

June 18, 2020

Patrizia Cavazzoni, M.D.
Acting Director, Center for Drug Evaluation and Research
U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Cavazzoni,

Earlier this year, the National Consumers League and March of Dimes convened a group of maternal and infant health stakeholders to discuss the urgent issue of improving health outcomes for mothers and babies. As you know, the leading cause of infant death in the U.S. is premature birth, which has devastating effects on families and is very costly to our health care system.ⁱ Among those babies who do survive, short and long-term complications can accompany preterm birth.

The preterm birth rate among U.S. black women is 49 percent higher than the rate among all other women.ⁱⁱ Research supports the premise that race itself is not the root cause of preterm birth and factors associated with being African American – including experiencing institutional racism, racial health inequities, and higher psychosocial stress – contribute to prematurity.^{iii,iv}

Lack of access to high-quality health care and support systems for pregnant women, biases in the health care system, poverty, a paucity of safe or effective therapeutic options, and the multifactorial etiology of preterm birth are among the complex factors that have historically contributed to prematurity. In the U.S., which has among the highest rates of industrialized nations in the world, African American, American Indian and Alaska Native and Hispanic women have substantially higher rates of preterm birth than white women.^v

There is no single solution that will improve maternal and infant health outcomes. Instead, we need every option available—from optimizing public policies to increased investments in women’s health research and improvements in the delivery of care—to prevent the devastating and life-long consequences that prematurity can have on infants, mothers and families, and our health care system. In this vein, a history of spontaneous preterm birth is a leading risk factor for recurrent preterm birth; women with this history are at 2.5 times increased risk of subsequent preterm birth.^{vi} Providers have few therapeutic options to prevent recurrent preterm birth for these at-risk mothers, many of whom are concerned based upon their own prior experience.

Among the topics we discussed at the earlier meeting was the anxiety expressed by leaders who are concerned about withdrawal of treatments for mothers who are at risk for preterm birth. It’s through this lens that **we urge careful, deliberate consideration of the potential impact on patients, including potential hospitalizations during these anxious times, and the public health consequences if FDA approval of 17P, or hydroxyprogesterone caproate (branded and generic formulations) is withdrawn.**

17P is the only FDA-approved therapy that reduces the risk of preterm birth and has been used for nearly a decade. Its approval was supported by a landmark multi-center randomized controlled trial conducted by the Maternal-Fetal Medicine Units (MFMU) Network.^{vii} There is extensive clinical experience using the product following the *New England Journal of Medicine* publication in 2003 and medical society guidelines continue to recommend its use in this patient population.^{viii,ix} Removing this safe option in the absence of suitable alternatives would leave patients and providers significantly disadvantaged in the fight against prematurity.

We understand that FDA required a second trial and that this trial, PROLONG, did not confirm the original MFMU reduction in recurrent preterm birth. As leaders in the fight against prematurity, we have serious concerns that a regulatory decision resulting in withdrawal of FDA-approved 17P would be predicated upon a single study largely conducted outside of the U.S., particularly when it is well recognized that the U.S. experiences markedly higher rates of preterm birth.

We know that the FDA is encountering tremendous challenges in addressing the ongoing COVID-19 pandemic. It is vitally important to underscore the deep public health need for ongoing access to approved treatment options for at-risk pregnant women, including those that reduce their risk of being admitted to the hospital for early delivery.

This is especially important within the current environment and beyond, as adverse outcomes such as preterm birth have been reported among babies born to mothers with COVID-19.^x Throughout this ongoing public health crisis, pregnant women and their unborn babies are undoubtedly under extreme stress and we speak with one voice in advocating for care that will help ensure the very best chances for full-term birth. Additionally, COVID-19 appears to disproportionately impact the same population that is most likely to experience preterm birth. As such, ensuring continued access to treatment is vital.

We applaud FDA for the careful and measured approach taken thus far, including holding a public Advisory Committee on October 29, 2019. While we know that additional data need to be generated to better understand which populations benefit the most from 17P, we do not believe that removing FDA-approved forms of 17P as a means for further study is either a feasible or reasonable approach. A new trial conducted in the U.S. would likely face similar enrollment challenges experienced during the PROLONG trial. Further, removal of FDA-approved 17P would deny at-risk pregnant women access to a therapy that previously demonstrated substantial efficacy and safety in the U.S. population (Meis study).

In addition, we are concerned that if providers can't access FDA-approved forms of 17P, this will expose pregnant women to non-evidence based or compounded medications, which have no labeling to provide guidance on administration, contraindications, or potential side effects. This can pose a safety risk to patients and lead to medical-legal risks for providers.

There is also the issue of study population differences between the original Meis trial and the more recent trial, PROLONG. In the Meis trial, 17P reduced the risk of recurrent preterm birth by one-third compared to placebo and was studied in American women with multiple preterm birth risk factors in primarily academic medical centers. In contrast, PROLONG, which did not show benefit although reaffirmed safety, studied 17P in mostly Eastern European women with significantly fewer risk factors

and much lower rates of preterm birth in the placebo group. It should also be noted that health care systems in these Eastern European countries offer routine access to preventive care and have implemented programs to improve maternal care.^{xi}

There is also recognition of the association between institutional racism and adverse birth outcomes among women of color.^{xii} Social determinants of health and inequality, such as where a woman lives, her socioeconomic status, access to health care as well as high-quality nutrition and other support systems have been recognized as important predictors of maternal morbidity and mortality by Black women’s advocacy groups and multiple medical organizations, including the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine.^{xiii, xiv}

Currently, the only pharmacological agent that exists to offer women to prevent a recurrent preterm birth is 17P. We are concerned that removing access to the only approved therapy could serve to deepen health inequities in this group of women. Moving forward, we feel it is vital to study the effects of 17P in patients that are most reflective of the populations of women that providers care for in the United States.

We also believe it is critical that providers and patients continue to have access to FDA-approved treatments that are held to rigorous manufacturing standards, GMP and have proven efficacy in a patient population based in or very similar to the U.S.

We urge the agency to consider alternative ways to further evaluate and define the patient populations that most benefit from 17P, without depriving women of access. Preterm birth places mothers and their babies at significant risk, and patient access to a proven intervention should not be compromised without substantial evidence that there is lack of benefit in the appropriate population—which we don’t believe we have today.

Thank you in advance for your always thoughtful and careful consideration of this issue and for understanding what is at stake for this vulnerable population.

Sincerely,
American Society for Reproductive Medicine
Association of Women’s Health, Obstetric & Neonatal Nurses
Black Mamas Matter Alliance
Black Women’s Health Imperative
Expecting Health
HealthyWomen
Jewish Women International
March of Dimes
National Birth Equity Collaborative
National Coalition for Infant Health
National Consumers League
National Medical Association
PA Foundation
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Audrey Gassman, M.D., Deputy, Division of Urology, Obstetrics and Gynecology

ⁱ March of Dimes. 2019 March of Dimes Report Card. <https://www.marchofdimes.org/mission/reportcard.aspx>. Accessed June 1, 2020.

ⁱⁱ March of Dimes. 2019 March of Dimes Report Card.

ⁱⁱⁱ Eichelberger KY, Alson JG, and Doll KM. Should Race Be Used as a Variable in Research on Preterm Birth? *AMA J Ethics*. 2018;20(3):296-302 <https://journalofethics.ama-assn.org/article/should-race-be-used-variable-research-preterm-birth/2018-03>.

^{iv} American College of Nurse-Midwives. Position Statement: Racism and Racial Bias.

<https://www.midwife.org/acnm/files/ACNMLibraryData/UPLOADFILENAME/00000000315/PS-Racism-and-Racial-Bias-26-Apr-18.pdf>. Accessed June 1, 2020.

^v March of Dimes. Born Too Soon. <https://www.marchofdimes.org/mission/global-preterm.aspx#tabs-3>.

Accessed June 1, 2020; March of Dimes. 2019 March of Dimes Report Card.

^{vi} Loftin RW, Habli M, Snyder C, et al. Late preterm birth. *Rev Obstet Gynecol*. 2010;3:10-19.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2876317>.

^{vii} Meis PJ, Klebanoff M, Thom E, et al. Prevention of Recurrent Preterm Delivery by 17 Alpha-Hydroxyprogesterone Caproate. *N Engl J Med*. 2003;348:2379-2385. <https://www.nejm.org/doi/full/10.1056/NEJMoa035140>.

^{viii} American College of Obstetricians and Gynecologists. Practice Advisory: Clinical guidance for integration of the findings of the PROLONG study: Progestin's Role in Optimizing Neonatal Gestation. <https://www.acog.org/Clinical-Guidance-and-Publications/Practice-Advisories/Clinical-guidance-for-integration-of-the-findings-of-The-PROLONG-study-Progestins-Role-in-Optimizing>. Accessed June 1, 2020.

^{ix} Society for Maternal-Fetal Medicine. Use of 17-alpha hydroxyprogesterone caproate for prevention of recurrent preterm birth. <https://www.sfm.org/publications/280-smfm-statement-use-of-17-alpha-hydroxyprogesterone-caproate-for-prevention-of-recurrent-preterm-birth>. Accessed June 1, 2020.

^x March of Dimes. Coronavirus Disease (COVID-19): What You Need to Know About Its Impact on Moms and Babies. <https://www.marchofdimes.org/complications/coronavirus-disease-covid-19-what-you-need-to-know.aspx>. Accessed June 1, 2020.

^{xi} MP Shuvalova et al. Maternity Care in Russia: Issues, Achievements, and Potential. *J Obstet Gynaecol Can*. 2015 Oct;37(10):865-71; United States Agency for International Development, Ukraine Maternal and Infant Health Project (MIHP-II) 2006-2011 Report at 1-18 (2011).

^{xii} Alhusen JL et al. Racial Discrimination and Adverse Birth Outcomes: An Integrative Review. *J Midwifery Womens Health*. 2016;61(6):707-720. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5206968>.

^{xiii} American College of Obstetricians and Gynecologists. Committee Opinion: Importance of Social Determinants of Health and Cultural Awareness in the Delivery of Reproductive Health Care. <https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/01/importance-of-social-determinants-of-health-and-cultural-awareness-in-the-delivery-of-reproductive-health-care>. Accessed June 1, 2020.

^{xiv} Society for Maternal-Fetal Medicine. Position Statement: Racial Disparities in Health Outcomes. <https://www.sfm.org/advocacy/positions>. Accessed June 1, 2020.