Pharmaceuticals in pregnancy: a multifaceted challenge in Australia

Recent supply constraints for labetalol, immediate-release nifedipine and misoprostol tablets in Australia have highlighted pregnant women's vulnerability to critical medication supply disruptions, and underscored the broader structural disadvantage this population faces in accessing effective, evidence-based pharmaceutical agents. In this perspective article, we summarise key challenges underpinning this disadvantage and propose some solutions.

Exclusion of pregnant women and women of childbearing age from clinical trials

Drug companies and regulatory authorities worldwide have demonstrated a longstanding reluctance to study the effects of medications in pregnancy and women of reproductive age. Consequently, these women are significantly under-represented in pharmacological clinical trials.[1] The thalidomide tragedy exemplifies the capacity for medications to cause birth defects. However, not developing new agents to treat medical conditions in pregnancy also causes harm by denying pregnant women pharmacotherapeutic advances enjoyed by other populations.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic reinforced this disadvantage: despite their greater risk of coronavirus disease 2019 (COVID-19)-related morbidity and mortality, pregnant women were systematically excluded from trials of vaccines and medical therapies,[2] resulting in fewer therapeutic options for this more vulnerable group. Conversely, a recent trial of maternal sildenafil therapy for fetal growth restriction (FGR) highlights the importance of research in guiding evidence-based perinatal practice.[3] In the absence of an alternative effective treatment, and given the biological plausibility of benefit, sildenafil was used off-label for FGR, but the STRIDER trial identified a potential excess risk of fatal neonatal persistent pulmonary hypertension, without FGR survival benefit. Sildenafil use in FGR thus cannot be justified.[4]

Indemnity costs and medicolegal concerns are only partially responsible for the reluctance to include pregnant women in therapeutic trials.[5] These considerations need to be reframed with reference to the inequity and risks of not including them.[6]

We have a narrow spectrum of medications known to be safe and efficacious for use in pregnancy. These medications tend to be old, off-patent, and — in Australia — are often used off-label, as sponsoring pharmaceutical companies have not sought to have them registered for treatment of pregnancy-specific conditions. For example, in contrast to the more than 50 antihypertensive agents available to the non-pregnant population, the *Hypertension in pregnancy guideline 2023*,[7] published by the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) and endorsed by the National Health and Medical Research Council (NHMRC), identifies only six medications with adequate safety and efficacy data in pregnancy for treating gestational high blood pressure, and of these six medications, all are more than 30 years old. Furthermore, exclusion of pregnant women from clinical trials has resulted in limited evidence about pharmacokinetics in pregnancy, thereby increasing the chance of inappropriate (usually inadequate) dosing due to fears of harm.

In addition to clinical trials, robust post-marketing surveillance systems (eg, the United States Food and Drug Administration's pregnancy exposure registries) have an important role in ensuring medications used in pregnancy are safe, as many adverse pharmacotherapy-related pregnancy outcomes are rare, so may not be identified in a randomised controlled trial unless it is very large.[8]

Sponsor-driven registration and regulation of medications

Many agents used frequently in maternity care, such as nifedipine for tocolysis and misoprostol for postpartum haemorrhage, have never been registered for these purposes in Australia, despite featuring in national and international clinical practice guidelines.[9,10] Indeed, pregnancy is a listed contraindication for immediate-release nifedipine, despite it being a first-line agent for treating both hypertension[7] and preterm labour.[11] Australia's pharmaceutical milieu generally relies on a commercial sponsor seeking registration of a medicine with the Therapeutic Goods Administration (TGA), with the sponsor's proposed list of indications (and pregnancy safety categorisation) applied once the agent is registered. Consequently, off-label indications — despite the evidence — are not well appreciated, and pharmaceutical companies can (with some justification) claim that decisions to remove certain agents from the market are acceptable because better, newer agents are available for the officially registered indications.

Substantial efficacy and safety evidence has accumulated over time for the agents we use in pregnancy, and these older drugs are often cheap with generic equivalents available. Indeed, the appropriate use of old, cheap drugs should be promoted by health systems and their funders. However, these agents are understandably unattractive to commercial sponsors given their negligible or non-existent profit margins, small Australian market, and high entry costs of registration and importation. These drugs are thus vulnerable to withdrawal on commercial grounds with no readily identifiable public-interest importer to fill the gap, as has occurred recently with immediate-release nifedipine.

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The commercial unattractiveness of these older, off-patent, off-label use medications means they are generally only imported by a single sponsor. If that sponsor elects to discontinue importation, or if manufacturing problems interrupt supply, pharmacies and health services can only import agents directly under the TGA Special Access Scheme, which is administratively burdensome and leaves less time for actual patient care. If a medication is indicated for use in pregnancy, section 19A of the *Therapeutic Goods Act 1989* (Cwlth) allows for importation of an equivalent agent, but this pathway is not an option for the many agents used off-label in pregnancy.

The TGA is "Australia's government authority responsible for evaluating, assessing and monitoring products that are defined as therapeutic goods. [It] regulates medicines, medical devices and biologicals to help Australians stay healthy and safe".[12] Although very proactive about warning the health sector of impending drug shortages, the TGA is not explicitly responsible for ensuring continuity of their supply, nor can it act to import medications directly when sponsors discontinue importation. It is unreasonable to expect commercial sponsors, who have a profit imperative and may be beholden to shareholders, to continue the importation of therapeutic agents with poorer profit margins. Alternative approaches are therefore required.

Categorisation of medications prescribed in pregnancy

Linked to the sponsor-driven regulatory environment is the TGA's ongoing use of the A, B, C, D and X categories for prescribing medicines in pregnancy.[13] The limitations of this system are well appreciated in the field, and were comprehensively outlined in the Journal more than ten years ago.[14] In particular, the system is not hierarchical, relies heavily on animal data, is not regularly updated as human data evolve, encompasses a wide spectrum of risk within each category, and allows sponsors to request a higher risk categorisation than extant data would support. This leads to over-emphasis on the risks of therapeutic agents in pregnancy, and often results in pregnant women being uncertain about, or being denied, medications that are clearly indicated and for which the benefits outweigh the risks.[15] This is true both for pre-existing medical conditions and those specific to pregnancy. Metronidazole is an example: despite its use in pregnancy for over 50 years without any attributable adverse outcome, it is categorised as B1, and prescription thereof prompts a substantial number of calls to medication information lines each year.[16] Similarly, despite copious evidence on its safety and efficacy in preventing preeclampsia, and consequent inclusion in international pregnancy hypertension guidelines,[17] aspirin is listed as category C, which has been shown to limit adherence.[18] A more nuanced, narrative approach to drug risk in pregnancy, as espoused by the 2024 *Australian medicines handbook*[19] (inter alia), is necessary to reframe the appreciation of risk versus benefit for therapeutic agents in pregnancy.

Even when a medication is listed as category A, the product and consumer medicine information may include advice to avoid use in pregnancy. Until recently, doxylamine (category A antihistamine used for nausea and vomiting in pregnancy) carried labels advising against its use by pregnant women, and the consumer medicine information (incorrectly) indicates uncertainty over its safety.

This is further evidence of women's systemic disadvantage in accessing sex-specific research and health care, with the default focus in many contexts being men.[20] Pregnancy serves as a further impediment in an environment of general disadvantage, such that maternity care is considered a useful barometer for the extent to which a health care system is equitable and effective. As is the case in many parts of the world, there is a pressing need for us to address these systematic biases in Australia.

Proposed solutions

What are potential solutions to these concerns? Some potential relief is available with the recently established TGA Medicines Repurposing Program,[21] which waives entry costs for sponsors applying to repurpose existing medications for a new indication. However, this requires sponsor buy-in and post-marketing surveillance obligations, so may be commercially unattractive. If we are to retain a sponsor-driven drug registration environment, it is time to consider creating a publicly funded, not-for-profit entity to register, import or manufacture, and distribute drugs considered to be critical in (and potentially outside of) pregnancy. This could obviate the need for maternity care providers to prescribe off-label medication, giving pregnant women greater confidence in their pharmacological treatment. Over time, supporting the local manufacture of critical medicines would further reduce the susceptibility of supply chains to disruption from a range of sources, political or otherwise. An alternative would be for the Australian Government Department of Health and Aged Care to take responsibility for the direct import of critical medications that are functionally unique to pregnancy (ie, little used in the non-pregnant population in contemporary clinical practice).

At the same time, the drug safety in the pregnancy categorisation system could be reformed to make it more clinically relevant: category X could be preserved, but all others abandoned in favour of frequently updated and readily available drug-specific information regarding potential or known risks in pregnancy and lactation.

We also need to explore novel strategies to mitigate risk-based concerns regarding the inclusion of pregnant women in therapeutic trials. This could include government-backed liability schemes, enhanced NHMRC standardised guidance regarding optimal study designs and specific monitoring required for pregnant trial participants, and targeted funding for this population.[5]

The structural disadvantage faced by pregnant women is untenable and a missed opportunity to improve

the health of future generations: addressing problems relating to pharmaceutical use in pregnancy would go a long way towards redressing this disadvantage and improving equity in health care.

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