nature portfolio

# Peer Review File

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

Reviewers' comments:

Reviewer #1 (Remarks to the Author):

This Brief commentary heralds a call to action to eliminate gender biases in product development for pregnancy-specific conditions. The authors identify four critical roadblocks to be overcome to better represent pregnant women's interests in global biomedical research that span the inappropriate classification of pregnant women as "vulnerable", knowledge gaps arising from gender-biased research, geographic disadvantage of women in the Global South; and undervaluation of pregnant women's perspective and experiences.

Their call to action is visionary and calls for: - growing reciprocal partnerships among research and regulatory stakeholders; - prioritizing multi-disciplinary research designed to answer how to safely encourage participation of pregnant women across all biomedical research; - raising awareness among stakeholders on the value and ethical imperative of new research and development knowledge to improve maternal health; - re-orienting ethics committees to improve focus on responsible inclusion rather than presumptive exclusion; and - conducting regulatory analyses in countries of the Global South to examine bottlenecks preventing equitable inclusion of pregnant women that culminate in implementable recommendations.

This is a cogent, well written, novel, forward-thinking synthesis of the importance, complexities, and current obstacles to including pregnant women across all biomedical research.

These comments are offered to strengthen the text. Given the complexity of the topic, my comments provide details to convey potential nuances and considerations for reorganizing the roadblocks.

1. The first heading 'indoctrination of pregnant women as "vulnerable"' is difficult to understand as the meaning or intent of the word "indoctrination" is open to interpretation and thus unclear. Perhaps something like "Unnecessary classification" or "Protectionist categorization" might be better.

2. The second heading "Critical knowledge gaps resulting from gender-biased research" is not clearly conveyed. The content in this section is great, but a couple of overarching principles merit reframing. This section conflates both sex and gender to gender. Gender is a social construct, but pregnancy is based on biologic sex. In biomedical research overall, "sex as a biologic variable" has been overlooked in fundamental basic, translational, and clinical research for both pregnant and non-pregnant females. The gender-biased rationale for such exclusion that "women are too

complicated because they cycle and get pregnant" leads to profound knowledge gaps. There is multiple issue at play.

As the authors point out, the physiologic and immunological changes during pregnancy render pregnant as distinct from nonpregnant and critically important to study on its own. Fundamental scientific investigation in pregnant females is lacking. Broadly, worldwide 14-22% individuals enter pregnancy with a chronic condition, yet the medical management of each of these conditions and the safety and efficacy of novel or repurposed therapeutics remain understudied. Then there are the conditions that arise during pregnancy like preeclampsia. We don't know the biologic underpinnings of preeclampsia, so we don't know how to identify and reverse or to prevent preeclampsia in females. We only have one repurposed agent (aspirin) used in pregnancy to prevent preeclampsia in those at high risk who have been identified using a clinical algorithm.

Taken together these represent a gender-bias in several ways. There is a gender-bias ignoring the biologic differences that arise from "sex as a biologic variable" in nonpregnant individuals and that there may be further differences that occur during pregnancy. And most importantly, there is a gender-bias in prioritization of research to be done to ensure the safety and optimal health of pregnant persons (and nonpregnant females, in general, although not the focus of this piece).

3. In the next bullet, the "double disadvantage of women in the Global South" is a complex topic that merits additional reframing. This double disadvantage is rooted in global racism and the resultant structural disparity arising from that circumstance. Outside of pregnancy, novel therapies have been tested in the Global South whose ultimate purpose is for use in high income countries without regard for financing its provision there. Additionally, when Ebola occurred in this region, vulnerable pregnant individuals suffered greatly; nearly all fetuses and newborns died and most of the pregnant women died. Yet, pregnant women were excluded from vaccine development studies because of the perceived risk of including them. Yet, in other circumstances, contraceptive methods and vaccination were imposed on these vulnerable populations. It is not surprising that females and women this region experience hesitancy related to participating in research. This complexity is related to all four points raised in this piece.

The 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" applies not only to vulnerable pregnant people in the Global South, but more broadly across the world. Should this point be included here or in the prior bullet?

In considering how to revise this bullet, the authors are to be commended for using the example of HIV in pregnant women and its treatment as a success and of the untapped potential conferred in studying pregnant women to improve the health of women world-wide. An additional positive step

in the Global South is that maternal mortality related to structural disparities is being tackled by strengthening healthcare networks within some countries. These countries are centering maternal health as a priority for their nations and might be used as a model to address structural disparity in maternal health everywhere. This centering could be used to study medical conditions and their treatment in pregnant people.

4. For point 4 “Undervaluation of pregnant women’s perspectives and experiences”, the examples come from the Global South. It might be better to move those examples to the bullet on the Global South. Across the world, the pregnant woman’s perspective and experiences are undervalued. As everyone in the world was born to a pregnant person, the health of the world is improved by centering on maternal health and the relationship between the maternal-fetal dyad. Pregnant women have not lost their minds because they became pregnant. They are quite capable of determining what they can and can’t do for their health and that of their unborn and already living children. The research needs to be centered on what matters to them and providing them with information to enter into shared decision making with the medical team.

Pamela Stratton, MD

Reviewer #2 (Remarks to the Author):

This is a very well-written and compelling essay describing the implications of evidence gaps for treatments in pregnancy as well as potential pathways forward. The paper should be of interest to those who are concerned about the maternal health crisis, and emphasizes an issue that could have an outsize effect on the problem. It helpfully foregrounds new and promising initiatives to advance the evidence base and center to values and lives of pregnant women in the biomedical research agenda.

My only comment regards the language around “off label” use, which has been an enduring point of confusion for the policy, research and clinical communities. This paper reinforces this confusion, by failing to distinguish between drugs that are used on-label (according to the US FDA, although not all countries) during pregnancy (e.g., ebola therapy or the COVID vaccine) but have not been sufficiently studies in pregnancy (and thus lack PK and fetal safety data); and drugs that are used off-label (e.g., current “treatments” for preterm birth or hyperemesis) for which PK, fetal safety AND efficacy are lacking. I believe from reviewing the website that the AIM project tends to focus on the latter, but the paper foregrounds maternal mortality, which is no doubt a product of all kinds of evidence gaps, both for pregnancy associated disease (like asthma or COVID) and pregnancy-specific disease (like preterm birth and hyperemesis). Given the different challenges in evidence

generation and authorization, as well as public confusion and concern about off-label use in pregnancy, it seems like it would be important to distinguish between the two, by (at least) revising the language in lines 52-54, 77-78, and 128-129. Are there different recommendations that relate to the development of drugs for pregnancy-specific conditions vs. conditions that co-occur with pregnancy but lack pregnancy-specific dosing or safety data?

Also, please consider using gender inclusive language when describing individuals who may become pregnant.

**Responses to feedback from referees**

| Referee feedback | Authors' response |
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| **REFEREE 1** | |
| 1. The first heading 'indoctrination of pregnant women as "vulnerable"' is difficult to understand as the meaning or intent of the word "indoctrination" is open to interpretation and thus unclear. Perhaps something like "Unnecessary classification" or "Protectionist categorization" might be better. | Thank you for this feedback. We have changed the heading to use the phrase "Protectionist mindset", noting that while the formal categorization of pregnant women as a vulnerable class in research has been revoked, protectionist mindsets continue to persist.<br><br>The section heading now reads **Protectionist mindset of pregnant women as "vulnerable"** |
| 2. The second heading "Critical knowledge gaps resulting from gender-biased research" is not clearly conveyed. The content in this section is great, but a couple of overarching principles merit reframing. This section conflates both sex and gender to gender. Gender is a social construct, but pregnancy is based on biologic sex. In biomedical research overall, "sex as a biologic variable" has been overlooked in fundamental basic, translational, and clinical research for both pregnant and non-pregnant females. The gender-biased rationale for such exclusion that "women are too complicated because | Thank you for raising this important distinction. We have substantially revised this section [Pages 2 and 3, lines 104-146] to differentiate and highlight the ways in which both sex and gender biases underpin exclusion of pregnant women and people from clinical research. |

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| they cycle and get pregnant" leads to profound knowledge gaps. There is multiple issue at play.<br><br>As the authors point out, the physiologic and immunological changes during pregnancy render pregnant as distinct from nonpregnant and critically important to study on its own. Fundamental scientific investigation in pregnant females is lacking. Broadly, worldwide 14-22% individuals enter pregnancy with a chronic condition, yet the medical management of each of these conditions and the safety and efficacy of novel or repurposed therapeutics remain understudied. Then there are the conditions that arise during pregnancy like preeclampsia. We don't know the biologic underpinnings of preeclampsia, so we don't know how to identify and reverse or to prevent preeclampsia in females. We only have one repurposed agent (aspirin) used in pregnancy to prevent preeclampsia in those at high risk who have been identified using a clinical algorithm.<br><br>Taken together these represent a gender-bias in several ways. There is a gender-bias ignoring the biologic differences that arise from "sex as a biologic variable" in nonpregnant individuals and that there may be further differences that occur during pregnancy. And most importantly, there is a gender-bias in prioritization of research to be done to ensure the safety and optimal health of pregnant persons (and nonpregnant females, in general, although not the focus of this piece). | |

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| 3. In the next bullet, the "double disadvantage of women in the Global South" is a complex topic that merits additional reframing. This double disadvantage is rooted in global racism and the resultant structural disparity arising from that circumstance. Outside of pregnancy, novel therapies have been tested in the Global South whose ultimate purpose is for use in high income countries without regard for financing its provision there. Additionally, when Ebola occurred in this region, vulnerable pregnant individuals suffered greatly; nearly all fetuses and newborns died and most of the pregnant women died. Yet, pregnant women were excluded from vaccine development studies because of the perceived risk of including them. Yet, in other circumstances, contraceptive methods and vaccination were imposed on these vulnerable populations. It is not surprising that females and women this region experience hesitancy related to participating in research. This complexity is related to all four points raised in this piece.<br><br>The 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" applies not only to vulnerable pregnant people in the Global South, but more broadly | Thank you for this feedback. We have now highlighted the influence of structural factors in the geographical disadvantage experienced by pregnant women and people living in low-and middle-income countries [Page 4, lines 156-163]. The additional text is included below. We have included the previous paragraph to provide context for the additional detail. We have also discussed and decided as an author team to replace Global North and Global South with 'high-income' and 'low- and middle-income countries' to articulate the contexts that we are referring to more clearly.<br><br>*****<br>Pregnant populations in low-and middle-income countries experience a disproportionate burden of maternal mortality, and their exclusion from biomedical research represents an intersectional 'double disadvantage': both their gender and country of residence contribute to reduced agency and fewer opportunities to participate in and benefit from therapeutic advances.<br><br>Among other aspects, their geographical disadvantage is underpinned by structural determinants — the socio-economic and political factors that shape power asymmetries[38, 39], in this case between research stakeholders in high-income and low-and middle-income countries. What health conditions and commodities get studied, what research is funded, and whether and how societal benefits of these interventions are realised in |

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| across the world. Should this point be included here or in the prior bullet?<br><br>In considering how to revise this bullet, the authors are to be commended for using the example of HIV in pregnant women and its treatment as a success and of the untapped potential conferred in studying pregnant women to improve the health of women world-wide. An additional positive step in the Global South is that maternal mortality related to structural disparities is being tackled by strengthening healthcare networks within some countries. These countries are centering maternal health as a priority for their nations and might be used as a model to address structural disparity in maternal health everywhere. This centering could be used to study medical conditions and their treatment in pregnant people. | the countries where trials are conducted are determined by powerful institutions and funders in high-income countries, with limited opportunity for locally-driven priority setting, research, and program implementation[40].<br><br>*****<br>We agree with the reviewer's comment about progress that has been made in low-and middle-income countries related to identifying and addressing disparities in access to maternal healthcare and life saving interventions to improve maternal health and survival. To this end, we think it is important to highlight the growing number of perinatal and maternal health clinical trials in these geographical settings, while also noting misalignment between trial focal areas and changing epidemiological burdens of causal factors. To make this point, we have decided to retain the example in this section but have further contextualized it as below [Pages 4-5, lines 165-178] to reiterate the importance of research being designed and implemented based on local needs and conditions.<br><br>Since 2000, maternal health has benefitted from becoming a visible global health priority in the Millennium Development Goals. One measure of research effort is the growing number of trials addressing behavioural, clinical, and health system factors to promote maternal and newborn health in low-and middle-income countries[41]. Yet, only one-quarter of these trials address major causes of maternal mortality, and trial questions are not representative of epidemiological burdens or priorities[41]. For |

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| | 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[41]. 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[42]. There is much to be learned and applied to the broader field of maternal health. |
| 4. For point 4 "Undervaluation of pregnant women's perspectives and experiences", the examples come from the Global South. It might be better to move those examples to the bullet on the Global South. Across the world, the pregnant woman's perspective and experiences are undervalued. As everyone in the world was born to a pregnant person, the health of the world is improved by centering on maternal health and the relationship between the maternal-fetal dyad. Pregnant women have not lost their minds because they became pregnant. They are quite capable of determining what they can and can't do for their health and that of their unborn and already living children. The research needs to | Thank you for this suggestion. We have decided to retain the example from Benin and information about AIM Gender's ongoing work in Nigeria and India within this section. While this information pertains to low-and middle-income contexts, they emphasize the value of integrating the knowledge and expertise of pregnant women and their communities in the design, implementation and evaluation of research.<br><br>However, as the reviewer notes, we acknowledge that the undervaluing of knowledge is not restricted to low-and middle-income contexts alone, and have made some minor modifications to language in this section to indicate as such [Page 5, lines 195-197]. |

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| be centered on what matters to them and providing them with information to enter into shared decision making with the medical team. | |
| **REFEREE 2** | |
| 1. My only comment regards the language around "off label" use, which has been an enduring point of confusion for the policy, research and clinical communities. This paper reinforces this confusion, by failing to distinguish between drugs that are used on-label (according to the US FDA, although not all countries) during pregnancy (e.g., ebola therapy or the COVID vaccine) but have not been sufficiently studies in pregnancy (and thus lack PK and fetal safety data); and drugs that are used off-label (e.g., current "treatments" for preterm birth or hyperemesis) for which PK, fetal safety AND efficacy are lacking. I believe from reviewing the website that the AIM project tends to focus on the latter, but the paper foregrounds maternal mortality, which is no doubt a product of all kinds of evidence gaps, both for pregnancy associated disease (like asthma or COVID) and pregnancy-specific disease (like preterm birth and hyperemesis). Given the different challenges in evidence generation and authorization, as well as public confusion and concern about off-label use | Thank you for raising these important distinctions. We have removed any reference to the phrase off-label, and instead used descriptive language to note the lack of fit-for-purpose drugs for pregnancy-related complications and use of medications without sufficient efficacy and safety data for treatment of co-occurring health conditions.<br><br>The changes made are as follows:<br>Page 2, lines 54-56: Most existing treatments for pregnancy-related complications are repurposed from other conditions, and medications for co-occurring health conditions are widely used without reliable efficacy and safety data for pregnant populations.<br><br>Page 3, lines 77-80: Deleted the phrase off-label use. The sentence now reads "Most concerningly, such a *risk-averse* approach has paradoxically shifted responsibility for (and potential risks of) therapeutic drug use from closely monitored clinical trials to everyday clinical care"<br><br>Page 3, lines 116-118: Deleted the phrase off-label use. Overwhelmingly, teratogenicity data are obtained from a patchwork of observational data that relies on accidental |

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| in pregnancy, it seems like it would be important to distinguish between the two, by (at least) revising the language in lines 52-54, 77-78, and 128-129. Are there different recommendations that relate to the development of drugs for pregnancy-specific conditions vs. conditions that co-occur with pregnancy but lack pregnancy-specific dosing or safety data? | exposures to drugs or vaccines (e.g., the first COVID-19 vaccinations[25]), or post-marketing pregnancy exposure registry data[26].<br><br>The process of generating, synthesizing and appraising data to determine safety and efficacy are no different for drugs for pregnancy-specific conditions vs conditions that co-occur with pregnancy. Hence, we are of the opinion that the recommendations are the same. However, with increasing age at pregnancy, and as fertility windows expand over a person's reproductive life course with assistance from reproductive technologies, the probability of co-occurring medical conditions such as diabetes, lupus, epilepsy etc., is increasing, making the need for pregnancy-specific dosing and safety data even more important. We have made some minor edits to the 4th recommendation in the Call to Action on Page 6, lines 218-223, as follows:<br><br>Fourth, re-orient funders, regulators and ethics committees to improve focus on responsible inclusion, rather than presumptive exclusion. Justifications should be given and scientifically defended when pregnant and lactating populations are excluded from interventional research that has potential for benefit. Such interventional research must include drugs for all conditions that affect pregnant populations, not only pregnancy-specific conditions. |
| 2. Also, please consider using gender inclusive language | Thank you for this comment, with which we broadly agree. We |

| Referee feedback | Authors' response |
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| when describing individuals who may become pregnant. | have discussed with the co-author team in detail and propose the following approach to ensure gender inclusivity.<br>In our Comment, we want to place special emphasis on 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. As more recent understandings of gender have evolved to include gender identity (e.g. transgender and non-binary people), we recognise and acknowledge the value of gender terminology that is representative of all individuals with the reproductive capacity become pregnant, while also ensuring that individual identities are not erased, for example, by referring only to 'pregnant people' or 'pregnant individuals'.<br><br>With these aspects in mind, we have taken the following approach to use of gendered language in this Comment:<br>• Updated text that broadly refers to the research needs and interests of individuals capable of getting pregnant to "pregnant women and gender diverse pregnant people"<br>• Retained "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. |

REVIEWERS' COMMENTS:

Reviewer #1 (Remarks to the Author):

This Brief commentary is a call to action to eliminate gender biases in product development that results in the fair inclusion of pregnant women and gender diverse pregnancy people in biomedical research. The authors identify four critical roadblocks to be overcome to better represent pregnant women's interests in global biomedical research that span the protectionist mindset of pregnant women as "vulnerable", critical knowledge gaps arising from sex- and gender-biased research, disadvantage of pregnant women and gender diverse pregnant people in low- and middle-income countries; and undervaluation of perspective and experiences of pregnant women and gender diverse people.

Their call to action is visionary and calls for: - growing reciprocal partnerships among research and regulatory stakeholders; - prioritizing multi-disciplinary research designed to answer how to safely encourage participation of pregnant populations across all biomedical research; - raising awareness among stakeholders on the value and ethical imperative of new research and development knowledge to improve maternal health; - re-orienting funders, regulators, and ethics committees to improve focus on responsible inclusion rather than presumptive exclusion; and - conducting regulatory analyses in low and middle income countries to examine bottlenecks preventing equitable inclusion of pregnant women that culminate in implementable recommendations.

This revision is a cogent, well written, novel, forward-thinking synthesis of the importance, complexities, and current obstacles to including pregnant women across all biomedical research. Overall, the quality and focus of this manuscript is outstanding.

The concerns and comments I raised in the prior review are addressed well.

I offer a couple of comments regarding word choices.

On page 2, In the sentence, "Such responses have also led to inaction by public and private biomedical research actors to advance health during pregnancy", the use of the word "actor" has a thespian connotation. Consider replacing it with a more descriptive but neutral word like enterprise or establishment or authorities.

On page 4 in the second to last paragraph “What health conditions and commodities get studied”, do you mean “commodities” or “comorbidities”. This reviewer is unfamiliar with commodities being studied in human health.

Reviewer #2 (Remarks to the Author):

The authors have addressed my concerns.

**Responses to feedback from referees**

| Referee feedback | Authors' response |
|---|---|
| **REFEREE 1** | |
| 1. On page 2, In the sentence, "Such responses have also led to inaction by public and private biomedical research actors to advance health during pregnancy", the use of the word "actor" has a thespian connotation. Consider replacing it with a more descriptive but neutral word like enterprise or establishment or authorities. | Thank you for this feedback. The Editor has offered an alternative word, which the authors are happy with. The sentence now reads:<br><br>"Such responses have resulted in inaction by public and private biomedical research organisations and limited advances that could improve health during pregnancy." |
| 2. On page 4 in the second to last paragraph "What health conditions and commodities get studied", do you mean "commodities" or "comorbidities". This reviewer is unfamiliar with commodities being studied in human health. | We have replaced the word "commodities" with "therapeutics". The sentence now reads:<br><br>"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 realised in the countries where trials are conducted." |
| **REFEREE 2** | |
| 1. The authors have addressed my concerns. | Thank you |