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Perspective

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Eliminating gender bias in biomedical research requires fair inclusion of pregnant women and gender diverse people

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Systematic under-representation of pregnant women and gender diverse pregnant people in clinical research has prevented them from benefitting fairly from biomedical advances. The resulting lack of pharmacological safety and efficacy data leads to medicine discontinuation, sub-optimal dosing, and reliance on repurposed therapies. We identify four roadblocks to fair inclusion. First, investment and research are inhibited by protectionist attitudes among research gatekeepers who view pregnancy as a vulnerable state. Second, exclusion ignores human-specific biological variations affecting medication absorption and impacts on the pregnant body. Third, pregnant populations in low-and middle-income countries face a double disadvantage due to gender and location, despite bearing a disproportionate maternal mortality burden. Fourth, perspectives and experiences of pregnant populations are undervalued in clinical intervention design. We propose five actions to optimize fair inclusion: fostering reciprocal partnerships, prioritizing multi-disciplinary research, awareness-raising of the need for pharmaceutical innovation, conducting regulatory analyses, and promoting responsible inclusion over presumptive exclusion.

Maternal mortality remains a significant global problem[1]. Preventable and treatable direct causes of maternal death, such as postpartum hemorrhage and pre-eclampsia, continue to pose substantial, disproportionate burdens[1], and are increasingly compounded by rises in co-morbidities[2]. Maternal complications can also impact fetal, newborn, and child outcomes by increasing the risk of growth restriction, stillbirth, preterm birth, low birth weight, and child mortality[3]. Between 2016 and 2020, declines in maternal mortality stagnated or mortality increased in 150 countries, whilst maternal mortality was reduced in only 31 countries[1]. In parallel, there is an under-representation of pregnant women and gender diverse pregnant people in biomedical research studies. This under-representation made headlines during the recent outbreaks of Zika in South America, Ebola in West Africa, and the COVID-19 pandemic[4,5]. Despite higher risk of severe illness, complications and mortality for both women and newborns, pregnant populations were systematically excluded from early vaccine trials and investigational treatments[4–7].

The exclusion of pregnant populations from research is often justified on the grounds that they and their infants need to be protected from possible adverse effects. Consequently, many of the 250 million women[8] who get pregnant each year are unable to access biomedical innovations that could maintain health throughout pre-conception, pregnancy, childbirth, and lactation periods. They also lack access to newly developed drugs, and instead rely on repurposed medications for prevention and treatment of many pregnancy-related complications. Even when treatments are available, pregnant populations often have to use sub-optimal doses or are uncertain about potential adverse side-effects[9]. Frequently, medications for pre-existing conditions are discontinued due to concerns the treatments might cause fetal harm[9].

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In this comment, we discuss how these profound health inequities have been sustained due to a long legacy of gender-biased health research (Fig. 1). We identify four critical roadblocks that must be overcome to better represent interests of pregnant women and gender diverse pregnant people in the global biomedical research agenda.

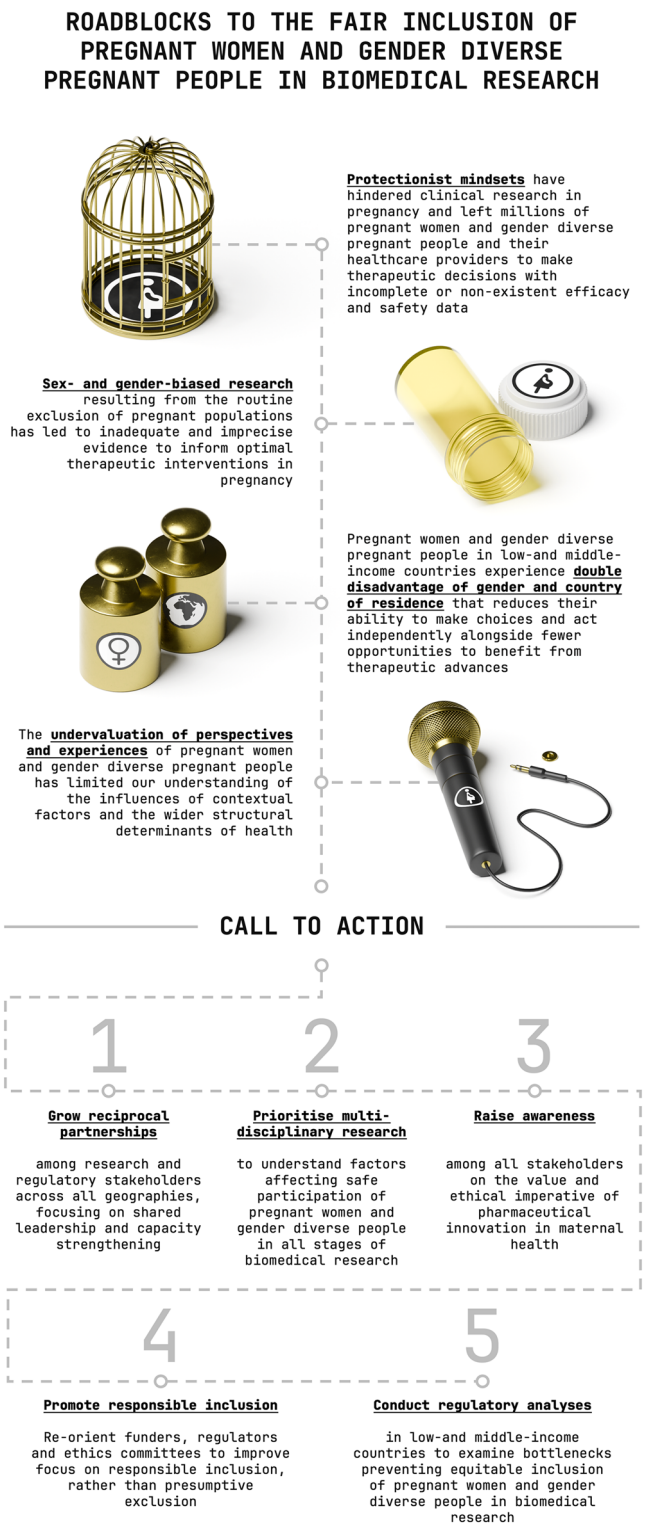

Fig. 1 | Roadblocks to the fair inclusion of pregnant women and gender diverse pregnant people in biomedical research. This figure depicts four critical roadblocks that must be overcome to better represent research and health interests of pregnant women and gender diverse pregnant people, and a call to action to achieve fair inclusion.

At the outset we recognize that pregnancy capable people have diverse gender identities, and that research to-date has focused almost exclusively on the experiences of cisgender women. In this comment, we also want to emphasize how research remains bound in highly gendered and binary mindsets, where historically and to the present day, pregnant women's health needs, choices and decisions are artificially constrained by patriarchal norms and customs. We have therefore taken a considered approach to our use of gendered language as follows. We use the terminology "pregnant women and gender diverse pregnant people" in reference to the research needs of pregnancy capable individuals. In doing so, we highlight that gender remains an important social determinant of health. We use the terminology "pregnant women" when referring to empirical or historical data where the focus has been on experiences of cisgender women, and/or, where we want to emphasize how the social construction of gender has contributed to patterns of bias in the ways in which clinical research has been conducted, as extrapolating this data to gender diverse pregnant populations would be inaccurate.

Protectionist mindset of pregnant women as vulnerable

The adverse consequences of using thalidomide and diethylstilbesterol during pregnancy demonstrated the potential ramifications of prescribing untested drugs to pregnant populations[10,11]. Critical repercussions included the notion that pregnant women are vulnerable and therefore need special protection. This led to regulations that restricted inclusion of pregnant women in research, which have been used to justify their systematic exclusion from research ever since[12]. However, to avoid similar future tragedies, it is important to undertake preclinical studies and also to include pregnant populations in early-phase clinical trials - with appropriate safeguards - to minimize the potential for harm[13].

These regulatory responses and their consequences have also perpetuated gendered assumptions regarding the ability of pregnant women to protect their own health interests, or their capacity for voluntary and autonomous decision-making[14]. Such responses have resulted in inaction by public and private biomedical research organisations and limited advances that could improve health during pregnancy. The regulatory environment implies that the ethical and practical complexities of drug research in pregnancy are too difficult to navigate and hence do not warrant investment and innovation. Most concerningly, such a risk-averse approach has paradoxically shifted responsibility for ensuring appropriate therapeutic drug use from closely monitored clinical trials to everyday clinical care. This has left millions of pregnant women and gender diverse pregnant people and their healthcare providers to make therapeutic decisions with incomplete or non-existent efficacy and safety data.

The attitude that pregnant women are vulnerable has also influenced other research and development gatekeepers, including institutional ethics committees that often take a paternalistic, protectionist approach[15]. One visible manifestation of this is through unequal expectations for researchers to justify inclusion or exclusion of pregnant participants. For example, a review found that no psychiatry trials evaluating pharmacological interventions included pregnant women and only 9% justified reasons for exclusion[16]. Ethical assessments of risks and benefits often view fetal safety and maternal health as disconnected, with the latter considered as an adjunct (except for life-threatening conditions), despite the intrinsic connectedness of maternal-fetal health and well-being. In a protection-by-exclusion approach, pregnant women and gender diverse pregnant people are denied the rights of autonomy and self-determination to make voluntary and informed decisions about the benefits of research to their own health in relation to fetal risks, and vice versa.

Decades of advocacy have led to conceptual shifts in regulatory mandates[17] and among professional organizations to explicitly recognize the research needs of pregnant populations, and formally withdraw their inclusion as a vulnerable category by Health and Human Services regulations in the United States[18]. However, the impact of decades of exclusion has been slow to shift, as evidenced from continued stagnation in investment and research[19], barring some notable exceptions[20,21].

Critical knowledge gaps resulting from sex-and gender-biased research

The ongoing inequitable access of pregnant populations to the health benefits of scientific advances is an often-overlooked manifestation of both sex and gender biases more broadly present in health research. Pregnancy is a unique physiological and immunological state, where the body undergoes substantial changes to support fetal development, birth, and lactation[22]. These adaptations have important implications for how medications are absorbed, distributed, and excreted (pharmacokinetics, PK), affecting their actions on the body (pharmacodynamics, PD), and consequently their efficacy and safety[23]. The approach of routinely excluding pregnant populations in basic, clinical, and translational research with humans, and relying on extrapolated PK/PD data from non-pregnant populations or pregnant animal models, overlooks critical species-specific biological variation through the life course. This results in inadequate and imprecise data to inform safety or dosing recommendations during pregnancy. Overwhelmingly, teratogenicity data are obtained from a patchwork of observational data that relies on accidental exposures to drugs or vaccines (e.g., the first COVID-19 vaccinations[24]), or post-marketing pregnancy exposure registry data[25]. These data are not optimal from clinical, methodological, nor ethical standpoints. They are prone to bias, typically not powered for statistical rigor, lack regulatory guidance, opportunistically mitigate accountability for poor outcomes, and capitalize on the precarious therapeutic positions of pregnant populations.

Pharmaceutical innovation for pregnancy-specific conditions also suffers from limited funding and research. Pregnancy symptoms of nausea and vomiting affect 70% of pregnant women[26], with the more severe hyperemesis gravidarum affecting 10% of pregnant women[27]. Despite high prevalence, associated physical and psychological distress lasting for weeks or months, and adverse perinatal outcomes, there is little recognition of the toll, and limited high-quality evidence exists to support any type of intervention, pharmaceutical or otherwise[28]. Similarly, pre-eclampsia accounts for nearly 15% of maternal deaths[1]; however the complex pathophysiology underlying cause and progression of this multi-organ disorder is poorly understood, with no curative treatments[29]. Currently preventative treatments for pre-eclampsia only include repurposed aspirin and calcium as prophylactic interventions for certain, high-risk pregnant populations[30,31]. Drug pipeline analyses suggest that new medications to slow or halt pre-eclampsia progression will not be available soon[32].

Sources of these critical knowledge gaps are related to stringent regulatory requirements and poor market incentives. There are high potential pharmaceutical liability and reputational risks, coupled with lower profitability[33]. Pregnancy's short duration over the life course and consequently limited timeframe for use of these drugs likewise detracts from investment. In addition to these barriers, there are the wider gender biases present in research. These include: whether, which, and how sex-related variations are studied, the prioritization of clinical conditions for pharmaceutical research and development (reflected by under-investment in health conditions such as endometriosis[34]), and which population groups either benefit from or are left behind in basic, clinical, and translational research (e.g., preference for male animal models in pre-clinical research[35]). These biases have further relegated research with pregnant populations and on new maternal therapeutics to being viewed as unfeasible[33].

The double disadvantage of pregnant women in low- and middle-income countries

Pregnant populations in low-and middle-income countries experience a disproportionate burden of maternal mortality[1]. Their exclusion from biomedical research represents a double disadvantage as both their gender and country of residence contribute to their reduced ability to make choices and act independently, and fewer opportunities to participate in and benefit from therapeutic advances.

Among other aspects, their geographical disadvantage is underpinned by structural determinants, such as the socio-economic and political factors that shape power asymmetries[36], in which research institutions and funders in high-income countries have disproportionate influence on the biomedical research agendas in low-and middle-income countries. This includes determining which health conditions and therapeutics are studied, what types of research are funded, and whether and how societal benefits of these interventions are realized in the countries where trials are conducted. These realities give limited opportunity for locally driven priority setting, research, and program implementation.

Since 2000, maternal health has benefitted from becoming a visible global health priority as one of the Millennium Development Goals. One measure of research effort is the growing number of trials addressing behavioral, clinical, and health system factors to promote maternal and newborn health in low-and middle-income countries[37]. Yet only one-quarter of these trials address major causes of maternal mortality, and trial questions are not representative of epidemiological burdens or priorities[37]. For example, while pre-existing maternal health conditions such as cardiac and endocrine diseases contribute to 14% of maternal deaths, only 4% of trials address these causes[37]. Pharmaceutical innovations for the maternal/fetal-infant dyad should be designed and implemented in-context and in-line with public health burden, accounting for health system characteristics, and local political, social and cultural determinants of health and well-being. The HIV field and successes of antiretroviral therapies to prevent mother-to-child transmission has demonstrated that fair inclusion of the maternal-fetal/infant dyad into trial research is feasible and enormously beneficial[17]. There is much that can be learned from these successes and applied to the broader field of maternal health.

Undervaluation of perspectives and experiences of pregnant populations

Biomedical research has historically undervalued the expertise of lived experience, including in maternal health[38]. Few pregnancy-related trials are informed by the perspectives of people targeted by or delivering the intervention[39]. Moreover, despite the potential for formative research and process evaluations to elicit important insights into what does and does not work, and why, these methods are not consistently used alongside trials. When they are, they can reveal critical information about the intersecting influences of the structural determinants of health. For example, a qualitative study conducted alongside a trial to introduce community-based screening and treatment for malaria in Benin found that fears of trial procedures and high loss-to-follow up was explained by the convergence of social, political, health system, and trial-related factors[40].

Currently, more is known about barriers and facilitators that prevent the inclusion of pregnant populations in research, but less about the perspectives and experiences of pregnant women and gender diverse pregnant people, families, and healthcare providers that can limit their participation in studies for which they are eligible. This is especially the case, but not limited to low-and middle-income countries that experience the highest burden of maternal ill-health. Key questions that must be asked include: How do these stakeholders understand biomedical research in their contexts, including therapeutic uncertainty and hope? How are risks and benefits to the maternal-fetal dyad balanced? How do gendered power relations within the health system and home environments affect research participation? To begin answering these questions, the ongoing Accelerating Innovation for Mothers-Gender (AIM-Gender) collaboration[41] has undertaken an evidence synthesis[42], with ongoing qualitative research in India and Nigeria to generate critical evidence in support of genuine and ethically-informed engagement of pregnant populations in research. Further similar research is warranted alongside studies which include these populations.

Our call to action

A substantial unfinished agenda to improve participation of pregnant populations in biomedical research exists. We call on the regulatory, research and development, innovation, and global health communities to act now to eliminate this harmful gender bias that negatively impacts maternal health. We propose the following actions. First, reciprocal

partnerships must grow between and among research and regulatory stakeholders across all geographies, focusing on shared leadership and strengthening collaborative research capacity. Second, multi-disciplinary research designed to answer complex questions about how to safely encourage participation of pregnant populations across all stages of biomedical research must be prioritized, particularly in settings with the greatest maternal mortality burden. Third, awareness must be raised among upstream and downstream stakeholders of the value and ethical imperative of new research and development knowledge to improve maternal health through pharmaceutical innovation. Fourth, funders, regulators and ethics committees must reorientate their focus to responsibly include, rather than presumptively exclude. Justifications should be given and scientifically defended when pregnant populations are excluded from interventional research that has potential for benefit. Such interventional research must include treatments for all conditions that affect pregnant populations, not only pregnancy-specific conditions. Fifth, regulatory analyses are required in low-and middle-income countries to examine existing bottlenecks preventing equitable inclusion of pregnant populations in biomedical research. This must then culminate in implementable recommendations.

Collective and simultaneous action holds great potential to advance the health entitlements of pregnant women and gender diverse pregnant people. Tackling these entrenched gender inequities affecting biomedical research and development via reciprocal partnerships, multi-disciplinary research, pharmaceutical innovation, responsible inclusion, and alleviating regulatory bottlenecks has the potential to transform the health and well-being for all.

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Competing interests

The authors declare no competing interests.

Additional information

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