Stress and Its Consequences—Biological Strain

David K. Stevenson, MD[1] Ian H. Gotlib, PhD[2] Jessica L. Buthmann, PhD[2] Ivana Marić, PhD[1]
Nima Aghaeepour, PhD[3] Brice Gaudilliere, MD, PhD[3] Martin S. Angst, MD[3] Gary L. Darmstadt, MD[1]
Maurice L. Druzin, MD[4] Ronald J. Wong, PhD[1] Gary M. Shaw, DrPH[1] Michael Katz, MD[1]

[1] Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, California
[2] Department of Psychology, Stanford University School of Humanities and Science, Stanford, California
[3] Department of Anesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, California
[4] Department of Obstetrics and Gynecology—Maternal-Fetal Medicine, Stanford University School of Medicine, Stanford, California

Address for correspondence David K. Stevenson, MD, Division of Neonatal and Developmental Medicine, Department of Pediatrics, Center for Academic Medicine (CAM), Stanford University School of Medicine, 453 Quarry Road, Stanford, CA 94305-5660 (e-mail: dstevenson@stanford.edu).

Am J Perinatol

Abstract

Understanding the role of stress in pregnancy and its consequences is important, particularly given documented associations between maternal stress and preterm birth and other pathological outcomes. Physical and psychological stressors can elicit the same biological responses, known as biological strain. Chronic stressors, like poverty and racism (race-based discriminatory treatment), may create a legacy or trajectory of biological strain that no amount of coping can relieve in the absence of larger-scale socio-behavioral or societal changes. An integrative approach that takes into consideration simultaneously social and biological determinants of stress may provide the best insights into the risk of preterm birth. The most successful computational approaches and the most predictive machine-learning models are likely to be those that combine information about the stressors and the biological strain (for example, as measured by different omics) experienced during pregnancy.

Keywords
- pregnancy
- preterm birth
- omics
- machine learning

The purpose of this short commentary is to provide a perspective on the role of maternal stress in pregnancy. First, however, it is important to recognize that there are both physical and psychological stressors and that they can have similar consequences for individuals, that is, both physical and psychological stressors can elicit the same biological responses. In this regard, individuals are limited in how they respond to stressors, whether physical or psychological in nature. In understanding the concept of "stress," it is useful to note that any physical or psychological event that provokes a shift toward a more extreme biological state can be defined as "stressful" or as a biological strain. The importance of measuring both stressors and strain has long been acknowledged in the field, since Holmes and Rahe[1] in 1967 first developed a rating scale of recent life changes requiring various degrees of social readjustment. Although it is flawed by the conflating of stressors and strain, this scale has been used to quantify the amount of strain and predict the onset of illness, likely due to ineffective coping.

A second important point is that the experience of stress is contextual. That is, the same stressor is not likely to elicit the same level of biological strain in all people, depending on the context (e.g., availability of resources) and the individuals' ability to relieve the stressful situation. Similarly, the same stressor may produce different levels of biological strain at different times for the same person, depending on the context and on what other stressors are co-occurring. Finally, chronic stressors, like poverty and race-based discriminatory treatment,[2] may create a legacy or trajectory of biological strain that personal coping cannot relieve. In such

received
December 6, 2021
accepted
March 11, 2022

DOI https://doi.org/10.1055/a-1798-1602.
ISSN 0735-1631.

a circumstance, persistent biological responses in the absence of socio-behavioral or societal changes that mitigate poverty and personally focused or systemic racism may be harmful to the individual.

Understanding the role of stress in pregnancy and its outcomes is especially important given the unique biological state of pregnancy—a stressor in itself, the documented associations between maternal stress and preterm birth and other pathological outcomes,[3] and the disparate rates of maternal mortality in the United States.[4] It is critical to note that simply identifying a possible stressor is not sufficient to predict the level of biological strain that the stressor (whether physical or psychological) might cause; instead, considering the putative stressor and the consequent biological strain together is essential for this purpose. Moreover, it is important to understand whether the biological strain associated with the occurrence of a stressor can be ameliorated sufficiently within a specified timeframe to avoid harm. Effectively resolving biological strain is a characteristic of resilience. Thus, an integrative approach that simultaneously considers the social (e.g., life changes) and the biological determinants of preterm birth should provide the best insight into the risk of preterm birth. The most successful computational approaches and the most predictive machine-learning models are likely to be ones that combine information about both the stressors and the biological and physiological strain (as measured by different omics) experienced by a person.[5]

Researchers have shown that acute stress due to the occurrence of a major life event (suggesting a need for social readjustment) can affect a pregnancy, especially when it occurs in the first trimester[6]; importantly, however, a woman's *perception* of an event can be at least as important as the event itself.[7] Moreover, chronic stress during pregnancy, regardless of how it is measured, has been found to be associated with an increased risk of preterm birth,[8,9] presumably because of the ongoing biologic strain. Disentangling a woman's experience of stress is especially difficult in the case of chronic stress that may arise from a wide and diverse range of stimuli. To address this challenge, recent machine-learning approaches that are capable of building meaningful models based on a large number of features can be used to analyze various factors that are involved in chronic stress. For example, graphical learning models have been used previously to capture complex relations among a large number of stress variables, preterm birth, and involved pathways.[10] In addition, nonlinear predictive modeling has been used successfully to identify psychosocial and stress-related factors occurring early in pregnancy that predict the risk of spontaneous preterm birth.[5]

Previous work integrating multiomics datasets (e.g., genomics, transcriptomics, proteomics, metabolomics, immunomics, epigenomics, lipidomics, and microbiomics) using machine-learning approaches has identified molecular changes that occur during pregnancy, resulting in highly accurate models predicting gestational age,[11] preterm birth,[12] onset of labor,[13,14] and preeclampsia. It is plausible that alterations in any of the omics measures due to stress can be captured in the mother and the offspring, including stress-related changes in DNA methylation,[15] microRNA,[16] and the metabolome.[17] Integrating multiomics with stressors and perceived stress variables could further elucidate the effects of stress on the outcomes of pregnancy, such as preterm birth, low birthweight, and various neonatal outcomes, thereby providing us with refined predictive models. Moreover, this integration could lead to the identification of associations between stressors and different measurements of women's omics biology and possible mechanisms by which they are related. These integrative approaches involve analyses of high-dimensional data with a relatively small number of samples (subjects) and an extremely large number of features. Existing forms of machine learning that apply feature reduction[18] and sparse modeling[19] can be used to identify the most important features and build meaningful and accurate models of pregnancy outcomes based on these predictors. Such integrative approaches might provide insight into how various stressors create strain, whether acute and resolvable, or chronic and intractable, with long-term health consequences. Advanced computational approaches, including knowledge graphs,[20] neural networks,[21] and ultimately, artificial general intelligence[22] might lead to the identification of stress-based modifiable factors that can steer biological systems (and, consequently, patient outcomes) without the need for costly pharmacological or physiological interventions. More precise interventions can improve patient outcomes and reduce high rates of maternal mortality, particularly among women of color.[4,23]

Because biological strain itself can influence the clinical trajectory of an individual and an individual's predisposition to develop pathological conditions (depending on their genetic capacity to respond to environmental challenges), it is essential that we alleviate both such biological strain and any identified stressors. For example, the chronic stress of racism, a social construct resulting in race-based personal or systemic discriminatory treatment, is particularly insidious because it is not easily resolved, and its associated biological strain can persist, even from one generation to the next through epigenetic influences, with damaging effects—sometimes acute and sometimes long term. Based on our research[24,25] and that of others,[23,26] the biological strain associated with racism in all its forms[2] may alter inflammatory functioning. Of course, there are likely to be many causative pathways that lead to one final common pathway for preterm parturition as a result of racism. Interestingly, although normal parturition involves inflammation, it is highly programmed with a transition point little less than 1 month before the onset of labor, characterized by a shift in gene expression and cell signaling from a disposition of tolerance to one of rejection—labor.[13,14] This biochemical shift is evidence of a transcriptomic or immune clock of pregnancy that can be strained or dysregulated by physical or psychological stressors.[11,27–29] The usefulness of an integrative approach for predicting preterm labor and a multifaceted approach to its prevention is logical strategies that can be derived from accumulating evidence.

In sum, whether some specific feature or collection of features that characterize a pregnant woman's circumstance are conceptualized as stressful requires more than simply

identifying the possible stressor(s). It requires measuring biology at various levels of "omics" interrogation. Thus, the degree of perturbation and its duration become relevant to determining the likelihood of harm or leading to an adverse outcome. Such an integrated approach to understanding stress also provides the opportunity to understand resilience, which reflects a rebalancing to a healthy state of repose. Such a state is characterized not by sustained moderation but by a flexibility of disposition or dynamism in response to life's stressors.

In conclusion, it is important to note that not all types of stress have negative effects on health or are necessarily associated with adverse outcomes. Stress can also contribute to useful, or even necessary, strain. For example, bone growth depends on mechanical stress. Similarly, pregnancy is itself a form of stress that shapes a woman's immunological, metabolic, and neurohormonal systems in ways that are necessary for the birth of a healthy offspring. Finally, in the simplest terms, "stress" is often defined by those who study it not by those who experience it. There is the rub. We must find ways to define stress in terms of what the person who is experiencing it considers "stressful" not by what an investigator believes. As a result, we need to define stress in terms of both the stressors themselves and the strain they create.

Conflict of Interest

None declared.

Acknowledgment

This work was supported, in part, by the Prematurity Research Fund, the March of Dimes Prematurity Research Center at Stanford University, the Charles B. and Ann L. Johnson Research Fund, the Christopher Hess Research Fund, the Providence Foundation Research Fund, the Roberts Foundation Research Fund, and the Stanford Maternal and Child Health Research Institute.

References

1 Holmes TH, Rahe RH. The social readjustment rating scale. J Psychosom Res 1967;11(02):213–218
2 Braveman PA, Arkin E, Proctor D, Kauh T, Holm N. Systemic and structural racism: definitions, examples, health damages, and approaches to dismantling. Health Aff (Millwood) 2022;41(02):171–178
3 Wadhwa PD, Entringer S, Buss C, Lu MC. The contribution of maternal stress to preterm birth: issues and considerations. Clin Perinatol 2011;38(03):351–384
4 Singh GK. Trends and social inequalities in maternal mortality in the United States, 1969–2018. Int J MCH AIDS 2021;10(01):29–42
5 Becker M, Mayo JA, Phogat NK, et al. Deleterious and protective psychosocial and stress-related factors predict risk of spontaneous preterm birth. Am J Perinatol 2021 (e-pub ahead of print). Doi: 10.1055/s-0041-1729162.
6 Hobel CJ, Goldstein A, Barrett ES. Psychosocial stress and pregnancy outcome. Clin Obstet Gynecol 2008;51(02):333–348
7 Hedegaard M, Henriksen TB, Secher NJ, Hatch MC, Sabroe S. Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology 1996;7(04):339–345
8 Guardino CM, Schetter CD. Coping during pregnancy: a systematic review and recommendations. Health Psychol Rev 2014;8(01):70–94
9 Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, Van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995;39(05):563–595
10 Mesner O, Davis A, Casman E, et al. Using graph learning to understand adverse pregnancy outcomes and stress pathways. PLoS One 2019;14(09):e0223319
11 Ghaemi MS, DiGiulio DB, Contrepois K, et al. Multiomics modeling of the immunome, transcriptome, microbiome, proteome and metabolome adaptations during human pregnancy. Bioinformatics 2019;35(01):95–103
12 Jehan F, Sazawal S, Baqui AH, et al; Alliance for Maternal and Newborn Health Improvement, the Global Alliance to Prevent Prematurity and Stillbirth, and the Prematurity Research Center at Stanford University. Multiomics characterization of preterm birth in low- and middle-income countries. JAMA Netw Open 2020;3(12):e2029655
13 Ando K, Hédou JJ, Feyaerts D, et al. A peripheral immune signature of labor induction. Front Immunol 2021;12:725989
14 Stelzer IA, Ghaemi MS, Han X, et al. Integrated trajectories of the maternal metabolome, proteome, and immunome predict labor onset. Sci Transl Med 2021;13(592):eabd9898
15 Cao-Lei L, Massart R, Suderman MJ, et al. DNA methylation signatures triggered by prenatal maternal stress exposure to a natural disaster: project Ice Storm. PLoS One 2014;9(09):e107653
16 Zucchi FC, Yao Y, Ward ID, et al. Maternal stress induces epigenetic signatures of psychiatric and neurological diseases in the offspring. PLoS One 2013;8(02):e56967
17 Paxman EJ, Boora NS, Kiss D, et al. Prenatal maternal stress from a natural disaster alters urinary metabolomic profiles in project ice storm participants. Sci Rep 2018;8(01):12932
18 Cunningham JP, Ghahramani Z. Linear dimensionality reduction: survey, insights, and generalizations. J Mach Learn Res 2015;16:2859–2900
19 Hastie T, Tibshirani R, Wainwright M. Statistical Learning with Sparsity: The Lasso and Generalization. Boca Raton, FL: CRC Press; 2015
20 Ruiz C, Zitnik M, Leskovec J. Identification of disease treatment mechanisms through the multiscale interactome. Nat Commun 2021;12(01):1796
21 Espinosa C, Becker M, Marić I, et al; Prematurity Research Center at Stanford. Data-driven modeling of pregnancy-related complications. Trends Mol Med 2021;27(08):762–776
22 Kazzazi F. The automation of doctors and machines: a classification for AI in medicine (ADAM framework). Future Healthc J 2021;8(02):e257–e262
23 Giurgescu C, Misra DP, Slaughter-Acey JC, et al. Neighborhoods, racism, stress, and preterm birth among African American women: a review. West J Nurs Res 2022;44(01):101–110
24 Lopez M, Ruiz MO, Rovnaghi CR, et al. The social ecology of childhood and early life adversity. Pediatr Res 2021;89(02):353–367
25 Stevenson DK, Wong RJ, Aghaeepour N, et al. Towards personalized medicine in maternal and child health: integrating biologic and social determinants. Pediatr Res 2021;89(02):252–258
26 Ajilore O, Thames AD. The fire this time: the stress of racism, inflammation and COVID-19. Brain Behav Immun 2020;88:66–67
27 Aghaeepour N, Ganio EA, Mcilwain D, et al. An immune clock of human pregnancy. Sci Immunol 2017;2(15):eaan2946
28 Aghaeepour N, Lehallier B, Baca Q, et al. A proteomic clock of human pregnancy. Am J Obstet Gynecol 2018;218(03):347.e1–347.e14
29 Peterson LS, Stelzer IA, Tsai AS, et al. Multiomic immune clockworks of pregnancy. Semin Immunopathol 2020;42(04):397–412