Health Policy

How the structural determinants of health inequities impact access to prescription medication for pregnant women in Australia: a narrative review

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Summary

Structural factors that contribute to health disparities (e.g., population-level policies, cultural norms) impact the distribution of resources in society and can affect medication accessibility; even in high-income countries like Australia. Industry practices and regulatory approaches (e.g., a conservative approach to testing medicines in pregnant women) influence the availability of safety and efficacy data necessary for the licencing and funding of prescription medications used during pregnancy. Consequently, pregnant women may be prescribed medications outside of regulatory or funder-approved indications, posing risks for both prescribers and pregnant women and potentially compromising equitable access to medications. This review examines the regulatory and legislative structural factors that contribute to health disparities and perpetuate the deeply ingrained social norm that we should be protecting pregnant women *from* clinical research rather than safeguarding them *through* such research. Addressing these challenges requires a renewed commitment to integrated, woman-centred maternal healthcare and strengthened collaboration across all sectors.

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Introduction

Prior research indicates >80% of women take at least one medication during pregnancy,[1–4] with an increasing need for medication use observed as more women enter pregnancy with chronic medical conditions and/or develop pregnancy related complications.[5,6] Despite increased demand, data to support safe, effective, and efficient medication use during pregnancy remains scarce. Between 2000 and 2010, only 26.7% of new drugs approved in the United States provided *any* human safety data for use during pregnancy, with sufficient data to determine teratogenic risk (i.e., probability of a substance causing fetal developmental abnormalities) being available for only four of those medications (2.3%).[7] In the absence of adequate data, undue risk is placed on women and their health practitioners. The major teratogenic effects of thalidomide,[8] diethylstilbestrol,[9] and sodium valproate[10] each provide solemn reminders of the potential harms that can result from medication use in pregnancy and why having robust safety assessments is critically important. The events surrounding these major teratogens also serve to augment ongoing fear and apprehension towards medication use in pregnant women. Complete avoidance of medications during pregnancy due to limited scientific data can place the mother and/or baby at greater risk of harm from an untreated illness (e.g., asthma, depression, epilepsy), and may impart lasting health and economic effects on mothers, children, and society as a whole.[11–16] Pregnant women are considered therapeutic orphans in their access to new medications,[17–19] and targeted actions to address this inequity are urgently required.

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Current legal and regulatory structures in pharmaceutical policy can either enable or hinder access to medications, and prompt attention must be given to their specific influence on access to medication during pregnancy. Catastrophic teratogenicity attributable to medications has resulted in a number of legal and regulatory barriers that restrict women's access to new and existing medications during pregnancy out of concern for unintended harm to the fetus. This is an example of structural determinants of health inequities, which are also defined by social institutions (e.g., family, the government, religion, education), population-level policies, deeply ingrained practices, and cultural norms. These highly 'upstream' structural determinants shape the distribution of the social determinants of health (i.e., non-medical factors that influence health outcomes[20]) among society and are considered to be the fundamental cause of health inequities.[21,22]

Unique market characteristics pertaining to prescription medications (e.g., information asymmetries, externalities, low price elasticity, patent-generated monopoly power) motivate regulatory and governmental intervention in these markets.[23,24] Population-level legal and regulatory structural determinants of inequities in medication access are complex and are subject to jurisdictional nuances. Australia boasts a public subsidy system for necessary and life-saving medications, where upholding efficient and equitable access to pharmaceuticals is of paramount importance.[23,25] When access to prescription medication is hindered or inappropriate there is potential for pregnant women and/or children to be placed at risk of harm.[11,12,26] This reflects an absence of people-centered healthcare, as pregnant women's health and wellbeing are not being placed at the centre of decision-making. The importance of person-centred health service provision was brought to the forefront in 2016 when The World Health Organisation (WHO) published a Framework on Integrated, People-Centred Health Services.[27]

This review aims to clearly articulate the regulatory and legislative structural determinants that affect the distribution of prescription medications among Australian women, and to link these with remedial strategies that facilitate a woman-centred, holistic, and multidisciplinary approach to the delivery of maternal health care in Australia. More specifically, the objectives of this review are to:

1) Identify, categorise, and describe the key regulatory and legislative structural determinants of access to prescription medications during pregnancy in Australia;
2) Assess the current propensity for structural determinants to act as enablers to maternal health care becoming progressively integrated and woman-centred in Australia;
3) Identify opportunities to modify structural determinants of health inequities to enhance pregnant women's access to safe, effective and efficient prescription medication, based upon reform activities implemented internationally.

Methods

A narrative review[28,29] was conducted to identify and map the current regulatory and legislative instruments that influence access to prescription medications for pregnant women in Australia. The review scope was limited to prescription medication since the regulatory processes and access pathways for non-prescription medications varies significantly and incorporation of both streams was beyond the parameters of this study. Structural determinants of medication access were included for both pregnancy-specific and non-pregnancy related conditions.

Search strategy and selection criteria

We anticipated the primary source for documents would be grey literature, since our review focuses on regulations, legislation, government documents, policies, and programmes. We adopted the consensus definition of grey literature from the 6th International Conference on Grey Literature (referred to as the Luxembourg Definition, 1997; expanded in New York, 2004).[30,31] Therefore, our primary search was an internet-based search on Google using the search terms ["policy" OR "regulation" OR "regulatory" OR "legislation" OR "government" OR "payment" OR "funding" OR "financing"] AND ["drug" OR "medication" OR "pharmaceutical" OR "therapy" OR "prescription"]. This initial search was supplemented by running the same search using search engine methods that restrict retrieved websites to those ending in ".gov.au", ".edu.au", or ".org" thereby prioritising recognised sources of grey literature. In addition, we identified organisations, associations, professional bodies, government agencies and industry bodies that were connected to the information sought and searched for relevant policy documents on their websites. Published books, policy papers, government websites, public reports, and reference lists of included policies were searched in an iterative manner to gather a complete picture of the legal and regulatory landscape. The primary search was conducted between 5th September and 24th November 2022, and re-run in August 2023 to incorporate any amendments or new information. No date limitations were placed on electronic searches.

The review objectives and eligibility criteria were established *a priori,* and further refined during the iterative review process. To be included in this review, regulatory and legislative policies were required to be:

- Relevant to pharmaceutical access arrangements during pregnancy;

- Currently applicable (in 2023);
- Relevant to the Australian context;
- Of relevance to prescription medications (NB: prescription medications are defined in this review as pharmaceutical agents included in Schedule 4 of the Poisons Standard[32]);
- Related to pharmaceuticals intended for human consumption.

We excluded policies that were only relevant to immunisations because the relevant pathways for licensing and funding vary.

H.J. screened all retrieved websites and documents for inclusion eligibility. The vast expanse of the internet made a comprehensive search of all results impractical; therefore we relied on Google's ranking algorithm[33] and reviewed the first 100 retrieved links for each search. H.J. assessed all documents retrieved from the search for eligibility by screening the title, headings, summary, table of contents, and/or abstract. H.J. then assessed full-text documents for inclusion in the review. All authors were then consulted to identify any further documents for inclusion and reached a consensus regarding the point of saturation; determined by additional searches consistently retrieving duplicate results. Some policies are subject to jurisdictional nuances (e.g., specific to state or organisational level). Provided there were no jurisdictional differences identified at the structural determinant level and all review authors agreed, these were included in our policy review under a broad policy term (e.g., The Pharmacy Act). Any disagreements were resolved through discussion between review authors.

Data charting and synthesis of results

Information on clinical evaluation, licencing, funding, and health service provider regulations relevant to medication access were extracted and consolidated into a schematic diagram describing the processes a new chemical entity must proceed through before a proprietary preparation is available for safe and appropriate consumption by a pregnant woman. This map is supplemented by a narrative description and tabulated summary of the relevant structural determinants and how they might serve as either enablers or barriers for pregnant women to access prescription medications in Australia. The World Health Organisation's Framework on Integrated, People-Centred Health Services[27] was then used to critique the structural determinants of access to prescription medications during pregnancy in Australia. Finally, international reform activities that aim to enhance access to medications during pregnancy were identified and mapped to the WHO Framework. One reviewer (H.J.) collated the information, which was then checked for accuracy and completeness by each of the other review authors. Any disagreements were resolved through discussion among all reviewers.

Role of the funding source

No funders played a role in the design of this study, data collection, data analysis, manuscript preparation, or in the decision to submit this paper.

Results

A flow diagram of the review process is provided in Fig. 1. A total of twenty-six legislative and regulatory policies were identified. Three policies (12%) were international policies detailing good manufacturing practices, good clinical practice, and ethical principles for medical research. All other included policies were Australian specific (n = 23; 88%), with 6 policies (23%) being subject to jurisdictional nuances within Australia and therefore incorporated in the review under a broad policy term. Included policies are outlined in the online Supplementary Material.

Fig. 2 shows a process flowchart that consolidates the relevant regulatory and legislative pathways that a new chemical entity is subject to; summarising the interplay between key stakeholders and governance processes that dictate access to prescription medications in Australia. Creation of this flowchart enabled us to classify the regulatory and legislative structural determinants of access to prescription medicines in Australia into four key categories for this review, being:

1) Experimental policies and processes;
2) Licensing arrangements;
3) Funding arrangements; and
4) Health service provider regulations.

Each element is summarised in Table 1 and discussed in detail in the online Supplementary Material. What follows below is a narrative description of each key category of structural determinants, focusing on the barriers they present to achieving equitable access to prescription medicines *during pregnancy*.

Experimental policies and processes

Clinical trials form the basis of the research and development processes to identify new chemical entities that are safe and efficacious, and therefore capable of being developed into patented pharmaceutical preparations. Pharmaceutical companies (i.e., sponsors) finance the drug discovery process and as private or listed companies, company and/or shareholder profit are at the forefront of their decision making. The maternal health care market is relatively small, and the enhanced regulatory hurdles (difficulties in acquiring insurance,[34] ethics application hurdles, physiological changes requiring dose modifications[35]) that add to production costs can significantly reduce commercial incentives to bring maternal health pharmaceuticals to market.[36]

Historically, pregnant women have been excluded from clinical trials. A study by Shields & Lyerly[37] found

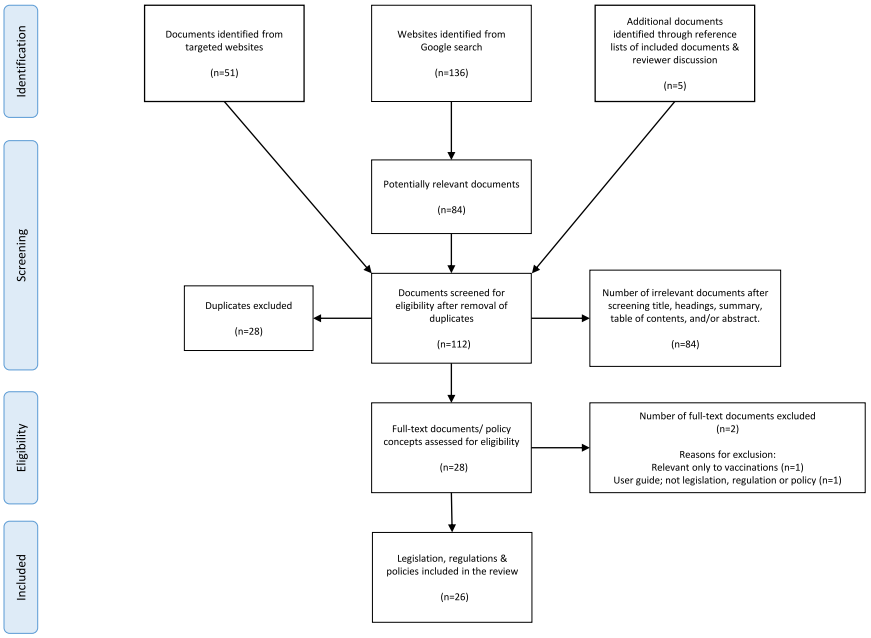

Fig. 1: **Flow diagram of the review process**.

only 1% of industry-sponsored clinical trials between October 2011 and January 2012 were specifically designed for pregnant women, with 98% of drug studies excluding pregnant women. Consequently, there is a paucity of safety and efficacy data in pregnant populations. This deeply entrenched social norm of excluding pregnant women from clinical trials perpetuates additional legal and regulatory structures (detailed below) that act as barriers to medication access.

Licencing arrangements

For new (or existing) pharmaceutical agents to be available for human use in Australia, a sponsor must gain pre-market approval from the Therapeutic Goods Administration (TGA) for entry of the product in the Australian Register of Therapeutic Goods (ARTG).[38] Once approved, medical practitioners can legally prescribe that medication to patients. TGA applications require extensive evidence to support the quality, safety and, in most cases, effectiveness of a medicine.[39] During the application process, the Advisory Committee on Medicines (ACM) will propose a pregnancy safety category (Category A, B1, B2, B3, C, D, or X) to be assigned to the medication (see TGA website for Australia's definition of pregnancy safety categories[40]). Importantly, structural barriers that discourage pregnant women's inclusion in clinical trials lead to insufficient evidence to accurately assess teratogenic risk, resulting in pregnancy safety classifications based upon an absence of evidence related to harm, rather than the actual level of harm. Unfortunately, pregnancy safety categories are seldom updated post market access,[7] and sponsors may apply more restrictive pregnancy safety classifications than clinical data suggests are appropriate,[41] or include additional pregnancy caution labels that limit access further.[42,43]

Funding arrangements

Due to the high cost of many medications, Australia, like many countries, has a policy system enabling government subsidisation of medication costs to promote equitable access. Publicly funded or subsidised access to medications encompassed by this review can be gained via the Pharmaceutical Benefits Scheme (PBS) or listing on a public hospital formulary. Access outside of these pathways occurs upon private prescription, with patients paying the full cost.

Pharmaceutical Benefits Scheme

Australia's primary public subsidy system for medications is the Pharmaceutical Benefits Scheme. The PBS provides public subsidy for approved medications that have demonstrated cost-effectiveness in a particular treatment population for specific indications. Items listed as restricted benefits (including Authority required benefits) can only be prescribed for PBS-approved therapeutic indications, however items listed as unrestricted benefits have no therapeutic restrictions associated with their prescribing. Accordingly, off-label use within the funding provisions of the PBS is plausible.

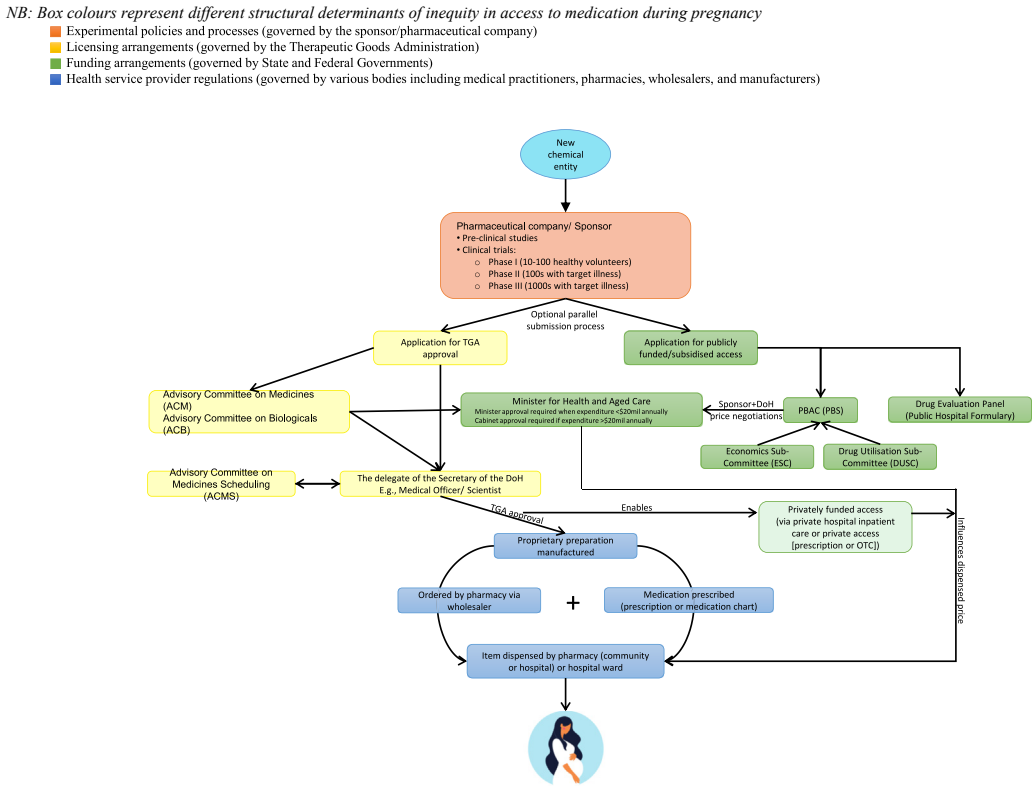

***Fig. 2:* Flowchart showing the process new chemical entities must proceed through in order to maximise safe, appropriate and equitable use of proprietary medicines**. Abbreviations: TGA: Therapeutic Goods Administration; PBAC: Pharmaceutical Benefits Advisory Committee; PBS: Pharmaceutical Benefits Scheme; DoH: Department of Health; OTC: over-the-counter.

When medications are legally prescribed outside of their TGA-approved therapeutic indication, formulation, or patient group, the prescribing approach is classified as 'off-label' use.[44] All PBS approvals must also have TGA approval. On 30th June 2022, there were 925 different medications listed on the PBS in 5178 brands.[45] A sponsor's submission for PBS approval must support a medication's clinical safety, efficacy, and economic efficiency. These economic evaluations usually employ models, which are populated with results from meta-analyses of randomised clinical trials. Here, again, the deep-seated social norm of excluding pregnant women from clinical studies means that establishing the economic efficiency of a medication in pregnant populations is challenging, thereby contributing to inequitable access to medications during pregnancy.

Furthermore, there are difficulties associated with measuring health outcomes (generally measured in quality adjusted life years (QALYs)) in pregnant women[46] and whether, or how, to incorporate both maternal health outcomes *and* fetal health outcomes, or any enduring effects medication use might impart on the offspring. The evaluation and incorporation of health outcomes other than those experienced by individuals in a trial is not common practice, although discussion around methods to facilitate this is increasing.[47–50] More research is required to better understand the most appropriate methods to be utilised in health economic analyses of interventions used during pregnancy. This will ensure decision-making is based on the best methodological practices thereby facilitating equitable access to medications and minimising the maldistribution of scarce health care resources.

Public hospitals (public hospital formularies)

The supply of pharmaceuticals to public hospital inpatients is the remit of the state and territory governments through the development of state-wide (or, in some cases, service-specific) formularies.[51,52] A formulary is a list of medications approved for use in a hospital, and specifies approved dose forms, indications and relevant prescribing restrictions (e.g., prescriber specialty, clinical indication). Economic assessment of a medication is required prior to gaining a formulary listing. It is worth noting, however, that methods employed in these economic evaluations may vary in comparison to the rigorous PBAC Guidelines,[53] with the

	STRUCTURAL DETERMINANTS			
	Experimental policies & processes	Licensing arrangements	Funding arrangements	Health service provider regulations
Legislation, regulations & policies	• Therapeutic Goods Act & Regulations • Clinical Trials Handbook - CTN Scheme - CTA Scheme • Declaration of Helsinki • National Statement on Ethical Conduct in Research • National Health and Medical Research Council Act 1992 • NHMRC codes & guidelines • ICH Guideline for Good Clinical Practice • Indemnity and insurance policies for clinical trials • National Mutual Acceptance of scientific and ethical review	• The Poisons Standard • Australian Register of Therapeutic Goods (ARTG) • Therapeutic Goods Act & Regulations	• National Health Act 1953 • National Health (Pharmaceutical Benefits) Regulations 2017 • Guidelines for preparing a submission to the PBAC • Closing the Gap (CTG) PBS Co-payment Program • Public Hospital formularies	• Acts & Regulations regulating or prohibiting the supply, possession & use of controlled substances (state/territory specific [a]) • The Pharmacy Act & Regulations (state/territory specific [a]) • 7th Community Pharmacy Agreement • Pharmacy location rules • Code of Good Manufacturing Practice
Key stakeholders	• Sponsor/ Pharmaceutical company • Trial Participants • Therapeutic Goods Administration • National Health and Medical Research Council (NHMRC) • Human Research Ethics Committees (HREC) • Australian Research Council (ARC) • Universities Australia	• Sponsor/ Pharmaceutical company • Delegate of the Secretary of the DoH • Therapeutic Goods Administration & relevant advisory committees - Advisory Committee on Medicines (ACM) - Advisory Committee on Biologicals (ACB) - Advisory Committee on Medicines Scheduling (ACMS)	• Sponsor/ Pharmaceutical company • Minister for Health and Aged Care • PBAC • Drug Evaluation Panel	• Medical practitioners, midwives, nurses • Maternity care providers • Pharmacies/ pharmacists • Wholesalers • Manufacturers • Women
Barriers for pregnant populations	• Pregnant populations under-represented in clinical trials • Deeply entrenched social norm of protecting pregnant women *from* clinical research • Difficulties in pharmaceutical companies acquiring adequate insurance policies to cover pregnant women in clinical studies	• Limited data available for use in pregnancy • Sponsors can assign more restrictive pregnancy safety classifications than evidence suggests • Safety classifications are rarely re-evaluated once real-world data becomes available	• Difficulties incorporating evidence for pregnant populations into economic evaluation	• Approval for public funding (or not) can give rise to inequities in health since women of higher SES have enhanced financial access to private prescriptions • In the public hospital maternity care system women usually see a midwife during consultations (often to facilitate continuity of care), but relatively few are endorsed to prescribe. This can limit women's access to prescriptions. • Patients cared for in a public hospital can access medications on the public hospital formulary, which is often less restrictive than PBS indications
Remedial pathways	• *Facilitate the inclusion of pregnant women in clinical trials* • Address insurance hurdles • Address ethics application hurdles • Provide incentives to encourage pharmaceutical companies to invest in R&D in maternal health care • Develop guidelines to assess pharmacokinetic differences in pregnant populations	• *Facilitate the inclusion of pregnant women in clinical trials* to enable data collection to support the quality, safety and effectiveness of medicines • Develop guidelines to encourage periodic re-assessment of pregnancy safety classifications as more real-world data becomes available • Develop regulations to prevent sponsors assigning more restrictive pregnancy classifications than evidence suggests are appropriate • Develop guidelines and regulations to facilitate applications for the repurposing of medicines in appropriate situations	• *Facilitate the inclusion of pregnant women in clinical trials* to enable accurate data collection (including costs) for input into economic evaluation • More research into measuring quality of life (QALYs) in pregnant women and whether (or how) to incorporate health outcomes for the developing fetus • Facilitate applications for the repurposing of medicines, including economic data to support an application for public subsidy	• Redesigning maternal health services to best support the needs of pregnant women

[a] State & territory government legislation regulates or prohibits the supply, possession & use of controlled substances, meaning these structural determinants are subject to jurisdictional nuances

Abbreviations: R&D: Research & Development; DoH: Department of Health; PBAC: Pharmaceutical Benefits Advisory Committee; PBS: Pharmaceutical Benefits Scheme; CTN Scheme: Clinical Trial Notification Scheme; CTA Scheme: Clinical Trial Approval Scheme; NHMRC: National Health and Medical Research Council; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. NB: Italicised text in the remedial pathways row highlights repeated concepts to address the structural barriers to medication access. Colour shades correspond to those defined in Fig. 2. [a]State & territory government legislation regulates or prohibits the supply, possession & use of controlled substances, meaning these structural determinants are subject to jurisdictional nuances

Table 1: **Structural determinants that influence access to prescription medications during pregnancy in Australia and the associated regulatory and legislative policies, key stakeholders, and implications for pregnant populations.**

comprehensiveness of assessments in this setting remaining largely unknown. The list of medicines on a hospital formulary is usually more limited in comparison to PBS-listings, and approved indications can differ from PBS-listed and/or TGA-approved indications for the same medication (i.e., off-label prescribing for restricted benefit items on the PBS can be funded publicly through public hospitals). This anomaly serves to enhance access to necessary medications in the acute care setting. Ondansetron provides a pertinent example (as outlined in Table 2). Ondansetron's PBS listing restricts publicly-funded access for nausea and vomiting associated with radiotherapy or chemotherapy to treat malignancy.[54] In contrast, many hospital formularies approve (and therefore publicly fund) ondansetron for severe nausea and vomiting associated with pregnancy. In this manner, the approved indication for the medication has effectively been increased beyond the restricted benefit imposed by the PBS and the TGA to enable pregnant women to access the medicine when a medical practitioner deems it clinically appropriate.

Private supply

Pregnant women can also access medications that are clinically relevant (as opposed to clinically indicated), regardless of PBS, TGA, or public hospital formulary restrictions through private prescriptions; either in the community or in a private hospital. Women pay the full cost for each medication dispensed via private prescription. Consequently, more affluent women appear to have enhanced financial access to a wider array of therapeutic options during pregnancy. There are no legal impediments to these prescribing practices; the responsibility and medico-legal risk for the clinical decision lies with the prescriber.

PBS 'leakage'

The deeply ingrained structural barriers to accessing medications through government-approved pathways has led to some informal pathways to access. PBS 'leakage' refers to the (PBS-subsidised) prescribing of medications for indications outside PBS-imposed therapeutic restrictions (i.e., for restricted benefit items).[55] This phenomenon can be influenced by medical practitioners favouring clinical 'need' and preservation of the doctor–patient relationship over regulatory guidelines, and a lack of understanding among medical practitioners about the PBS standard for establishing efficacy and cost-effectiveness prior to listing. It often involves newer, more expensive

Community	Public hospital inpatient or emergency department	Private hospital
1. Pregnant woman sees a medical practitioner for an assessment (specialist/midwife rooms or GP clinic).	1. Pregnant woman presents to emergency department and/or is admitted to hospital.	1. Pregnant woman admitted to hospital.
2. Health practitioner who is endorsed to prescribe writes a private prescription for ondansetron.[a]	2. Health practitioner (must be endorsed to prescribe) prescribes ondansetron on medication chart. Approved use should be in line with the hospital formulary, which is usually more inclusive than PBS eligibility criteria.	2. Health practitioner (must be endorsed to prescribe) prescribes medication on medication chart.
3. Patient takes prescription to a community pharmacy.	3. Nurse, doctor or pharmacist sends a copy of medication request (medication chart) to pharmacy dispensary (or item is collected from ward stock).	3. Nurse, doctor or pharmacist sends a copy of medication request (medication chart) to pharmacy (or item is collected from ward stock).
4. Community pharmacist dispenses the prescription.	4. Hospital pharmacist dispenses ondansetron to patient for nurse administration while in hospital (if item is not ward stock).	4. Hospital pharmacist dispenses medication to patient (if item is not ward stock).
5. Patient pays the private price for the prescription (i.e., there are no government subsidies and no reduced price for concession card holders). Patients with private health insurance that covers prescription pharmaceuticals may be eligible for an additional rebate on the prescription cost.	5. Nurse administers ondansetron to patient (no patient charge).	5. Nurse administers ondansetron to patient (no direct patient charge for medication but the admission episode may be subject to a deductible/excess fee).
	6. Upon discharge, medical practitioners (in some Australian states) can write a private prescription for further ondansetron supply.[b]	6. Upon discharge, medical practitioner can write a private prescription for any medications required to continue.
	7. Patient can take that prescription to a community pharmacy for dispensing as a private prescription. Patients with private health insurance that covers prescription pharmaceuticals may be eligible for an additional rebate on the prescription cost. Alternatively, the patient can present that prescription to the public hospital pharmacy department for dispensing. NB: If the prescription meets public hospital formulary criteria, ondansetron may be supplied at a reduced price from the public hospital pharmacy department (i.e., the standard patient co-payment), and concession card holders will be dispensed ondansetron at a subsidised price.[b]	7. Patient can take that prescription to a community pharmacy, or to the private hospital pharmacy department for dispensing. NB: Private hospital pharmacy costs will be comparable to community pharmacy costs in this scenario (although prices can vary between pharmacies). There are no government subsidies and no reduced price for concession card holders. Patients with private health insurance that covers prescription pharmaceuticals may be eligible for an additional rebate on the prescription cost.

[a]PBS subsidised supply of ondansetron is approved for nausea and vomiting associated with radiotherapy or cytotoxic chemotherapy to treat malignancy. [b]NB: This system is subject to jurisdictional nuances and is not practised in all states.

Table 2: **How pregnant women can access ondansetron for hyperemesis gravidarum within the community, public hospital or private hospital setting and the influence this can have on patient out-of-pocket payments.**

medications that are approved for serious ailments being prescribed for less serious conditions that could be managed by less expensive alternatives. This mode of prescribing has been observed for ondansetron.[56]

Health service provider regulations

In a community setting, pregnant women can access prescription-only medications via an authorised prescriber (e.g., midwife endorsed to prescribe), general practitioner, or a specialist (e.g., obstetrician) who can provide them with a (PBS or private) prescription that can be dispensed by a community pharmacy. In the public hospital system (where around 76% of births occur[57]), pregnant women commonly have their antenatal care provided by a midwife, although only 3% of midwives are endorsed to prescribe.[58] In addition, authorised midwives can only prescribe a select number of medicines, with the list varying between different jurisdictions. In March 2023, 31 different pharmaceutical preparations (19 different medications) were eligible for supply via a PBS prescription by approved midwives.[59] Consequently, general practitioners are typically the key prescribers during pregnancy and women are required to arrange an additional consultation (for which they may incur a cost) if the therapeutic indication has been raised as a concern during a midwife consultation. With private obstetric care, every antenatal consultation is with an obstetrician, improving access to medications for women paying for private care. Table 2 provides an outline of the various steps to access an antinausea agent, ondansetron, through the common antenatal care pathways; clarifying the financial implications of access to a medication that is not PBS-subsidised during pregnancy and thereby highlighting the inequities of access that current structural determinants can impose.

Are the structural determinants of medication access responsive to pregnant women's needs?

Australia

The World Health Organisation's Framework on Integrated, People-Centred Health Services[27] was developed to improve health outcomes by engaging patients, showing them dignity and respect, and involving them in all aspects of care and decisions about their health. Table 3 maps Australia's structural determinants of

pregnant women's medication access to prescription medication against the five strategies to enhance integrated, people-centred health services, showing where regulatory and legislative policies have made progress toward woman-centred maternity care, and where progress is slow or lacking. This clearly indicates current structural determinants do not support woman-centred maternity care. Instead, current experimental policies and processes lack any focus or progress that supports pregnant women to have "equal access to quality health services that are co-produced in a way that meets their life course needs, are coordinated across the continuum of care, and are comprehensive, safe, effective, timely, efficient and acceptable"[27]—a vision of the aforementioned WHO Framework. This insufficiency stems from the reluctance of Australian pharmaceutical policy to address deeply ingrained regulatory and legislative hurdles that avert inclusion of pregnant women in clinical trials.

Systems-level change is required to promote a cultural shift toward safety *through* research for pregnant women, rather than safety *from* clinical research. While Australian policies do not explicitly prohibit research in pregnant women, they currently fail to support a renewed focus on generating evidence for medication use in this population. Unfortunately, the deeply entrenched social norms preserved by current experimental policies perpetuate the barriers associated with other structural determinants classified in this review. Nevertheless, a move toward woman-centred progress has been initiated within licensing and funding arrangements in Australia, with the TGA's public consultation to better understand the barriers around repurposing of medicines currently underway. In addition, information systems and knowledge management has been strengthened through the ability to create and gain (heavily restricted) access to population-level linked administrative datasets, enabling researchers to strive for ongoing quality and safety improvements in medication use. Health service provider regulations have seen the greatest progress by redesigning maternal health services to align with pregnant women's values through adoption of continuity of care and carer models. Transformational leadership and attention to how this model of care is financed remains necessary to augment women's access to this gold-standard model of maternity care.

	STRUCTURAL DETERMINANTS			
	Experimental policies & processes	**Licensing arrangements**	**Funding arrangements**	**Health service provider regulations**
WHO STRATEGIES FOR INTEGRATED, PEOPLE-CENTRED HEALTH SERVICES	*Structural determinants that act as <u>enablers</u> to maternal healthcare becoming increasingly integrated and woman-centred*			
1. Empowering and engaging people and communities	• Pregnant women (an underserved population) are not engaged in or empowered by research; they are in fact often excluded. • Inclusion of pregnant women in clinical trials through appropriate informed consent would serve to engage and empower this underserved population.	• Frequent exclusion of pregnant women in clinical trials that influence licensing decisions limits knowledge and empowerment, and underserves this population. • Licencing processes are rarely re-visited once real-world data becomes available. • Insufficient incentives exist for sponsors to modify pregnancy safety classifications to be less restrictive.	• Frequent exclusion of pregnant women in clinical trials limits the data available for economic evaluation; again, excluding rather than engaging and empowering pregnant women. • More research is required around how to measure (& value) health outcomes in pregnant women	• Maternal health services are being re-designed to support the needs of pregnant women with obstetric services that foster continuity of care and carer gradually becoming more available and accessible. • Some midwives are endorsed to prescribe a limited number of prescription medications. • Public hospital formularies often enable publicly-funded access to a greater array of medications during pregnancy, reaching the underserved and marginalised to a greater degree.
2. Strengthening governance and accountability	• The National Health and Medical Research Council (NHMRC) provides guidance for (reactive) actions when a trial participant becomes pregnant, although the Australian clinical trial handbook does not make specific reference to pregnancy. Methods to address insurance and ethics hurdles to the inclusion of women in trials should be further developed. • A national advocacy coalition responsible for delivering a consistent and strengthened message regarding medicines in pregnancy to people, communities, organizations (public and private), and regulatory agencies would aid in connecting equity goals with maternal health policy objectives.	• TGA public consultation to better understand the barriers to repurposing[a] of medicines in Australia is underway, and should enhance mutual accountability (sponsor, Government and patient) and make navigation of the health system easier for prescribers. • TGA and Medicines Australia formulated a set of guidelines for post-marketing surveillance studies in 2021. • Creation of and access to linked administrative datasets enhances mutual accountability (government, prescriber, patient and sponsor) and strengthens patient-centred data governance and management.	• The TGA consultation on the repurposing of medicines should bring a spotlight on funding-related access issues for prescription medications in marginalised pregnant populations. • Government-initiated post-market reviews to re-assess list prices are possible, yet remain infrequent. • More research is needed to better understand how to value health outcomes in pregnant patients.	• Australian Health Ministers' Advisory Committee recommends continuity of midwifery care models as gold standard care, however few women have access to this form of care as there is no requirement for health services to provide this mode of service.
3. Reorienting the model of care	• A health needs assessment and continuous monitoring of the health status of pregnant women and their offspring is required, with incentives for sponsors to conduct research in this area. Pharmaceutical innovation in maternity care is lacking, with pregnant women currently referred to as therapeutic orphans. • Inclusion of women in clinical trials could serve to re-orient health services to embrace a woman-centred and family-centred approach.	• Timely, evidence-based updates to pregnancy safety information need to be encouraged and facilitated with clear documentation pathways. This will enable a focus on the safe provision of pharmaceuticals across all levels of the health service, and hopefully reduce inpatient admissions.	• Appropriate methods for Health Technology Assessment in this population require further research. • Incentives to stimulate formal repurposing of medicines that include PBAC applications is required. • Hospital inpatients generally have access to a wider variety of publicly-funded medications compared to community-based patients.	• There is strengthened action to re-orient maternity care services to be increasingly woman centred, prioritising continuity of care and carer models of care, and incorporating patient reported outcome and experience measures (PROMs and PREMs) in health service evaluation. • Some midwives are endorsed to prescribe a limited number of prescription medications.
4. Coordinating services within and across sectors	• Insurance structures for trials that incorporate pregnant women requires attention to modify current disincentives for inclusion – a major structural barrier for industry. This approach acknowledges the typical approaches are required to reach underserved populations. • Investment in pregnancy-related research should be incentivised and fostered, including facilitation of a network of research centres (public, private, NGOs, etc.) to bolster the output attained from restricted funding sources.	• Creation of and access to linked-administrative datasets for research is facilitated by Government. • Incentives for research results to stimulate a sponsor to consider a formal update of product information or a new submission to re-purpose an old medication are currently lacking.	• Authorised midwives (i.e., endorsed to prescribe) can prescribe a limited number of prescription products under the funding provisions of the PBS, signalling integration of once alternative health services pathways into national health systems. • Reimbursement methods for continuity of carer models in public health systems may require greater attention, as additional staffing costs are perceived to be a barrier to wider provision of these services.	• Maternity care services are relatively well integrated into national health systems, with midwife-led maternity care now considered gold-standard.
5. Creating an enabling environment	• Improved alignment of regulatory frameworks would enable and encourage pharmaceutical development and clinical trials that include pregnant women. • Systems-level change is required to promote a cultural shift to safety *through* research for pregnant women.	• Guidelines and regulations to mandate periodic re-evaluation of pregnancy safety classifications would elicit a culture of accurate and reliable pregnancy safety classifications and continuous safety monitoring through strengthened information systems and knowledge management. • Stimulation of appropriate repurposing of medicines would align clinical use with regulatory frameworks.	• Government-initiated post-market reviews to re-assess list prices are possible, yet remain infrequent. Re-assessment of economic efficiency in pregnant populations for general PBS listings that exhibit high levels of expenditure may be warranted. • Health system financing may need to be adapted to encourage the provision of continuity of carer in maternity care services.	• Reorienting the workforce to enable a health services environment that promotes continuity of carer for maternity care is happening; albeit slowly. Transformational leadership is required in this area. • Training of more midwives to prescribe a limited group of prescription medicines should be encouraged.

[a] Repurposing of medicines involves the identification of formal opportunities to approve new therapeutic indications for older medicines through new research and evidence (in contrast to continued 'off-label' use).

Abbreviations: WHO: World Health Organization; TGA: Therapeutic Goods Administration; PROMs: patient reported outcome measures; PREMs: patient reported experience measures. Legend: , no progress; , moving toward progress; , progress being made. [a]Repurposing of medicines involves the identification of formal opportunities to approve new therapeutic indications for older medicines through new research and evidence (in contrast to continued 'off-label' use).

***Table 3*: Regulatory and legislative structural determinants in Australia that act as enablers (or barriers) to maternal health care becoming increasingly integrated and woman-centred.**

International comparisons

Strategies implemented to reduce structural barriers across different international jurisdictions (non-exhaustive) are presented in Table 4, serving as stimuli for progress in the delivery of integrated, people-centred maternity care services. Across the remedial actions presented, efforts to empower and engage people and communities, and strengthen governance and accountability are strategies where real changes in structural determinants have been seen internationally. Australia is gaining momentum around better governance and accountability for woman-centred maternity care, but currently shows little prioritisation for engaging and empowering pregnant women and their families in the development of safe, timely, efficient, and appropriate access to prescription medicines during pregnancy.

Discussion

The information deficit surrounding medication use in pregnancy is a consequence of the complex legal and legislative landscape both in Australia and globally, thereby impeding transformational change and delaying the adoption of supportive strategies and frameworks. Prompt and measurable changes are required. This narrative review identified four main categories of regulatory and legislative structural determinants of access to prescription medications: experimental policies and processes (i.e., clinical research), licencing arrangements, funding arrangements, and health service provider regulations; and found the current regulatory environment in Australia does little to support widespread adoption of integrated and woman-centred maternity care services.

A major structural barrier to equitable access to prescription medicines is the exclusion of pregnant women from clinical trials. This deeply ingrained practise exacerbates the gender health gap, fails women, and can potentially harm them since there is a clear need for medication use but vastly insufficient evidence and knowledge regarding safe, effective and efficient use of prescription medications during pregnancy. Gender-based inequities in pharmaceutical research are known issues,[66–68] with unequal opportunities for women, particularly pregnant women, to be included in clinical trials, thereby placing greater constraints on information generation for women compared to men and therefore unequal opportunity to maximise health. Despite being a significant structural barrier to access and a longstanding issue (identified around three decades ago),[69] progress in this realm of maternal health remains slow.

To expedite pregnant women's access to prescription medication, enhanced access to de-identified post-marketing surveillance data, incentives for analysis, and increased visibility of results would be advantageous and serves to maintain a collaborative and sustainable medicines industry in Australia; a central pillar of Australia's National Medicines Policy.[70] Policies and processes require modification to ensure there is feedback of knowledge gained from post marketing studies back into these processes to enable, or even mandate, updates to safety, efficacy, and efficiency information for medication use in pregnancy. Policies targeting the supply side of the equation (i.e., pharmaceutical companies) will likely have a higher impact than strategies aimed at mediating pharmaceutical demand (e.g., via prescribers or patients)[71] since they are further reaching, easier to enforce and monitor, and are less likely to impact health equity.

Facilitating the inclusion of pregnant women in clinical trials is essential to enable accurate data collection for economic evaluations, thereby improving current funding processes. Although cost-effectiveness analyses using real world data have been increasing,[72] they are associated with known limitations (e.g., inability to control for all confounding factors, recording errors, an absence of data for relevant variables).[73] Ubiquitous incorporation of generic patient-reported outcome measures (PROMs) that enable utility measurements (e.g., EQ-5D) as routinely collected data in health systems would provide opportunities to evaluate and enhance the efficiency of medication use during pregnancy at a meso (organisational) and macro level, supporting policy makers to make appropriate, timely, and informed resource allocation decisions.

Finally, modifications to current health service provider regulations that enable redesigning of health services to support the needs of pregnant women are needed. Remedial strategies recommended by the United Kingdom's Pregnancy Policy Commission[34] are a robust set of recommendations to enhance momentum for change in the structural determinants of inequities in maternal health, and would support health systems to become increasingly integrated and woman-centred. Australia has made some progress towards remediation in these legislative structural determinants, but this review highlights that the Australian system lags behind international progress; supporting policies and processes that minimise medico-legal risks and favour protecting pharmaceutical companies and the government from being liable for mishaps, at the expense of women who should truly be at the centre of care. Prior studies have outlined the origins of existing structural barriers to the inclusion of pregnant women in clinical studies.[74,75] Future research efforts may focus on mapping changes in all of the regulatory and legislative structural determinants identified in this review, highlighting reasons contributing to their evolution over time. This would enhance understanding of the origins and intentions of legal and regulatory structural barriers and may uncover new approaches to surmount the barriers to equitable access to medications.

	WHO strategies for integrated, people-centred health services				
	1. Empowering and engaging people and communities	2. Strengthening governance and accountability	3. Reorienting the model of care	4. Coordinating services within and across sectors	5. Creating an enabling environment
Australia					
• TGA public consultation underway to understand barriers around repurposing of medicines.		◐		◐	
• Creation of and access to linked-administrative datasets for research is facilitated.		✓		✓	
• TGA and Medicines Australia formulated a set of guidelines for post-marketing surveillance studies.		◐			
• Government-initiated post-market reviews to re-assess list prices and safety classifications is possible, yet infrequent.		◐			◐
• Australian Health Ministers' Advisory Committee recommends continuity of midwifery care models as gold standard care, showing strengthened action to re-orient maternity care services to be increasingly woman centred.	◐	◐	✓	✓	
• Authorised midwives (i.e., endorsed to prescribe) can prescribe a limited number of prescription products under the funding provisions of the PBS, signalling integration of once alternative health services pathways into national health systems.			✓	✓	✓
United States					
• Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)[60] established in 2016, which developed an implementation plan for including pregnant women in clinical studies.	◐	✓		◐	◐
• CURE Drug Repurposing Collaboratory (CDRC) established in 2020 to promote drug repurposing.	✓				✓
• Pregnancy safety categories renounced in 2015 due to reported misinterpretation; new recommendations embrace pharmacovigilance complexities.[61]	✓				
• FDA drafted a guidance document[62] for sponsors and investigators on post-approval pregnancy safety studies in May 2019.	✓	✓			✓
Europe (including United Kingdom)					
• Safer Medicines in Pregnancy and Breastfeeding Information Consortium established in 2021 (United Kingdom).	✓	✓		✓	
• European Commission created an Expert Group on Safe and Timely Access to Medicines for Patients (STAMP), which launched a pilot for the framework to support repurposing of medicines through NFPs and academia in October 2021. STAMP's pilot project incorporates fee reductions and waivers for a subset of applications where the public health benefit is expected to be extensive.		◐		◐	
• ConcePTION (Continuum of Evidence from Pregnancy Exposures, Reproductive Toxicology and Breastfeeding to Improve Outcomes Now) project[63] established in 2019 to construct an evidence ecosystem for medication use in pregnancy.	✓	✓		✓	✓
• EMA Guidelines on good pharmacovigilance practices (GVP)[64] updated in 2019.	✓	✓			
• Guidance on how to plan, implement and monitor midwifery continuity of carer models at full scale was published by NHS England in 2021. The NHS supports Midwifery Continuity of Carer as the default model of maternity care. Similar to Australia, midwives who are endorsed to prescribe can write prescriptions for a select number of medicines within the regulatory restrictions.			✓		
Noteworthy global initiatives					
• Accelerating Innovation for Mothers (AIM) Project[65]		✓			✓

Abbreviations: WHO: World Health Organization; TGA: Therapeutic Goods Administration; EMA: European Medicines Agency; NFP: not-for-profit; NHS: National Health Service. Legend: ◐, Moving toward progress; ✓, Progress made.

Table 4: **Remedial structural determinants that have been implemented in different countries to enhance pregnant women's access to prescription pharmaceuticals and their ability to foster integrated, people-centred health services.**

The systems-level change that is required is not a small undertaking, but we believe step-wise implementation represents a more efficient pathway to improvements in equitable maternal medication access in comparison to the lag-time associated with a top-down approach; acknowledging that both a top-down and bottom-up approach is required to reduce the gender health equity gap and support the health and wellbeing of pregnant women, their children and their families.

Strengths and limitations

To our knowledge, this is the first review that distils the structural determinants that influence access to medication during pregnancy. Nevertheless, limitations associated with narrative reviews are well-documented,[28,29] however we believe it provides a strong framework for collating and synthesising Australian drug policies and facilitating discussion of how current processes can act as enablers and/or barriers to pregnant women accessing medications; particularly for new medications. In addition, the policies and processes included in this review are not an exhaustive list. Instead, we have provided a summary of the key stakeholders and processes involved in medication access in a bid to highlight the shortcomings in current governance processes and hope it serves to encourage further research questions and policy initiatives in this area.

Conclusion

Australia's regulatory and legislative structural determinants of medication access remain focused on medico-legal risk and protecting pharmaceutical companies and the government from being liable for calamities, at the expense of pregnant women who should truly be at the centre of care. Health systems have a duty to ensure that *all* women have equitable access to safe and appropriate woman-centred health care; particularly during pregnancy. This begins with a pivot away from the deeply ingrained social norm of protecting women *from* clinical research to promoting their safety and wellbeing *through* participation in clinical research, enabling generation of knowledge. Remedial progress made in other jurisdictions can serve as exemplary standards to propel momentum for change in this neglected area of maternal healthcare.

Contributors

All authors contributed to the conceptualisation of the study. H.J. conducted the primary literature search, which was further supplemented incorporating the knowledge and feedback from all authors. H.J. wrote the original draft (article, figures and tables), which was reviewed and edited by all authors. All authors approved the final version of the article and accept accountability for the integrity of the research.

Declaration of interests

E.C. reports grants from Ferring Pharmaceuticals, outside the submitted work; and a role as Vice President of Women's Healthcare Australasia. No other authors have any conflicts of interest to disclose.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100934.

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