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EDITORIAL COMMENT

To Breastfeed or Not to Breastfeed With Peripartum Cardiomyopathy*

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Peripartum cardiomyopathy (PPCM) is a disease of maternal cardiac systolic dysfunction, often accompanied by ventricular dilation, that afflicts ~1 in 2,000 births worldwide (1,2). PPCM accounts for most cases of cardiogenic shock in pregnancy (3) and is increasingly a leading cause of peripartum maternal death in the United States and abroad (4,5). Gestational hypertension, multiparous pregnancies, and African heritage are the strongest known risk factors for PPCM. Treatment mirrors that of dilated cardiomyopathy, focusing on supportive measures, neurohormonal blockade, and, when necessary, mechanical support or even cardiac transplantation. Prognosis is relatively favorable, with recovery of systolic function in the majority of women. However, a significant subset of women, who are typically otherwise young and healthy, and with a new infant to nurture, do not recover and are faced with prolonged cardiac insufficiency, need for cardiac transplantation, or premature mortality.

The cause of PPCM remains poorly understood. Approximately 10% of women with PPCM bear truncating mutations in the gene TTN, encoding for the sarcomeric protein titin, indicating a genetic cause to PPCM in at least a subset of cases (6). In addition, numerous studies in model organisms have advanced the hypothesis that PPCM is caused by vasculotoxic hormones, released from the placenta and pituitary during late gestation and early postpartum periods (1,7–10). These toxic hormones damage the cardiac microvasculature, in turn leading to cardiomyocyte dysfunction and contractile failure. One of these potentially toxic hormones is prolactin (10). The maternal pituitary secretes prolactin late in gestation and continues to do so postpartum in response to breastfeeding. Prolactin acts directly on mammary glands to promote generation of milk. However, in some contexts, prolactin can be cleaved by extracellular proteases to yield a 16 kD peptide that is profoundly vasculotoxic. Studies in mice suggest that this action may occur in certain predisposed individuals, leading to loss of cardiac microvasculature, global ischemia, and cardiomyopathy.

SEE PAGE 291

These studies have raised the possibility that suppressing prolactin production may benefit patients with PPCM by removing a key mechanistic driver of this disease. There are 2 readily available ways to suppress prolactin production: 1) treatment with dopamine agonists, such as bromocriptine, which act directly on the pituitary to suppress dopamine synthesis; or 2) cessation of breastfeeding. We refer the reader to recent sources for discussions on the use of dopamine agonists in PPCM (11–15); controversy remains on this topic.

What of breastfeeding in PPCM? On the basis of the preclinical experimental findings with prolactin, and of suggestive studies with bromocriptine, the 2010 European position statement on PPCM recommended cessation of breastfeeding in PPCM (16). A more recent European Society of Cardiology study group recommended that breastfeeding should be "encouraged in women with mild cardiac dysfunction" but is "not advisable in cases of severely

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impaired systolic function" (17). However, there are remarkably few published data that directly address the question of breastfeeding in PPCM, in part because most PPCM studies do not report on breastfeeding. A single, small (N = 55) retrospective Internet-recruited study in the United States that directly addressed the question suggested that breastfeeding was associated with better, rather than worse, maternal outcome (18); and a similar single-center retrospective study (N = 27) suggested no difference in outcome based on breastfeeding status (19). Both studies are retrospective and therefore may have been biased by ascertainment. Prospective studies were entirely lacking.

Enter the IPAC (Investigations of Pregnancy-Associated Cardiomyopathy) study. IPAC is a U.S.-based, multicenter prospective study that followed 100 women for 12 months immediately after the diagnosis of PPCM (20). A number of important studies have emanated from this cohort. In this issue of *JACC: Basic to Translational Research*, Koczo et al. (21) focus on the question of breastfeeding. Of 100 women, 15 were breastfeeding at entry, and 85 were not. This percentage is substantially below the U.S. national rate of breastfeeding at 6 months (57.6%; CDC report card [22]). Only 1 woman received a dopamine agonist. There were no obvious differences in demographic, hemodynamic, or obstetric parameters between women who breastfed and those who did not. The women who breastfed had a trend toward higher ejection fraction at presentation (breastfeeding 0.39 ± 0.06 vs. nonbreastfeeding 0.34 ± 0.10; $p = 0.06$). The key observation of the study, however, is that no difference was seen in mean change in left ventricular ejection fraction from entry to 6 months (breastfeeding 0.17 ± 0.09 vs. nonbreastfeeding 0.16 ± 0.11; $p = 0.46$) or 12 months (breastfeeding 0.18 ± 0.08 vs. nonbreastfeeding 0.17 ± 0.11; $p = 0.68$). In other words, breastfeeding seemed to have no impact whatsoever on recovery rates.

The strength of this study (21) lies in the fact that participants were followed up prospectively and all subjects underwent comprehensive phenotyping, and it thus provides important new data to instruct decision-making in a clinical setting that lacks clear guidelines. Nonetheless, the study has limitations. First, the small size of the trial provides limited power. It should be noted, however, that the lack of even a trend toward an adverse effect of breastfeeding makes it unlikely that a type II error biased the statistical outcome of the study. Second, the study is observational (i.e., it is not randomized). Is it possible, for example, that self-selection of a less ill cohort to breastfeeding could have biased the outcome to favor breastfeeding? This possibility is suggested by the relatively low percentage of women breastfeeding, and the trend to higher ejection fraction at entry in this group. The only way to conclusively address this question is a prospective and randomized trial, an unlikely outcome. In sum, the study does not definitively report that breastfeeding is safe in women with PPCM, but it strongly suggests that it is so.

The decision of whether to breastfeed with PPCM must also consider the potential benefits of breastfeeding to both mother and infant. Critical nutrients and factors, both known and unknown, pass from mother to child via breast milk. In developing countries, where undernutrition and unsafe water supplies account for the majority of childhood mortality and where breast milk substitutes are expensive, discontinuation of breastfeeding can be catastrophic to the infant (23). Breastfeeding promotes bonding, immunoprotection, metabolic protection, an appropriate microbiome population, and profound protection against diarrheal and respiratory diseases and otitis media, while reducing risk of sudden infant death (24). Most of these findings are true in both high- and low-income countries. In addition, in high-income countries, breastfeeding is associated with protection from obesity and diabetes and with higher performance on intelligence tests. Strong evidence also implicates breastfeeding in maternal protection from breast and ovarian cancer. Prolactin itself has been implicated in many of these processes, in particular immunoprotection, and indeed Koczo et al. (21) show in their study that $CD8^+$ cytotoxic T cells were higher in breastfeeding women with PPCM (in contrast to $CD4^+$ helper cells, which tended to be lower). Both the World Health Organization and the American Academy of Pediatrics recommend exclusive breastfeeding for 6 months, and continued breastfeeding for at least 1 to 2 years. In short, discontinuation of breastfeeding should not be taken lightly.

Conversely, women with PPCM are a special case, because the majority are taking medicines for heart failure. Are these drugs transmitted to the fetus, and if so, are they safe? Levels of loop diuretics expressed in breast milk are likely too low to have an effect in the infant (25). Similarly, negligible amounts of bioactive derivatives of most angiotensin-converting enzyme inhibitors, mineralocorticoid receptor antagonists, beta-blockers, hydralazine, or nitrates are detected in milk, typically leading to <1% infant exposure on a weight-adjusted basis. With judicious choice of drugs, and appropriate monitoring of the infant, standard PPCM therapy thus seems safe for the infant and should not be a contraindication for breastfeeding.

Finally, returning to the context of the possible use of dopamine agonists such as bromocriptine, 2 points should be made about breastfeeding. First, once the decision has been made to use dopamine agonists, the question of whether to breastfeed is then obviously moot, as these drugs will suppress lactation. However, second, the observations that breastfeeding seems to be safe in PPCM suggests that continued stimulation of prolactin secretion into the maternal circulation is not harmful, somewhat calling into question the rationale for using dopamine agonists. Once again, only a placebo-controlled, randomized trial will adequately resolve this quandary. The lost benefits of breastfeeding should therefore be factored into the decision of using a dopamine agonist.

In conclusion, few direct clinical data exist to guide the decision of whether a woman with PPCM should breastfeed. The study by Koczo et al. (21) provides substantially more data than existed in aggregate in the antecedent literature, but it still leaves us without certainty. To date, there is no direct evidence that breastfeeding in women with PPCM is harmful, and in fact increasing evidence that it is safe. Cessation of breastfeeding should thus be recommended only with caution.

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