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Improving Knowledge on Safety is Key to Enabling Drug Access for Pregnant and Breastfeeding Women

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If pregnant women were an ethnic minority group, or perhaps elderly citizens, imagine the indignation if they were systematically excluded from clinical trials, research, and new treatments. The well-rehearsed argument that deliberately excluding pregnant women from trials is in their best interests (typically because of concerns over reproductive toxicity for the fetus) has hindered evaluation of new treatments for pregnancy-specific conditions (such as pre-eclampsia or fetal growth restriction), and assessment of medicines routinely used for co-existing medical conditions.

Interventional studies specifically for pregnancy represent a paltry 1.9% of clinical trials in a major trial registry,[1] and such studies were at greater risk of early discontinuation compared with all others. There may be perceived disincentives to investing in pregnancy trials in high-income settings (such as concerns of medicolegal risk arising from unanticipated adverse fetal effects, and limited market size), and even greater barriers in low and middle-income countries, where despite the burden of disease being highest, the financial and regulatory deterrents may be greater.

With few exceptions, women who become pregnant do not get a break from their co-existing medical conditions. Some diseases worsen with pregnancy; lupus erythematosus can flare, glycaemic control can worsen for those with pre-existing diabetes, and women at risk of thromboembolic disease become more prothrombotic. Pregnancy-induced changes (such as alterations in liver and kidney function and expansion of the maternal vascular compartment) may change circulating concentrations of medications resulting in altered efficacy and safety. There is a pervasive hesitancy by many physicians to prescribe medicines that pregnant women need to control co-existing medical conditions. Healthcare providers and pregnant women tend to overestimate the risks of medications during pregnancy.[2] Pregnant women may shy away from taking prescription drugs,[3] although doing this may cause harm. Healthcare providers may think twice before prescribing a medicine; besides their conflated perception about the possible risks,[2] they may be dissuaded by the fact that for many drugs, their administration during pregnancy is considered "off label" use.

The situation is barely improved for breastfeeding women where the woman, or their doctor, may be concerned (often unnecessarily) about the risks posed by drugs crossing to the newborn via the breastmilk. Withholding medication to this group of women is certainly not optimal, given breastfeeding may continue for months, or years.

The path to greatly facilitating the access to drugs for pregnant and breastfeeding women is to obtain high quality data on efficacy, effectiveness, and safety of drugs for these groups (including evaluation of drug dose adjustment during pregnancy and postpartum). In this issue of *Clinical Pharmacology and Therapeutics*, representatives from the major drug regulatory bodies from The United States (the US Food and Drug Administration), Europe (European Medicines Agency), and the United Kingdom (Medicines and Healthcare products Regulatory Agency) propose solutions to reduce the barriers impeding knowledge gain regarding drug safety during pregnancy and breastfeeding.[4] They step through the different stages of drug development, from preclinical testing, clinical trials to postmarketing surveillance.

At the preclinical toxicology stage (where various doses of drugs are administered to pregnant animal models to establish safety), they highlight the fact that the longstanding approach toward interpreting toxicology data errs toward the overly conservative, where the attitude is to establish "possible" harm rather than "likely" harm. This means if there is a suggestion of harm observed in animal toxicology experiments arising from doses far exceeding the likely circulating concentrations in humans, it still typically results in a ruling that the drug is best avoided altogether during pregnancy.

There is no easy solution to this. Although the authors propose several paths forward to decrease barriers to drug access that are erected at the early toxicology stage, they are challenging. For instance, they suggest unearthing data from prior reproduction toxicology studies of compounds that did not progress to clinical trials (much of which is never published) because sharing these experimental results

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may generate a more sophisticated understanding of the mechanisms disrupting fetal development. Presumably the insights gleaned could help us anticipate the likely risk of other medicines, but the concept seems ambitious, and its potential for clinical impact perhaps distant.

It is crucial that we move forward from a situation where most clinical trials evaluating new therapeutics deliberately exclude pregnant or breastfeeding women. The historic rationale has been to protect the fetus or child, but when considering the net risk of harm (vs. possible benefit), such a blanket approach for many of these trials is ethically questionable.[5] This is especially the case in serious pre-existing conditions where the probability of benefit (due to avoidance of deteriorating disease) likely outweigh that of risk from the medication. The authors make an important point: do not automatically exclude pregnant and breastfeeding women from clinical trials. They note "we must move beyond decades of thinking driven by old biases and fear and use sound ethics and safety provisions to make changes encouraging inclusivity."[4] Whereas fear of litigation is often cited as a perceived barrier, an analysis of 10 years of maternity claims from the UK National Health System (NHS) Litigation Authority did not report participation in research trials as a cause of litigation.[6]

Analyses of participation of pregnant women in clinical trials of coronavirus disease 2019 (COVID-19) treatments have shown that the tendency to exclude pregnant women from trials has continued. Recent analyses of clinical trial registries have reported that around three quarters of clinical trials for COVID-19 treatments excluded pregnant women, despite a lack of justification as many of the treatments being evaluated had no or low safety concerns during pregnancy.[7] One welcome anomaly is the RECOVERY trial, to our knowledge the largest platform trial of COVID-19 treatments globally. This trial ensured that pregnant women were not excluded, and shortly after its rapid commencement in the early days of the pandemic, the trial started actively including them in all treatment arms where the benefits of the intervention were considered to outweigh the risks. Some drugs were repurposed, such as hydroxychloroquine (used in pregnancy for lupus), lopinavir-ritonavir (for HIV), and azithromycin (for chlamydia). For drugs such as steroids, alteration was made to the choice of treatment. Although two doses of dexamethasone are commonly used to induce fetal lung maturity with impending preterm birth, longer-term use can have deleterious effects on fetal growth and brain development. In the RECOVERY trial, 10 days of dexamethasone was replaced with prednisolone or hydrocortisone, which do not cross the placenta, to enable participation of pregnant women. This enabled the finding of reduced mortality with dexamethasone to be rapidly adopted into clinical practice for pregnant women (using prednisolone or hydrocortisone).

However, pregnant and breastfeeding women were excluded from COVID-19 vaccine trials in 2020, leading to perpetuation of inequity of access to vaccines, with these groups having to balance risks of exposure to COVID-19 and its complications against uncertain (and likely very small) risks of the vaccine, whilst further definitive evidence of vaccine efficacy, effectiveness, and safety is awaited.

Finally, the article addresses the gaps around marketed drugs and advocates the need for stronger postmarketing follow-up to collect real-world data on the safety of drugs administered during pregnancy and breastfeeding. This could be achieved by the implementation of high-quality registries. Although the authors note a few examples, registries tailored for drug risk during pregnancy are still extemporised. It is particularly challenging to obtain high quality data on the risk of drugs administered during breastfeeding using electronic health databases or registries, as information on the duration of breastfeeding is typically poorly recorded in routine care records.

The importance of postmarketing follow-up has been thrown into sharp relief by the publication of a comprehensive UK report in 2020. Entitled "First Do No Harm," it details the failure in recognizing the major fetal risks of sodium valproate and hormone pregnancy tests that were used in the 1970s, together with the far-reaching consequences for the women.[8] Among its many excellent recommendations, is showed that databases and registries are implemented to track the safety of drugs (and therapeutic devices). The report also delineates the important distinction between a database and a registry, the latter being an approach that collects multifaceted information in an ongoing manner. However, agreement over who is responsible for funding such complex and long-term programs remain unclear; a joint pharmaceutical-academic collaborative approach is likely to ensure that what is currently perceived as no-one's business becomes everyone's business.

Over the years, there has been much written about the barriers facing women in accessing drugs to treat medical conditions, as well as the dearth of drugs to treat pregnancy conditions themselves.[9] This linked article represents a powerful force for change, penned by representatives of the major regulatory bodies representing the United States, the United Kingdom, and Europe who boldly declare their intent to act on their recommendations.

For many years, children were often excluded from clinical drug trials. But the launch of the Paediatric Investigational Plan[10] in 2007 by the European Medicines Agency changed the landscape by ensuring that it has become standard to obtain data for authorisation of new medicines in children, through clinical trials specifically in this group, unless the medicine is exempt because of a deferral or waiver. Committing to a similar concept of a Maternity Investigational Plan[9] becoming a standard part of drug development would be one step toward ensuring overdue equity of access to medicines for pregnant and breastfeeding women. If we can see a shift toward a collaborative approach among regulatory agencies, pharmaceutical companies, researchers, and women themselves, and a healthy pipeline of new interventions being evaluated alongside current treatments, there will be greater hope that pregnant women and breastfeeding women can more easily access medicines safely, impacting on maternal and perinatal morbidity and mortality.

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