Target trials support drug safety in pregnant patients

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Out of concern for fetal safety, pregnant people have typically been excluded from drug trials. And when human health is on the line, drug studies assessing fetal safety in animal models may be viewed as far from definitive.

Due to sheer lack of data concerning implications for fetal and maternal safety, clinicians are often unsure about prescribing drugs to pregnant patients.

That's the situation as outlined in a position paper in *Nature Medicine* by Anup Challa, David Aronoff, MD, and colleagues. A woeful knowledge deficit leads to undertreatment of chronic and acute illness in pregnant people, while, creepily enough, also posing additional risk of adverse drug reactions for this group.

The authors' solution: use electronic health record (EHR) data to emulate randomized controlled trials (RCTs).

Used to compare treatments, RCTs involve enrollment of subjects who undergo interventions carried out in real time. By contrast, so-called target trials are a type of observational study that painstakingly emulates an RCT through retrospective analysis of existing clinical data.

Several methods can help uncover and eliminate bias that can limit these observational studies. Provided enough data (Vanderbilt University Medical Center has EHRs from 2 million patients and counting), investigators can design and conduct "trials" that simulate not only a real trial's treatment strategies (drug versus no drug) and outcomes, but also eligibility criteria and random assignment to treatment at baseline.

Ideally, target trials can provide a basis for causal inference, the authors note. Such trials are arguably "the only ethical way to gather human drug exposure data for pregnant people on a significant scale and across all classes of drugs," the paper states.

Certain common genetic variants are known to mimic drug effects. So, in the case of drugs for which there may be insufficient prescription data in pregnant people's records, genomic data can provide a proxy for drug

exposures in target trials.

So-called organ-on-a-chip technologies—newer lab methods that recapitulate drug exposures in human tissue—stand ready to help validate results of target trails.

According to the authors, "this is one of very few valid, ethical workflows that can accommodate large-scale drug screening. Never before in the history of medicine have we been afforded sufficient data to tackle this problem ethically and effectively."

More information: Anup P. Challa et al, EHRs could clarify drug safety in pregnant people, *Nature Medicine* (2020). DOI: 10.1038/s41591-020-0925-1

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