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VIEWPOINT

Gaps, Obstacles, and Ethics in Peripartum Cardiomyopathy Research

Where Are We Now?

Amudha Kumar, MD,[a] Aarti Asnani, MD,[b] Emily S. Lau, MD, MPH,[c] Jawahar L. Mehta, MD, PhD,[d] Garima Sharma, MD[e]

Heart failure (HF) is one of the leading causes of maternal morbidity and mortality in the United States, with peripartum cardiomyopathy (PPCM) accounting for nearly 70% of it.[1] The clinical course of PPCM varies from mild disease symptoms and presentation with spontaneous recovery to persistent myocardial dysfunction and severe HF, ultimately leading to death in up to 10% of patients.[2] Despite the recent advances in cardio-obstetric research, evidence-based recommendations for the management of PPCM remain limited. The reported incidence of PPCM ranges from 1 in 20,000 to 1 in 100 live births across the globe, yet a sizable proportion remains underdiagnosed or misdiagnosed, with considerable delays in diagnosis.[1]

Multiple factors, including limited awareness and clinical experience of the disease process among health care providers, lack of routine antenatal cardiovascular risk screening, and fragmented postpartum care, contribute to the delays and underdiagnosis. A significant proportion of women with clinical HF in the peripartum period but with left ventricular ejection fraction >45% are not included in the current definition of PPCM but likely represent patients with milder phenotype or those who have had partial recovery. As several pregnancy-related conditions are increasingly being recognized as risk factors for cardiovascular disease,[3] could this undiagnosed and untreated PPCM be a potential risk factor for overt HF among women later in life?

WHAT IS THE STATUS OF PREGNANT WOMEN IN CLINICAL TRIALS?

Pregnant women are often not included in many PPCM and HF clinical trials owing to the purported ethical concerns of harming the unborn fetus.[4] Recent examples of exclusion of pregnant women in clinical trials is that of COVID-19 vaccine trials, which caused vaccine hesitancy from the lack of or delay in safety and efficacy data.[5] The underrepresentation translates to a lack of high-quality efficacy and safety data necessary to make informed clinical decisions for this high-risk population. Pregnancy causes significant cardiovascular, hemodynamic, and metabolic changes. These changes impact the pharmacokinetics and pharmacodynamics of therapeutic agents, which influences the dosing, efficacy, and maternal and fetal safety of the drugs. This further emphasizes the need for more clinical and experimental data on the pregnant population.[4] Similar underrepresentation in clinical research is seen in lactating mothers. For instance, bromocriptine, a prolactin inhibitor, is shown to be effective in a few experimental PPCM models but found to affect lactational ability postpartum.[6] Lactation cessation due to bromocriptine also affects blinding in clinical trials. The beneficial role of breastfeeding in mothers and infants needs to be leveraged against the cardioprotective role of bromocriptine in PPCM. Suppose the benefits of bromocriptine are deemed to be higher than its risks

From the [a]Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; [b]Cardiovascular Institute, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts, USA; [c]Division of Cardiology, Massachusetts General Hospital, Boston, Massachusetts, USA; [d]Division of Cardiovascular Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA; and the [e]Division of Cardiology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

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in this select population, should we consider prophylactic treatment in high-risk groups? Will it help eliminate the propagation of the pathogenic prolactin cycle? We hope the ongoing REBIRTH (Randomized Evaluation of Bromocriptine In Myocardial Recovery Therapy for Peripartum Cardiomyopathy) trial,[7] a double-blinded randomized control trial aimed at investigating the role of bromocriptine and lactation on myocardial recovery in patients with PPCM, will be able to answer some of these unanswered questions.

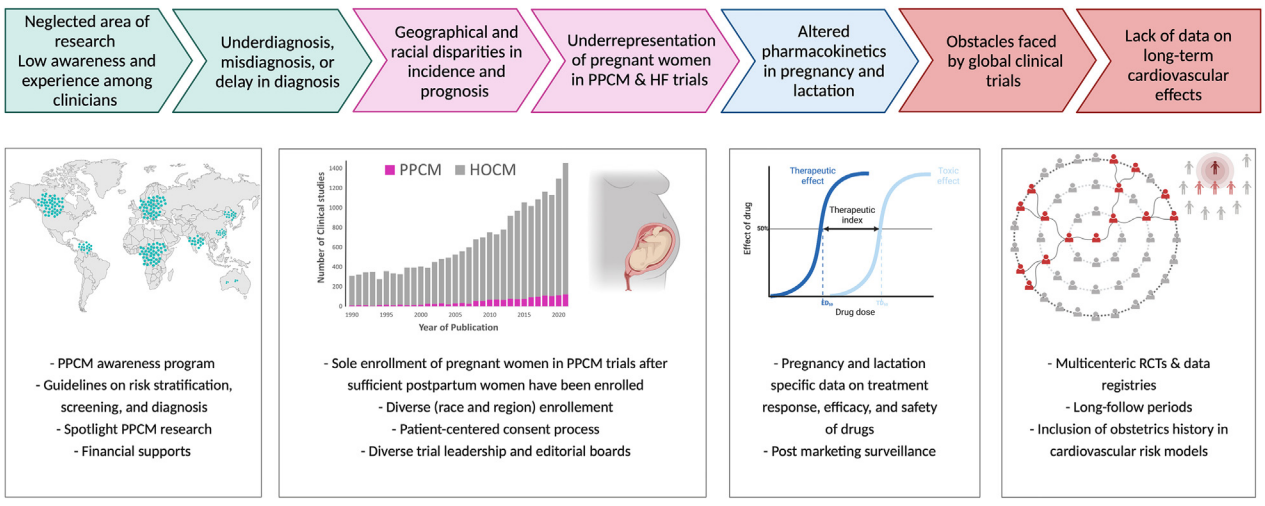
WHAT CAN CARDIOVASCULAR WORKFORCE DO?

1. To improve screening, diagnosis, and potentially increase eligible PPCM population for research:
   - Spotlight PPCM research in educational conferences, journal publications, and research grants.
   - Set up PPCM educational programs for clinicians, care teams, and patients.[8]
   - Draft practical guidelines for clinicians on risk stratification, screening, and diagnosis to enable early specialist referrals.
   - Identify potential PPCM-specific biomarkers that could be utilized in the initial screening process.
   - Provide financial support in the form of insurance coverage for peripartum follow-ups to avoid breaks in the continuity of care (**Figure 1**).
2. To increase representation of pregnant women in PPCM and HF trials:
   - Avoid systematic exclusion of pregnant and lactating women in HF trials.
   - Exclusively enroll pregnant women after sufficient postpartum women have been enrolled in PPCM trials.
   - Develop patient-centered consent processes that are accommodative of the mother's time, and place of consenting will enable detailed discussion of maternal and fetal risks and benefits.
   - Form diverse and inclusive clinical trial leadership and editorial boards.

WHAT IS THE ROLE OF CLINICAL REGISTRIES?

PPCM is a highly heterogeneous disease with wide racial and geographical variations in incidence, clinical presentations, and outcomes.[1] Therefore, a large multicenter and multinational randomized controlled trial is warranted to eliminate confounders, explore high-risk subgroups, and ensure validity, precision, and generalizability of results.[9] Such global clinical trials are multifaceted; involve immense human and capital resources for establishing study sites, training study personnel, and recruitment of patients; and are subject to various rules and regulations in conduct of the trial.[9] This is when regional clinical data registries

FIGURE 1 Challenges and Limitations of Peripartum Cardiomyopathy Research



Illustrates the challenges faced in peripartum cardiomyopathy research and the strategies that help overcome those challenges. HF = heart failure; HOCM = hypertrophic obstructive cardiomyopathy; PPCM = peripartum cardiomyopathy; RCT = randomized controlled trial.

play a crucial role. These registries provide real-world evidence, including data on clinical characteristics, prognostic factors, outcomes, as well as relative effectiveness and safety of the therapeutic interventions specific to the population of interest.[10] Additionally, the longitudinal nature of these registries generates immense data for registry-based pragmatic clinical trials.

PPCM can have important implications in women's cardiovascular health and quality of life beyond the pregnancy and postpartum period.[3] A recent study by Rosman et al[11] showed that more than 53% of PPCM patients meet the criteria for generalized anxiety disorder, which was higher than reported among healthy women of similar age, perinatal samples, and patients with HF. The study also describes the quality-of-life concerns seen in PPCM at various stages of recovery.[11] Future research should focus on understanding these long-term effects of the disease and the associated psychological stress through studies with longer follow-up periods beyond cardiac recovery. Similarly, obtaining obstetric history during cardiovascular risk stratification will help identify sex-specific cardiac risk factors. To enable early diagnosis, risk stratification, and evidence-based management of patients with PPCM, the generation of data through multicenter trials and clinical data registries inclusive of pregnant and postpartum women of various races, ethnicities, and socioeconomic statuses is imperative.

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ADDRESS FOR CORRESPONDENCE: Dr Garima Sharma, Johns Hopkins University School of Medicine, 1800 Orleans Street, Baltimore, Maryland 21287, USA. E-mail: gsharma8@jhmi.edu. Twitter: @GarimaVSharmaMD.

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