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Emulating a Target Trial in Perinatal Pharmacoepidemiology: Challenges and Methodological Approaches

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Abstract

Purpose of Review The objective of this review is to examine the application of target trial emulation in perinatal pharmacoepidemiology research. Given that randomized clinical trials—the gold standard for causal inference—are often not feasible or ethical for studying medication safety during pregnancy, alternative methodologies are critically needed. This paper delves into the challenges and potential mitigation strategies of using target trial emulation in the specific context of perinatal pharmacoepidemiology research.

Recent Findings Our review of identified studies ($n = 9$) reveals several unique considerations when leveraging target trial emulation for perinatal pharmacoepidemiology research. These include the alignment of the research question with the clinically relevant outcomes, identification of etiologically relevant time windows, defining relevant treatment strategies, and anchoring of exposure, eligibility criteria, and the start of follow-up. Despite these challenges, the methodology shows promise in bridging the gap between randomized clinical trials and observational research through the employment of a transparent and well-defined approach.

Summary Target trial emulation serves as a valuable tool in perinatal pharmacoepidemiology, allowing researchers to generate more reliable evidence concerning medication safety during pregnancy. Although the approach comes with specific challenges, strategies can be implemented to mitigate these difficulties. Overall, the adoption of target trial emulation has the potential to substantially enhance evidence quality, inform clinical decisions, and ultimately improve health outcomes for birthing people and their infants.

Keywords Perinatal pharmacoepidemiology · Target trial emulation · Pregnancy · Observational data · Real-world evidence

Introduction

Randomized clinical trials (RCTs) are widely recognized as the gold standard for estimating causal effects [1]. However, pregnant individuals have been systematically excluded from participation in RCTs due to ethical concerns around the unknown safety profile of the medication under study, and the potential harms posed to both the birthing person and the fetus [2•]. This has raised considerable uncertainty regarding the efficacy and safety of medications used during pregnancy [3]. Consequently, the use of healthcare databases, including electronic medical records, administrative health, and insurance claims, are commonly used to assess safety concerns for medication use during pregnancy [4, 5•, 6•]. These data sources provide a means of overcoming challenges related to the feasibility of conducting a RCT or reliance on passive surveillance systems (i.e., mandated registries), including the generalizability/transportability of findings, sufficient sample

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size, and, importantly, the generation of evidence in a timely fashion. However, observational studies of comparative effectiveness and safety using these data are susceptible to common biases including confounding, selection, misclassification, and immortal time [7, 8].

Hernán and colleagues have proposed an approach to address the feasibility of conducting clinical trials in a timely fashion and the common biases inherent in observational studies [9]. This approach, known as *target trial emulation*, involves leveraging observational data to explicitly mimic a hypothetical pragmatic trial when such a trial is not feasible or ethical. To facilitate emulating a target trial, researchers need to provide a clearly defined protocol for both the hypothetical trial and its emulation using observational data with seven key components, including (1) participant eligibility; (2) the assigned treatment strategies, including their specific start and end times; (3) assignment procedures; (4) the start and duration of the follow-up period; (5) the primary outcome of interest; (6) the causal comparisons of interest; and (7) the analytical plan [9]. The process of explicitly outlining the characteristics of the emulated trial aims to minimize biases inherent in observational studies and facilitates aligning the research question and causal parameter of interest [9, 10].

Perinatal pharmacoepidemiologic research using observational data presents unique challenges to causal inference. These challenges include identifying pregnancies, the comparatively short timescale of pregnancy compared to many other outcomes studied in pharmacoepidemiology, the time-dependent nature of sensitive periods of exposure and outcomes defined based on gestational age, varying lengths of gestation, and left censoring and truncation, all of which can introduce time-related biases if not considered in the design and analysis of the study [11]. The target trial approach can be a powerful tool to address these possible sources of bias; however, care is needed to appropriately generate and interpret evidence from these studies [12].

Given the many considerations inherent in target trial emulation and the recent uptake of this approach, the primary aim of this review is to provide an overview of methodologic challenges common to perinatal pharmacoepidemiology research, and ways in which recent target trial emulations have sought to mitigate biases arising from these challenges. This review will also provide a discussion of the potential role and considerations for the implementation of target trial emulation in future studies in perinatal pharmacoepidemiology.

Methods

We conducted a literature search in Medline, EMBASE, and PubMed databases from the date of inception to May 2023 to identify articles related to target trials in perinatal epidemiology. Our search strategy included the following search terms: ("Pregnancy"[Mesh] OR perinatal OR neonatal OR childbirth OR obstetrics) AND ("target trial" OR "target trials"). Given the recent popularity of target trial emulation in perinatal epidemiology more broadly, we chose not to restrict our search strategy or keywords to articles focused exclusively on examining the safety and/or effectiveness of medication use in pregnancy. However, this review will highlight only identified studies evaluating the safety or effectiveness of medication use during pregnancy.

An independent reviewer (SC) screened the titles and abstracts of the identified articles and selected those that were deemed relevant for a comprehensive full-text review, using Covidence software. The reference lists of identified articles were manually searched for additional relevant studies. A total of nine articles, including one preprint, published between 2018 and 2023, specifically focused on target trial emulation in perinatal pharmacoepidemiology were identified.

Among the identified articles, five involved an emulation of a target trial using observational data aimed at evaluating the effectiveness and safety of medications used during pregnancy [2•, 13–16], while the remaining four articles provided guidance on target trial emulation and methodological considerations [5•, 11, 17, 18]. For the purposes of this review, we focused on select examples from the identified studies to highlight key challenges and mitigation strategies in perinatal pharmacoepidemiology (refer to Online Table 1 in the supplementary material for a detailed description of identified articles).

Improving the Quality of Evidence in Perinatal Pharmacoepidemiology Research Through the Emulation of Target Trials Using Observational Data

Target trials offer a promising approach to bridge the gap between RCTs and observational studies, enabling a shift toward robust evaluation of treatment effects in real-world settings. Emulation of target trials facilitates answering causal questions using observational data through the alignment of the study question with the clinically relevant question. By designing the target trial to specifically address these questions, we can ensure that the results directly inform clinical and regulatory decision-making.

Causal inference requires transparency and clearly defined research questions [19], both of which are fundamental aspects of target trial emulation. Key components of these trials include pre-specification of the eligibility criteria, time zero (the index date), exposure, and outcomes. Moreover, the alignment of eligibility criteria, treatment assignment, and time zero in target trials minimizes the potential for inducing time-related biases and selection bias. Even with the perfect

alignment of these factors, it is important to note that the reliability of drawing causal inferences from observational data may still be subject to bias if treatment assignment is not independent of baseline covariates [9].

A clearly defined research question inherently leads to a clearer definition of the etiologically relevant time window for exposure or the time period during pregnancy in which exposures are likely to have a causal effect on the outcome. The target trial approach requires anchoring eligibility criteria and the start of treatment with time zero or treatment assignment/randomization. This criterion is especially important in target trials in perinatal pharmacoepidemiology, given the relatively short duration of pregnancy (up to 40 weeks) and the importance of targeting the etiologically relevant time window for exposures. For instance, if time zero is set to 12 weeks, but the research question involves studying the effect of a medication taken prior to conception or early in the first trimester on the risk of spontaneous abortions, many of the relevant outcomes may be missed since the distribution of risk for spontaneous abortions is highest in the first 8 weeks of pregnancy.

Important considerations in the appropriate selection of time zero when studying treatment effects in pregnancy were highlighted in a recent review by Hernandez-Diaz et al. [5•]. The authors discuss potential anchors for defining time zero based on gestational age and the etiologically relevant time windows for outcomes of interest. For example, when studying the risk of birth defects associated with medication use in pregnancy, the authors propose emulating a periconceptional target trial, with time zero anchored to either the last menstrual period or the estimated date of conception [5•]. If the outcome of interest occurs later in pregnancy, for example, preterm birth, time zero can be assigned at any point during pregnancy until the completion of the 37th gestational week, since pregnancies beyond this stage are no longer susceptible to experiencing the outcome [11]. The target trial framework enables researchers to clearly articulate the design of the hypothetical target trial (including the specification of the population, treatment assignment, and start of follow-up), ensuring it aligns with the clinical question at hand [9].

Pregnancy studies are particularly prone to conditioning on future events. An important benefit of the target trial emulation approach in perinatal pharmacoepidemiology is that it emphasizes only using information that is available to the researcher at time zero. In a standard RCT, researchers cannot predict whether a given pregnancy will result in a live birth at the time of recruitment and treatment assignment. The target trial emulation approach should mirror this principle by avoiding looking into the future to obtain knowledge of such outcomes. Access to entire exposure histories, due to the nature of observational data, can increase the number of opportunities for inappropriately assigning cohort membership and exposure, based on the availability of information on future exposures [20]. Through the careful design of the hypothetical target trial, researchers can mitigate time-related biases in observational studies.

Methodological Challenges and Potential Mitigation Strategies

Eligibility Criteria and Cohort Entry/Start of Follow-up

A challenge that is often encountered in perinatal target trials using observational data, particularly when utilizing administrative health or insurance claims databases, is the limited availability of historical data for the assessment of eligibility criteria for study inclusion. This presents a challenge primarily when the inclusion/exclusion criteria are based on obstetrical history. Without a sufficient look-back period to assess prior obstetrical history, it becomes challenging to ensure that the sample population accurately represents the target population of interest. For instance, if the research question is specific to individuals with no prior history of a delivery (nulliparous individuals), without complete historical data on parity or gravidity, researchers cannot ensure that their sample population includes nulliparous individuals. The lack of historical information can also introduce selection bias through the systematic exclusion of select subgroups of the target population due to the paucity of key variables used to assess eligibility. For instance, certain variables that are associated with survival (e.g., race/ethnicity, comorbidities), and thus, a person's ability to participate in the study, may also be associated with the outcome under investigation [21].

A commonly used strategy to overcome selection bias resulting from the absence of medical history is to restrict the sample population to individuals who receive continuous care from the same healthcare provider or system, who are in regular contact with their healthcare provider, or who have been enrolled with a provider for a minimum period of time (e.g., those who attended regular check-ups, filled a prescription within the 2 previous years, up-to-date on their scheduled vaccinations) [5•, 9]. However, this strategy by design may inherently impact generalizability, as individuals who are in regular contact with the healthcare system may be healthier and have better access to care, which may not reflect the target population of interest [22]. This introduces a trade-off similar to that observed in RCTs, where internal validity may be improved at the expense of external validity, limiting the generalizability of the findings beyond the sample population [23].

An additional consideration for setting eligibility criteria in target trials is the need to establish a precise description of time zero, defined as the point at which eligibility to enter

the trial is met and follow-up begins [9]. In a RCT, time zero is defined as the time at which an individual meets the eligibility criteria and is eligible to participate and is subsequently randomized to an assigned treatment. In the setting of a point exposure, the alignment of time zero and treatment assignment is straightforward. Consider a hypothetical target trial examining the safety of the COVID-19 booster dose in pregnancy described by Hernández-Diaz and colleagues. In this scenario, a pregnant individual qualifies for the study upon meeting its eligibility criteria and, subsequently, receives the COVID-19 booster, which denotes time zero [5•]. However, for medications/vaccines or point exposures that can be administered repeatedly during pregnancy (e.g., antibiotics), this may involve multiple eligible time points per woman during pregnancy. As described by Hernandez-Diaz, two strategies are commonly used to mitigate issues surrounding multiple eligible time points for trial eligibility (i.e., for point exposures) [9]. The first strategy involves choosing a single eligible time point, either the first eligible time point or a random eligible time point. The second strategy can involve the selection of all eligible time points within an individual or a large subset thereof; this strategy would require emulating multiple sequential nested trials (as described in the next section on *Immortal Time Bias)*, with each trial beginning at a set point in time during follow-up (e.g., at each gestational week). However, researchers must ensure that the eligible time points align with the etiologically relevant window of exposure for the outcome of interest.

In the setting of prevalent users of medications for chronic conditions, the alignment of time zero and eligibility is more complex. Consider a hypothetical target trial examining the effect of continuing versus discontinuing antidepressant therapy at the time of conception on fetal outcomes among birthing people. Unlike a vaccination, which is a point exposure, antidepressants are typically administered as a chronic, sustained treatment and discontinuation could occur at any point during pregnancy, which makes determining the appropriate time zero an important challenge. Each potential time zero introduces unique considerations, as the trimester of exposure during pregnancy and its impact on outcomes vary, thereby dictating the gestational age/trimester at which time zero should be anchored. An additional consideration involves the duration of treatment before pregnancy. For instance, should the inclusion criteria restrict to individuals who have been on treatment for a prespecified time frame prior to conception?

While many individuals who are trying to conceive may choose to discontinue chronic pharmacotherapies due to the potentially harmful effects on fetal development, other individuals may opt to continue their medications to avoid the negative consequences of discontinuing medication (both to the birthing individual and the fetus) [11]. However, it is important to note that the decision to discontinue, switch, or modify pre-pregnancy medication is closely tied to the severity of the condition. For example, individuals with more severe depression may be less likely to stop medications, based on recommendations from their doctor, and their concern with their overall health and that of their fetus. All in all, a change in medication regimes in individuals who become pregnant can pose challenges in the design of the target trial, specifically in the alignment of the eligibility criteria and treatment assignment [11].

The challenge in chronic use of medications prior to pregnancy, is the potential for prevalent user bias, resulting from the spurious association between exposures and outcomes due to an overrepresentation of individuals who are less susceptible to the outcome of interest. This concept, known as depletion of susceptibles, results in the depletion of higher-risk individuals from the population-at-risk of an outcome and the subsequent inclusion of individuals who are less susceptible to treatment-related effects [24]. However, some researchers argue that even if the pregnant person is a prevalent user of the medication in question, the fetus should be considered a new user, further complicating this issue [6•].

To address issues related to prevalent user bias, one approach involves conducting a stratified analysis, which entails separately analyzing new and prevalent users, taking into account their distinct characteristics and treatment patterns that may differentially influence outcomes. Another strategy involves anchoring time zero based on lab results or clinical encounters with physicians. For instance, consider a target trial investigating the use of antihypertensive pharmacotherapy during pregnancy [11]. Patients with hypertension diagnosed prior to pregnancy, and patients who had hypertension diagnosed in early pregnancy, are both eligible to participate in the trial. Implementing a "treatment decision design" (formulated by Brookhart (2015) [25] and described by Wood et al. (2023) in the context of pregnancy [11]) anchors time zero at relevant decision points based on lab results or clinical encounters and aligns treatment assignment with the diagnostic criteria that render an individual eligible for treatment. In this scenario, Wood and colleagues suggest stratifying randomization by antihypertensive use prior to pregnancy and analyzing these subpopulations separately [11]. This strategy creates a clear distinction between new users (who initiate treatment after meeting the criteria) and prevalent users (who have been using the treatment prior to the study period), thereby mitigating prevalent user bias. By carefully employing these methods, researchers can improve the validity of their findings and better inform clinical decision-making.

Immortal Time Bias

Immortal time bias is a time-related bias that is commonly seen in pharmacoepidemiologic studies often occurring from the misalignment of treatment initiation and the start of follow-up. This bias arises when the treatment is initiated after the start of follow-up, and the period between the start of follow-up (time zero) and treatment initiation is classified as "exposed" person-time (Fig. 1). This period is referred to as "immortal" since by design an individual cannot experience the outcome of interest during this time period. As a result, individuals who have not yet initiated treatment are inherently immortal from experiencing the outcome of interest, leading to inaccurate estimates of the true effect of treatment (resulting in either an over or underestimation of the true underlying effect). Notably, immortal time is induced when analyzing persons versus person-time (e.g., exposed people versus exposed person-time). This bias can also arise when the immortal person-time is differently excluded for individuals who later go on to be exposed, resulting in a misclassification of person-time [26].

Immortal time bias is particularly relevant for studies in perinatal pharmacoepidemiology as medication use can vary widely during pregnancy based on the indication of use (transient/point exposure or chronic use) and timing of initiation of prenatal care. When exposure is defined using a time-fixed approach (exposed or not during a specified time period), the potential to induce immortal time bias increases. Moreover, the timing of prenatal care initiation, which can vary widely between individuals [27, 28], can further influence the alignment of treatment initiation and the start of follow-up, potentially exacerbating the risk of immortal time bias.

A recent study by Caniglia and colleagues, examining the safety of antibiotic initiation between 24- and 37-week gestation and the risk of preterm delivery, highlights how the target trial approach can be leveraged to help mitigate immortal time bias [2•]. Immortal time bias can occur when exposures are defined as occurring at any time during a prespecified period; in the case of the Caniglia study, any time between 24- and 37-week gestation. For example, if a pregnant individual initiated antibiotics at 30-week gestation and the start of follow-up (time zero) is set to 24-week gestation, any observed outcomes that occur prior to 30-week gestation would erroneously be classified as exposed based on this predefined exposure definition, leading to potentially biased

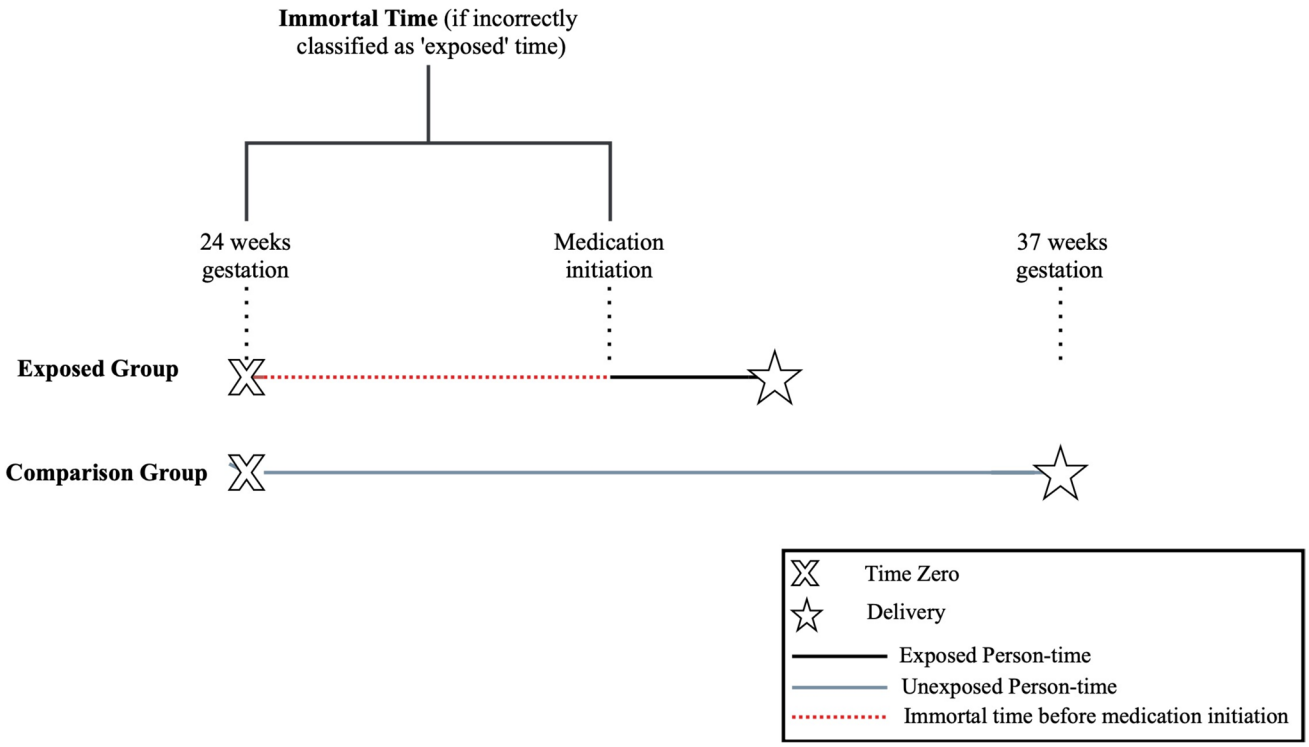

Fig. 1 Immortal time bias in a hypothetical target trial of medication use in pregnancy. This figure outlines a scenario in which immortal time bias is induced through the misalignment of time zero and treatment initiation. Immortal time bias results from the misclassification of unexposed person-time as exposed person-time (induced by looking into the future) from the start of follow-up until the time of initiation of treatment among exposed individuals. This period is defined as immortal since the exposed group cannot experience the event of interest during this time. The dotted red line denotes a time interval in the exposed group prior to medication initiation, where incorrectly classifying this interval as "exposed" would induce immortal time bias

estimates of the true association between antibiotic use and preterm delivery (Fig. 1). The extent of bias will depend on the length of the defined time window for exposure with longer time windows being more susceptible to bias.

Since relatively few individuals initiate antibiotics in any given week, and because the authors were interested in the effects of antibiotic initiation throughout pregnancy, the authors emulated a sequence of nested target trials to mitigate immortal time bias. This method entailed the emulation of sequential trials at each gestational week, starting at 24-week gestation until 36-week gestation (each with a 1-week enrollment period). Participants who had not initiated antibiotics in the previous trial were pregnant at the start of the following gestational week and continued to meet the eligibility criteria were eligible for inclusion in subsequent trials, up until the end of follow-up. A schematic outlining the sequential nested target trial approach used in this study is displayed in Fig. 2. By aligning time zero, eligibility, and treatment assignment, the authors were able to estimate the risk of preterm birth, comparing individuals who initiated antibiotics versus those who did not, through the pooling of effect estimates across the 13 sequential trials emulated from 24- to 36-week gestation, thereby mitigating the potential for immortal time bias from the misclassification of exposed person-time.

To illustrate the potential impact of immortal time bias on estimation of causal parameters, the authors conducted an additional analysis where the exposure was defined as antibiotic initiation at any time between 24- and 37-week gestation. Since the time period between time zero and treatment initiation is by design "immortal" with respect to the outcome, the risk ratio (RR) using a time-fixed definition found a spuriously protective effect of antibiotics for preterm delivery [2•]. In contrast, in the sequential nested target trial approach with treatment assignment occurring at each gestational week, RRs suggested a small increased risk of preterm delivery comparing antibiotic initiation with no initiation during pregnancy, although as the authors note, data on bacterial infection was not available, and these results are likely prone to confounding by indication (as described in the subsequent section on confounding). If data on bacterial infection were available, the authors could have considered including prior infection status as an eligibility criterion for the trial, thereby addressing issues relating to confounding by disease severity.

In summary, avoiding immortal time bias requires alignment of treatment initiation and the start of the trial (time zero) [10], with a secondary approach involving the emulation of multiple nested sequential target trials as per the Caniglia study. An additional strategy includes the use of an intention-to-treat (ITT) approach, which ignores changes to assigned treatment throughout the follow-up period. This approach, particularly when treatment is anchored to time zero, can potentially mitigate the risk of immortal time bias. A final strategy involves the "treatment decision design," as previously described. A major challenge in target trial emulation using observational studies is the choice of time zero when comparing treatment to no treatment (versus treatment A to treatment B), particularly for individuals not using treatment. The treatment decision design minimizes these concerns through the assignment of time zero independent of the timing of a prescription fill, therefore minimizing the potential for immortal time bias.

Exposure and Outcome Assessment

Exposure Assessment

The challenges surrounding exposure assessment in perinatal epidemiology are inherently complex, and the application of the target trial framework illustrates the extent of these challenges. For instance, the availability or lack of information on the timing of medication initiation or discontinuation poses a challenge in defining the start or end of treatment periods. Many data sources do not include detailed records on the duration of prescriptions or documented discontinuation of medications. Prior evidence also demonstrates that pregnant people self-discontinue medications and/or are less adherent than non-pregnant populations [29–32]. These challenges make it difficult to define etiologically relevant time windows for exposure and to align the initiation of treatment with time zero and the start of follow-up. Researchers often rely on assumptions or approximations, which can introduce varying degrees of exposure misclassification and could introduce immortal time bias as previously discussed.

Treatment decisions often extend beyond point exposures, especially in the context of chronic disease. A dynamic treatment regimen involves using decision rules to adjust treatments for patients in accordance with their treatment progress, the occurrence of side effects, their tolerance to medication, or their evolving health condition [33]. Dynamic treatment regimens pose unique challenges in exposure assignment in target trials, since treatments are highly dependent on disease progression, primarily informed by biochemical markers. For instance, in the case of HIV treatments both during and outside of pregnancy, the choice and timing of interventions may vary depending on the individual's disease trajectory. Emulating target trials for dynamic treatment regimens requires an understanding of the timing and sequencing of interventions, and the need to account for changes in treatment strategies over time, which can pose unique challenges in determining the appropriate treatment assignments.

A study by Caniglia et al. (2018) compared the effects of pre-conception initiation of zidovudine, lamivudine,

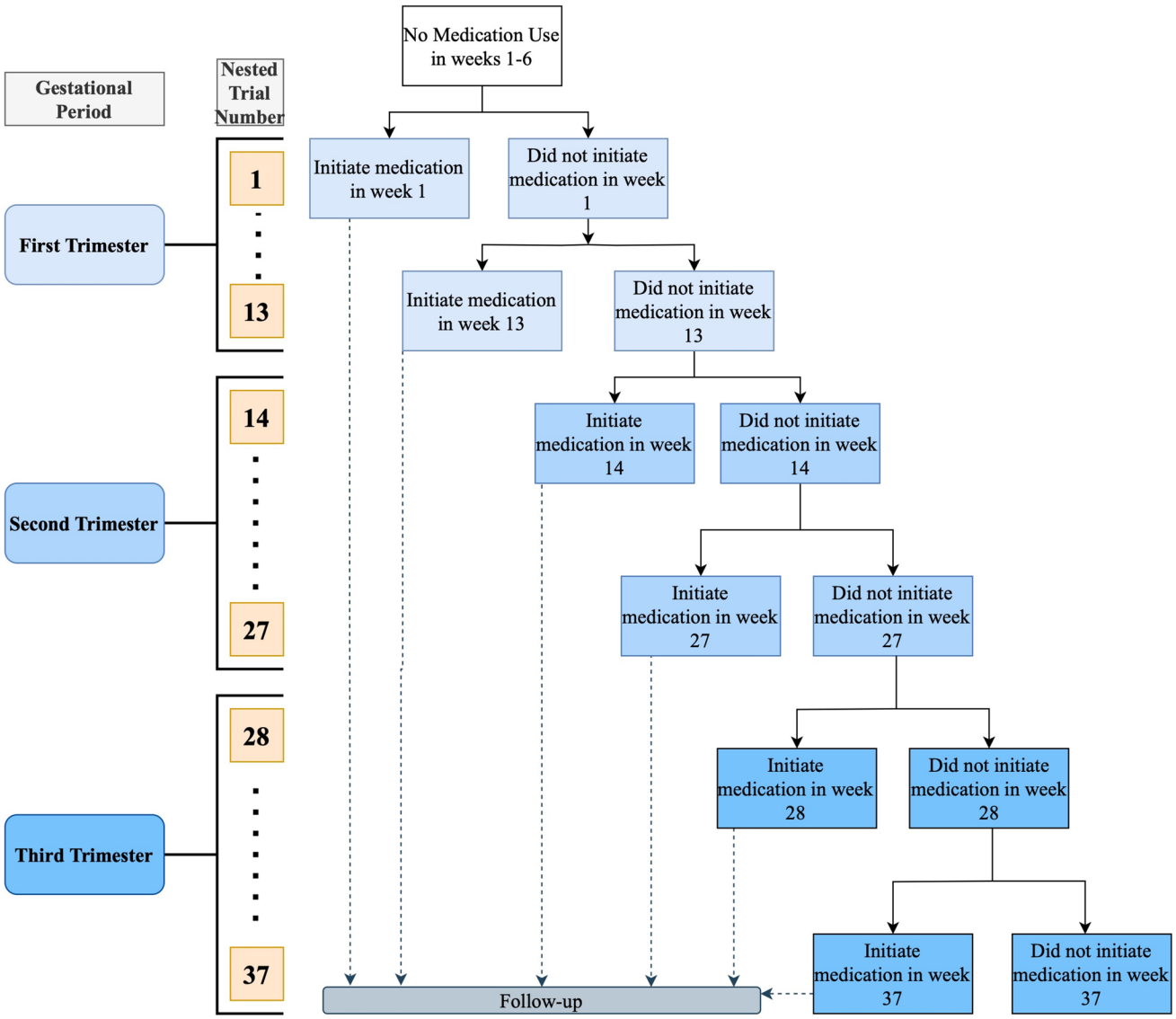

Fig. 2 Hypothetical emulation of sequential target trials of medication initiation at each gestational week beginning at the date of conception until 36-week gestation. The figure outlines the emulation of a series of sequential nested target trials emulated at each gestational week beginning at the time of conception until 36-week gestation. Individuals who are eligible for the trial are assigned to either treatment or no treatment and followed until the outcome of interest or the end of follow-up. Those who do not initiate treatment and who continue to remain eligible can contribute to multiple trials throughout the follow-up period until either they initiate treatment or are censored due to the outcome of interest or delivery date. The figure also highlights how researchers can align the start and end of the series of sequential target trials with the etiologically relevant time window for exposure based on the outcome of interest

nevirapine (ZDV/3TC/NVP) versus tenofovir, emtricitabine, efavirenz (TDF/FTC/EFV) for HIV treatment on adverse birth outcomes [15]. To address the challenges of adjusting for time-varying confounding in dynamic treatment scenarios, the authors employed historical and contemporaneous comparisons. In the historical comparison, individuals who initiated treatment were grouped based on the treatment strategy recommended by guidelines at the time of initiation. This approach helped account for potential differences in the characteristics of individuals who initiated one treatment versus another (confounding by indication). The contemporaneous comparison involved individuals who initiated two different treatments during the same time period to account for temporal trends in the outcome of interest while minimizing time-varying confounding due to differences in guideline-recommended treatment strategies. In sum, accounting for the dynamic aspects of treatment regimens is necessary to avoid time-varying confounding and effectively estimate treatment effects.

Outcome Assessment

In perinatal epidemiology, observational studies are often restricted to individuals who have a documented pregnancy outcome in the database, rather than the individuals eligible for exposure (which may include early pregnancy losses). An emulated target trial comparing the effectiveness and safety of assisted reproductive technology versus intrauterine insemination highlights this issue [13]. The authors identified pregnancies by the presence of codes for pregnancy outcomes (abortion, termination, stillbirth, or live birth) in the database. The results of pregnancy tests are not systematically recorded in many databases and birthing individuals may not see their healthcare provider when a pregnancy loss occurs. As such, using only recorded outcomes could potentially introduce selection bias. This therefore leads to the systematic exclusion of individuals from the study, limiting the generalizability of the findings to the broader target population of individuals attempting to conceive.

In observational studies of medication use during pregnancy, the potential for competing events during pregnancy is also an important consideration For instance, in a study interested in preterm birth, we might be concerned with the competing events of pregnancy loss (i.e., stillbirth or spontaneous abortion). While competing events are an important concern in perinatal epidemiology, questions surrounding the appropriate method to account for competing events, particularly how to interpret causal estimands resulting from methods to deal with these events, remain. While target trial emulation may help us clarify and interpret various target estimands, a more in-depth discussion of possible estimands, particularly in the setting of competing events, is beyond the scope of this paper [34–37].

Random Assignment/Exchangeability

Random assignment is an essential component of RCTs to ensure that treatment groups are exchangeable at baseline. In emulated target trials using observational data, we can achieve exchangeability through the careful adjustment of confounders measured prior to cohort entry. Various strategies for confounder adjustment, primarily in the context of data sources used in pharmacoepidemiology, are readily used, including matching, standardization, propensity score methods, such as matching, adjustment, or inverse probability weighting, as well as g-estimation, and targeted maximum likelihood estimation [9]. These methods attempt to optimize exchangeability through adjustment of baseline, and when relevant, time-varying confounders.

Achieving adequate exchangeability in target trials, however, can be challenging due to the potential absence of all relevant confounders in the dataset. In the absence of random assignment, confounding by indication is a major concern for studies in pharmacoepidemiology. In perinatal pharmacoepidemiology specifically, this poses a particular challenge as the severity of disease during pregnancy and use of medications in pregnancy can vary extensively posing a problem for ensuring exchangeability/random assignment in target trials.

The potential influence of confounding by indication is illustrated in the study by Meyer et al. (2022) where they evaluated the benefits and risks of anti-tumor necrosis factor continuation after 24 weeks of pregnancy for birthing individuals with irritable bowel syndrome (IBS) and their offspring [14]. The team used a national administrative health database from France, which lacks information on clinical or biomarker data, specifically C-reactive protein, and fecal calprotectin. The inability to effectively account for indicators of disease severity may have induced confounding by indication and a lack of exchangeability between groups, providing a biased estimate of the true effect of treatment on outcomes of interest.

A second example illustrating the potential for confounding by indication was found in the Caniglia study of antibiotic use and preterm delivery [2•]. The inability of the authors to adjust for the primary indications for antibiotic initiation, such as maternal infections, may have resulted in residual confounding and lack of exchangeability between groups. More specifically, this results in a comparison of a group of people who had infections and received antibiotic treatment, to a group of people who did not receive antibiotics (some of whom may have had infections, and some of whom did not). Since infections and inflammation are associated with preterm delivery [2•], residual confounding may have biased the results in the Caniglia study making antibiotics appear more harmful, as individuals with infections (who are more likely to be prescribed antibiotics) were also at higher risk of experiencing a preterm delivery.

More recently, the application of high-dimensional propensity scores or machine learning methods (either separately or in combination) has been shown to provide improvements over standard approaches by leveraging a broader set of covariates and modeling complex relationships, especially in the setting of rare exposures and outcomes [38–41]. For example, in the case of congenital malformations or rare medication exposure in pregnancy (e.g., anti-psychotics), where data may be limited, machine learning algorithms, such as random forests or neural networks, may help to identify important predictors and uncover non-linear relationships that may otherwise not be identified by traditional approaches [42]. These strategies enhance the potential to adjust for relevant confounders and provide a viable solution to reduce the potential impact of confounding by indication and improved exchangeability.

Public Health Importance

The shifting demographics of birthing individuals, including the older age at first pregnancy, increase in comorbidities at conception, and increasing use of infertility treatments, provide an impetus for the generation of reliable evidence to guide decisions regarding the initiation or discontinuation of medication use during pregnancy. Identifying effective and safe treatments for pregnant individuals is a public health priority [43], particularly since new or pre-existing conditions can be uncovered or exacerbated during pregnancy, thus increasing the need for pharmacotherapy [3, 44]. Additionally, pregnancy is associated with physiological changes that can alter the pharmacodynamics and pharmacokinetics of medications, impacting their efficacy and safety for both pregnant individuals and their infants [45]. Therefore, understanding the potential harmful or beneficial effects of medication use in pregnancy remains a critical focus area for maternal and child health research [3].

Despite this, there is a paucity of research focused on the safety and effectiveness of many medications used during pregnancy and lactation. As mentioned, most RCTs exclude pregnant individuals from participating due to ethical concerns, with information largely originating from post-marketing surveillance and mandated registries [2•, 4, 5•]. To address this dearth of evidence, the use of target trial emulation in perinatal pharmacoepidemiology offers a promising step forward. Properly conducted target trial emulations can enhance transparency and provide valuable insights into causal questions, empowering practitioners, and patients to make informed decisions about medication use in pregnancy. Importantly, observational studies can provide answers to urgent public health questions, and target trial emulation is a robust study design option. These studies can, when well-conducted, provide the best available evidence on treatment effects.

In summary, the integration of target trial emulation into perinatal pharmacoepidemiologic research holds immense potential for optimizing the design and analysis of observational studies. By adopting this approach, researchers can gather crucial evidence to inform both clinical and regulatory decisions, leading to enhanced healthcare outcomes for birthing people and their infants. The judicious use of target trial emulation bridges the gap in knowledge regarding the use of medications during pregnancy; it empowers healthcare professionals and pregnant individuals to make well-informed decisions, ensuring a safer and healthier trajectory in pregnancy and childbirth with long-term health benefits for both mothers and children.

Conclusion

The target trial framework offers a valuable approach for advancing perinatal pharmacoepidemiology research by bridging the gap between RCTs and traditional observational studies. This framework allows for the estimation of treatment effects in real-world settings through the alignment of the research question with clinically relevant outcomes, identification of the etiologically relevant time windows, and anchoring of exposure, eligibility criteria, and the start of follow-up to minimize common biases in observational research. While methodological challenges in the implementation of target trials using observational data exist, a paradigm shift toward the adoption of target trial emulation more broadly in perinatal pharmacoepidemiologic studies holds significant promise in informing clinical decision-making and regulatory actions. By employing transparent and well-defined research approaches, target trials can contribute to improving the evidence base for treatment effects of medications used during pregnancy and ultimately enhance the delivery of care and health of birthing people and their infants.

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Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest MW is a member of the Center for Pharmacoepidemiology (CPE) at UNC, which receives funding from industry partners (AbbVie, Boehringer Ingleheim, GSK, Takeda, UCB, Sarepta, Astellas). They do not receive salary support from the CPE; funds are used to support student stipends and related expenses. They received a starter grant from the PhRMA Foundation to study the treatment of chronic hypertension in pregnancy. They are a co-I on grants from the CDC, NIH, and the Kuni Foundation, unrelated to the current work.
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All other authors have no conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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