

Three Great Needs in Peripartum Cardiomyopathy

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Abstract

Important advances have been made in the past 15 years in the treatment and outcomes for peripartum cardiomyopathy (PPCM) subjects. Despite that, PPCM remains one of the leading causes of maternal mortality all over the world and for those who survive too many are still left with a chronic cardiomyopathy of varying severity. Recent reports in the medical literature document the advances. This report emphasizes three important needs for the advancement of understanding and outcomes for PPCM.

Keywords: Peripartum cardiomyopathy; PPCM; Heart failure; Pregnancy; Outcomes

Three Great Needs in Peripartum Cardiomyopathy

Important advances have been made in the past 15 years in the treatment and outcomes for peripartum cardiomyopathy (PPCM) subjects. Despite that, PPCM remains one of the leading causes of maternal mortality all over the world and for those who survive too many are still left with a chronic cardiomyopathy of varying severity. Recent reports in the medical literature document the advances [1-3]. The purpose of this report is to discuss what appear to me to stand out as the greatest current needs in making additional advances for PPCM: 1) more promotion of awareness, 2) greater understanding of the leading hypotheses of the cause(s) of PPCM and 3) the need for newer intervention strategies of treatment that will help those who present with function that characterize them as more slow to recover. Those slower to recover or at higher risk for non-recovery are the PPCM mothers with the very greatest systolic dysfunction; identified by echocardiographic parameters at diagnosis of left ventricular ejection fraction (LVEF) <35%; and the greatest remodeling of the left ventricle; namely left ventricular end-diastolic diameter (LVEDD) ≥ 60 mms [4,5].

Awareness

Even today there are those peripartum women who are caught totally by surprise that they are in heart failure. Despite prenatal care these persons and their caregivers have often missed the signs and symptoms that might have alerted them to developing difficulties. Often, when they reflect back, they realize that perhaps they could have identified deteriorating heart function earlier [6].

Does it not seem reasonable that prenatal education should at least mention the possibility that despite entering pregnancy with a perfectly normal heart it is nevertheless possible to develop a devastating condition that would imperil life and future function? PPCM is not difficult to diagnose when one is aware of the potential (although infrequent) condition that is still one of the leading causes of

maternal mortality. Although there are instances of fulminant myocarditis that proceed very rapidly, most PPCM pathophysiology occurs very gradually leading to step-wise deterioration of systolic heart function. A high index of suspicion will lead to doing the confirmatory echocardiogram. Identification of rising B-type Natriuretic Peptide, an inexpensive test, showing stress on the left ventricle will help in this process of early recognition. A simple but effective self-test has been developed for use by perinatal subjects to help distinguish early signs and symptoms of heart failure from normal term pregnancy signs and symptoms, as discussed in the following [7].

It is important to be vigilant in looking for PPCM in any pregnancy associated with hypertension since one-third to one-half of PPCM subjects have a pregnancy in which hypertension occurs [8]. In this respect, there may be a role for soluble FLT1, which may be a biomarker for the early recognition of preeclampsia [9]. It may also play a role in the pathophysiology of PPCM.

Greater understanding of leading hypotheses of pathogenesis of PPCM: Bello and Arany have eloquently summarized the leading hypotheses explaining the molecular mechanisms for the pathogenesis of peripartum cardiomyopathy (PPCM) [10]. Founded in sound laboratory investigations involving both laboratory animals and human experience, it should be remembered that many of these are still hypotheses, involving two main potentially anti-angiogenic agents: namely the hormone systems of a) lactational hormone prolactin, with potentially toxic prolactin metabolites and b) soluble FMS-like tyrosine kinase, sFLT1. Each system has well-documented rationale explaining the potential cardiotoxic effects [11,12].

a) Role of prolactin: Of the two systems, the prolactin hypothesis has had greater expansion as a possible explanation why these women can enter a pregnancy with perfectly normal cardiac function but emerge in the latter part of pregnancy with severely failing systolic heart function. Although it is easier to understand why various genetic and pathophysiological factors may lead to activation of Cathepsin D, the subsequent cleavage of normal 23 kDa prolactin into a more cardiotoxic metabolite, 16-kDa prolactin, nevertheless it is not yet

clear about who and why some will have more toxic effects because up to now, testing for the 16 kDa prolactin fragment is not readily accomplished.

The potential for parent prolactin and its 16-kDa metabolite to be not only an important biological marker, but also a potential therapeutic target, is enhanced because of the existence of bromocriptine, a dopamine D2-receptor agonist, capable of inhibiting the production of prolactin even to zero. This potential therapeutic tool has generated a great deal of excitement with treatment application in PPCM, temptingly even without carefully controlled, randomly assigned study populations ahead of general application.

Thankfully, PPCM is a unique cardiomyopathy with perhaps the greatest potential for recovery of any other cardiomyopathy. Using only (no bromocriptine) “evidence-based” treatment outlined in the ESC and AHA Guidelines for treatment [13,14] is giving comparable recovery results to those found in any of the studies using bromocriptine in addition to the Guidelines therapy.

Aside from the single-center studies coming out of South Africa and Haiti [15,16], very important studies, each with around 100 subjects and both prospective in nature, are being done by collaborative University hospitals in Germany and academic medical centers in North America, awaiting final 12-month outcome report [17-19]. Each of those studies is showing encouraging and quite amazing full recovery levels, low mortality rates, and low rates of adverse outcomes. The German study involves 64 subjects who received both “Guideline therapy” and bromocriptine compared with 32 subjects who received only “Guideline therapy;” they could not demonstrate any significant difference in full recovery between the two groups. The North American study of 100 subjects, currently in progress, with final results pending, is demonstrating quite amazingly similar full recovery outcomes, but uses no bromocriptine. We eagerly await results from the ongoing German study with random assignment of PPCM subjects into the group either with or without bromocriptine.

Associated with the bromocriptine studies is the question of the role for “MicroRNA -146a.” [20]. It is possible this will become an important role player, biomarker and therapeutic target; but at this early stage of investigations in the field of microRNA’s, it is important to continue to investigate to see if they are that specific for a condition and if their presence and titers are reproducible and clinically useful.

At least two concerns remain unresolved with respect to the use of bromocriptine to inhibit prolactin: 1) Can we be sure that bromocriptine used in the peripartum period is safe for the cardiovascular system? And 2) Can we be sure enough of the importance of inhibiting prolactin production that we are willing to abandon breastfeeding in PPCM subjects?

With respect to 1), this has troubled clinicians over the years regarding potential catastrophic cardiovascular events associated with the peripartum use of bromocriptine. Additional concerns appear on the horizon with the important report of Duncker, et al., [21], also participants in the German collaborative studies, indicating possibly a higher rate of ventricular tachyarrhythmia in PPCM subjects at the lower levels of systolic function than we had previously thought. In view of what seems like a very high rate, although in relatively small numbers overall, there is still concern for any potential role of bromocriptine in catastrophic cardiovascular events as all subjects received bromocriptine in some dosage for some period of time, either to suppress lactation or with the hope of benefit in outcomes.

What we seem to be learning from these reports about bromocriptine use is that those PPCM subjects at the lower levels of systolic function ($EF < 0.35$) do not appear to respond very well for whatever the reason(s) [17,21]. Those are, of course, the ones who are in greatest need for extra support and newer intervention strategies. We must be sure that bromocriptine is effective and at the same time safe in the peripartum setting. Duncker et al’s report [21] are convincing that PPCM subjects in this diagnostic level of $LVEF < 0.35$ must be continuously monitored in order to identify and treat ventricular tachyarrhythmias.

With respect to breastfeeding, since we are finding very comparable recovery outcomes either with or without the use of bromocriptine, this would not be the time to make any firm recommendations about suspending the ability to breastfeed, particular in areas of the world where the survival of the newborn is greatly threatened by the lack of available breastmilk [22].

At this stage, the decision is still out about the safety and efficacy of bromocriptine inhibition of prolactin. Brilliant hypotheses that have strong scientific backing in solid bench-work at the molecular level. Strong potential, but work yet to be done to assure both efficacy and safety.

b) Role of sFLT1: In this “2-hit” hypothesis, it appears that sFLT1 is no less important nor promising. It is a newer component, also brilliantly explained in earlier publications [12]. It may be both an important biomarker and potential therapeutic target in PPCM, but for now is more strongly tied to preeclampsia, having great promise to predict severe preeclampsia even early in pregnancy even before the onset of hypertension, and certainly before the onset of preeclampsia [9]. The greatest source of sFLT1 is the placenta, although there appears to be a component from vascular endothelium. There appears little doubt that sFLT1 is cardiotoxic. Because many PPCM patients, perhaps 25 %, also have preeclampsia, it is natural to link the two in doing investigations of PPCM at the molecular level [8].

Because most diagnoses of PPCM are made at the very end of pregnancy or in the immediate postpartum period, the placenta is disappearing or has already disappeared, taking with it the main source of peripheral vascular sFLT1. That being the case it is difficult to look at sFLT1 levels in a PPCM pregnancy and subsequently try to correlate those levels with ultimate recovery observations. Are higher levels associated with those PPCM subjects who are recognized with very low systolic function ($LVEF < 0.35$) and/or very dilated left ventricles ($LVEDD \geq 60$ mm)? Those are the PPCM subjects now recognized as less likely to reach recovery levels, which we mostly define as $LVEF \geq 0.50$ by whatever time frame used, now more commonly 12 months postpartum since some who recover do so by the 12-month stage but not by the 6-month stage postpartum.

With the strong evidence for cardiotoxicity of sFLT1, it is important to look more closely at sFLT1 levels during a pregnancy which is in the process of developing PPCM. This can be done while observing pregnancies with preeclampsia since some of those are going to go on to also have cardiac dysfunction. These sFLT1 levels could also be observed in a post-PPCM pregnancy since up to 20 % of recovered PPCM subjects are going to develop a relapse of heart failure [18]. This prospective study of post-PPCM pregnancies is urgently needed since even those who we think are fully recovered can still relapse, and the reason(s) are still unknown. Periodic sFLT1 levels during the pregnancy will enable us to know what is happening to their levels, and subsequently to see if there is a statistically significant increase in

sFLT1 levels in those who relapse compared to those who do not relapse; as well as to see if there is correlation between those less likely to recover systolic heart function. Currently, we are encouraged that early application of evidence-based treatment with the onset is effective and that the LVEF will return to normal pre-subsequent pregnancy function [18].

Both the prolactin hypothesis and sFLT1 hypothesis describing potential molecular mechanisms in the development of peripartum cardiomyopathy must be carefully pursued in our search for answers. PPCM is one of the leading causes of maternal mortality and morbidity wherever in the world it occurs. We have a clear challenge about what most needs investigation so that the necessary therapeutic regimens can be found to help those PPCM subjects who are currently failing to reach recovery levels and who are experiencing most of the adverse outcomes.

Newer intervention strategies: These are needed to help those with the greatest risk for non-recovery as identified above. For all others, current application of published evidence-based guidelines for the treatment of heart failure with decreased LVEF will result in recovery to LVEF ≥ 0.50 in the overwhelming majority of PPCM subjects [19,20]. Carefully developed research protocol interventional studies must be devised to apply to those in greatest need. One intervention that merits additional study is the elimination or neutralization of anti-cardiac antibodies [23-25]. There have not yet been any controlled studies but anecdotal reports are promising. The challenge is to identify other effective strategies of intervention that will particularly help those in greatest need: those with both severe systolic dysfunction and those with the greatest remodeling of the left ventricle. Anyone interested in seeing greater detail, an illustrated free full copy review of recent developments in understanding PPCM is available on-line [5].

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