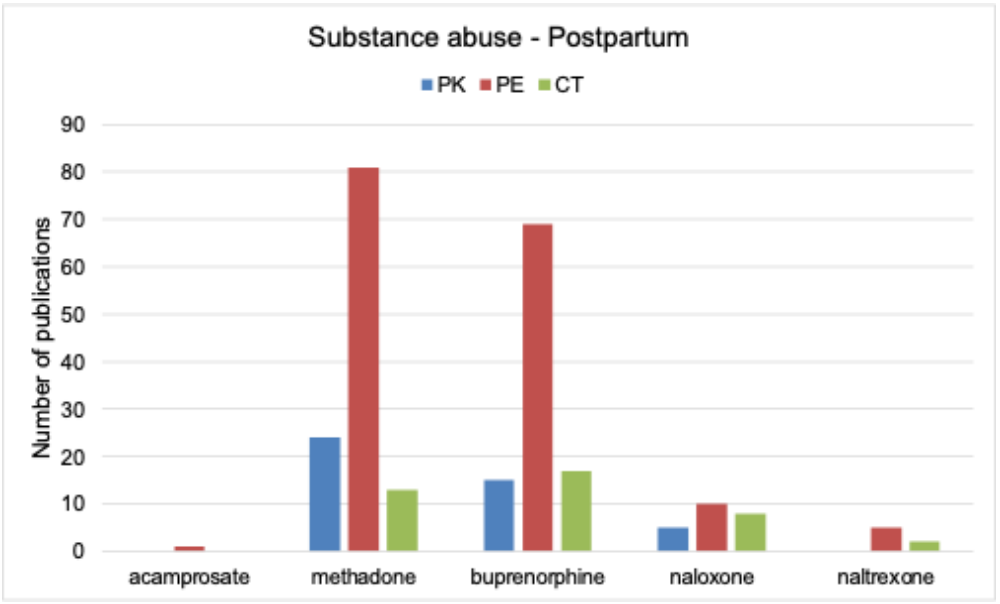
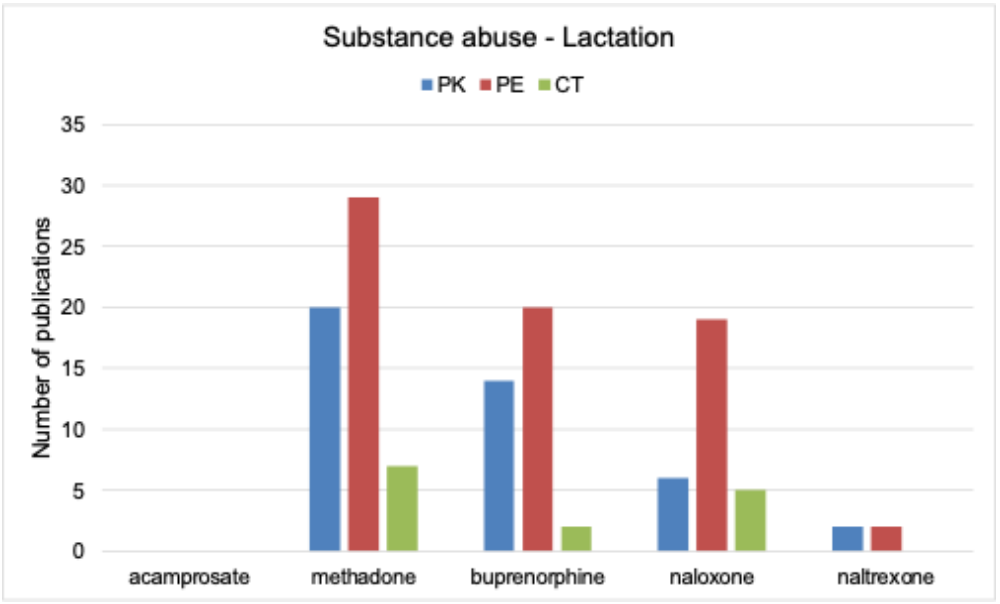
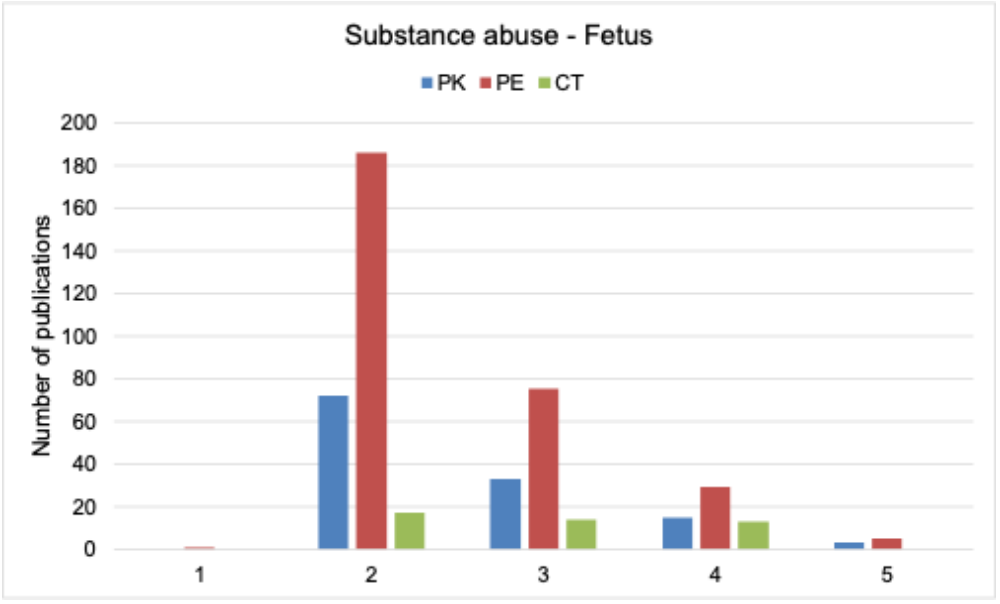


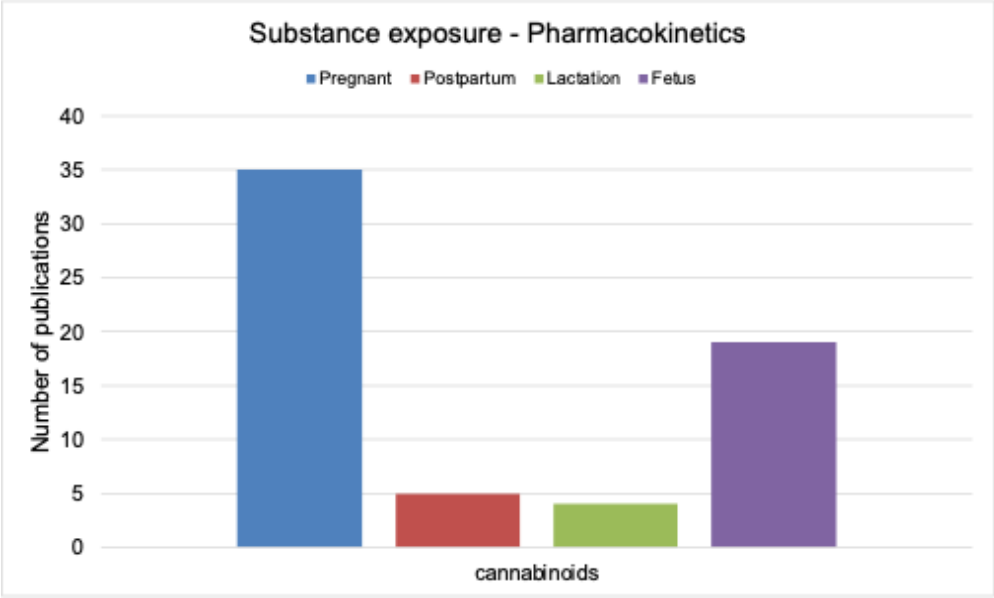
Substance abuse nominations



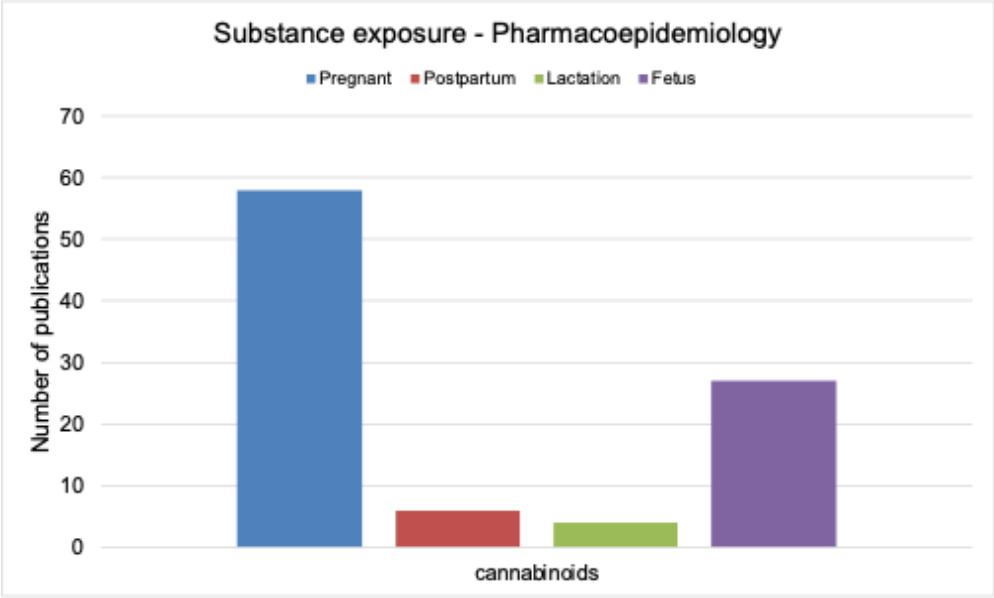
Substance abuse nominations



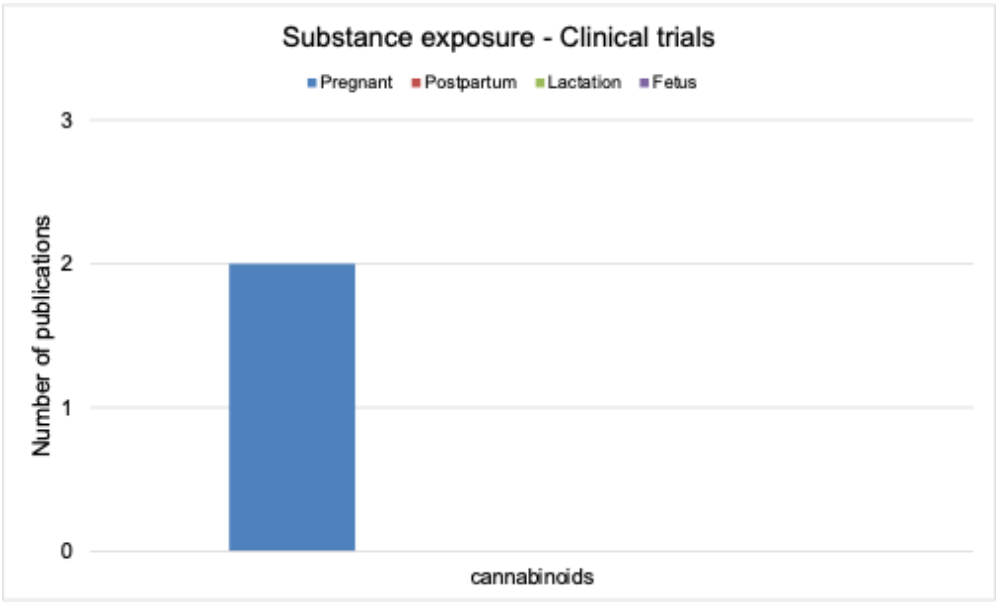
Substance exposure nominations



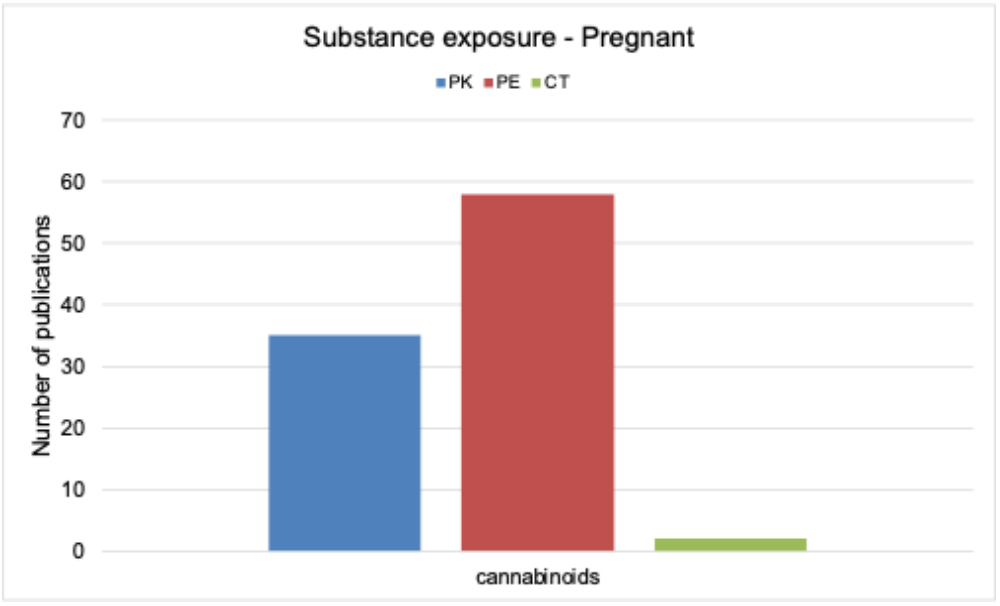
Substance exposure nominations



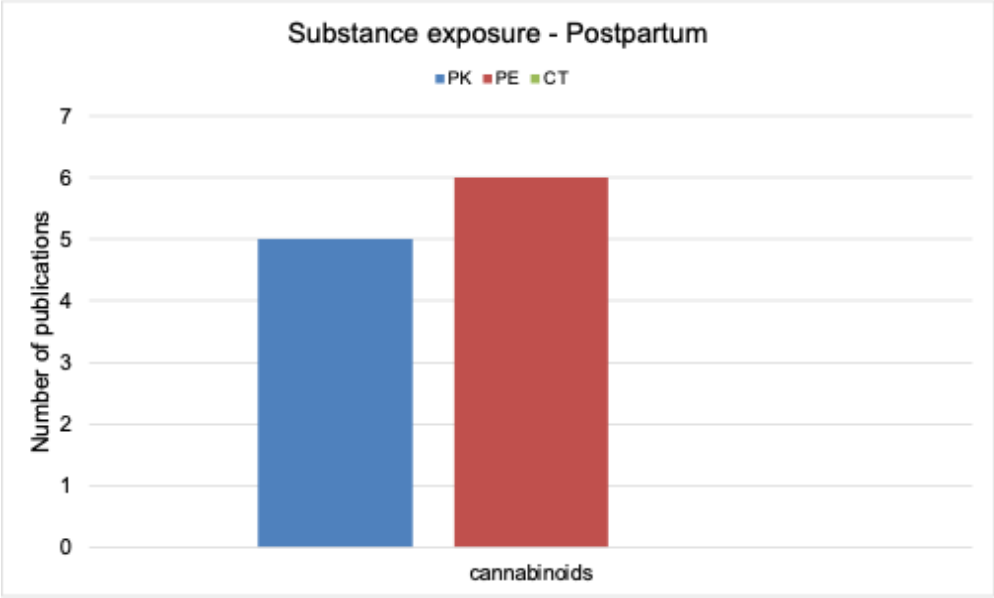
Substance exposure nominations



Substance exposure nominations



Substance exposure nominations



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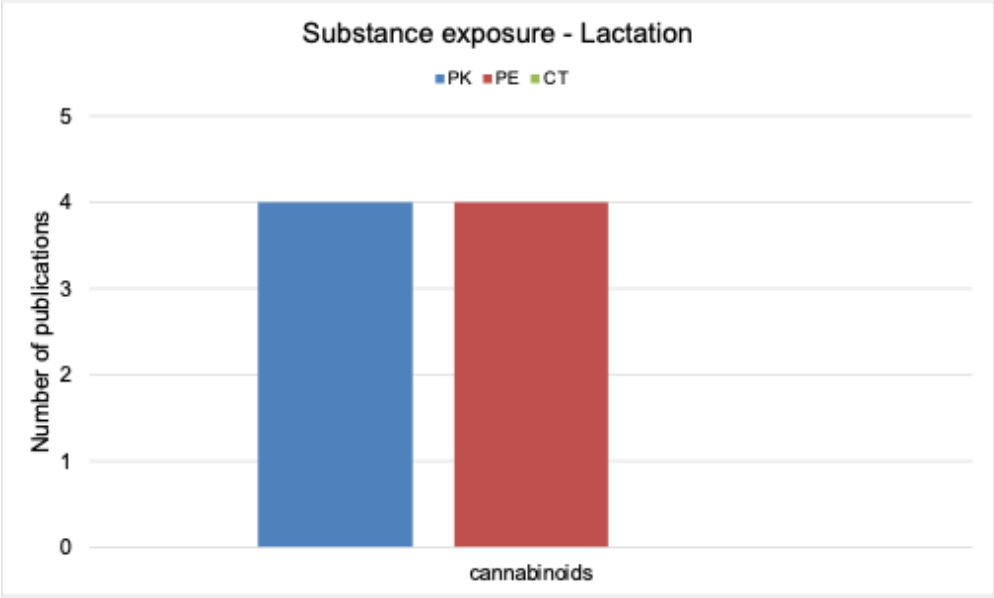

Substance exposure nominations