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A Strategy for the Prevention of Relapse of Heart Failure in a Post-Peripartum Cardiomyopathy Pregnancy

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ABSTRACT

Excellent progress has been made in the past two decades in understanding peripartum cardiomyopathy (PPCM). A strategy is outlined for steps that can be taken before, during and after pregnancy to improve outcomes for subsequent pregnancies following recovery from a diagnosis of heart failure from peripartum cardiomyopathy. This strategy has helped to save the lives of mothers and children. Treatment and monitoring strategies can also be used to reach "full recovery" with the first diagnosis of PPCM.

Keywords: Heart failure, Pregnancy, Cardiomyopathy

INTRODUCTION

Excellent progress has been made in the past two decades in understanding peripartum cardiomyopathy (PPCM) [1-5]. The pathophysiology and treatment of PPCM have become much clearer. In this process I outline an effective path in guiding PPCM mothers in their quandaries about the risks of a subsequent pregnancy. Herein, I present important considerations relative to the safety and advisability of any future pregnancies:

What can a peripartum cardiomyopathy (PPCM) subject do to reduce the risks of relapse of heart failure in a subsequent pregnancy?

Before the post-PPCM pregnancy

1) Adequate treatment of first episode to help reach left ventricular ejection fraction (LVEF) of 55% (anything higher considered a "variant of normal") [6] **(Figure 1)**.

2) Be sure that "contractile reserve" is adequate; defined as increase of LVEF by at least 10-15% from resting heart rate to target exercise heart rate on exercise stress echocardiography (example: from LVEF 55% to 63%) [5-9] **(Figure 2)**.

3) Maintain normal heart function (LVEF 55%) after phase-out of medication that would not be safe during conception/pregnancy; such as Angiotensin-Converting Enzyme Inhibitor (ACEI) or angiotensin hormone receptor blocker (ARB) [10] **(Figure 3)**.

4) "Full recovery" confers lower risk, and means

a) Return of LVEF to ≥ 55%;

b) Normal contractile reserve on exercise stress echocardiography;

c) No deterioration of LVEF when wean off ARB/ACEI Rx;

d) No diastolic dysfunction; if that exists more Rx indicated;

e) No late Gadolinium enhancement (LGE) on cardiac MRI (CMR) [11];

f) Size of left ventricle <6 cm or <3.5 cm/M2 BSA.

During the post-PPCM pregnancy

1) Establish base-line serum B-type Natriuretic Peptide (BNP) and monitor serum BNP level each trimester. Look for levels that are rising and/or above "cut-off" level for that particular lab's test. The NT-ProBNP test is recommended because it appears to be the least affected by pregnancy alone **(Figure 4)**.

2) Monitor LVEF by echocardiography each trimester and more often if serum BNP is rising and/or above "cut-

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off" value.

3) Rising serum BNP above "cut-off" is an indication to consider starting a treatment because the rise in serum BNP comes hours to days to weeks before any fall in LVEF.

4) Monitor the "self-test" monthly for recognition of signs and symptoms of heart failure during pregnancy [12]. The "self-test" consists of 6 clinical signs/symptoms:

   a. Orthopnea (difficulty breathing when lying flat): (a) None 0 points; (b) Need to elevate head 1 point; (c) Need to elevate 45° or more 2 points.

   b. Dyspnea (shortness of breath on exertion): (a) None 0 points; (b) Climbing 8 or more steps 1 point; (c) Walking on level 2 points.

   c. Unexplained cough: (a) None 0 points; (b) At night 1 point; (c) Day and night 2 points.

   d. Swelling (pitting edema) lower extremities: (a) None 0 points; (b) Below knee 1 point; (c) Above and below knee 2 points.

   e. Excessive weight gain during last month of pregnancy: (a) Under 2 pounds per week 0 points; (b) 2 to 4 pounds per week 1 point; (c) Over 4 pounds per week 2 points.

   f. Palpitations (sensation of irregular heartbeats): (a) None 0 points; (b) When lying down at night 1 point; (c) Day and night, any position 2 points.

ACTION: 5 or more points=see cardiologist re: plasma BNP and echocardiogram.

5) Watch for further developments of this research tool (angiogenic imbalance) [5,13-15]:

   a. Serum soluble FLT1 >100 pg/ml

   b. Ratio of serum sFLT1 to Placenta Growth Factor (PlGF)>45 @ 24 weeks gestation. This may be predictive of trouble at 32 weeks gestation. What applies to preeclampsia may also apply to PPCM [15].

6) Development of gestational hypertension or preeclampsia during pregnancy identifies higher risk for relapse of heart failure in a post-PPCM pregnancy [1,3,5,14] because:

   a. One-third to one-half of PPCM mothers also has either preeclampsia or gestational hypertension.

   b. Pathophysiology of these two conditions appears to have many similarities to the pathophysiology of PPCM, particularly the angiogenic imbalance resulting from alteration of normal patterns of placental production of sFLT-1 and/or PlGF.

   c. These two conditions alert the medical team to the need for even closer monitoring of the pregnancy; and the need to initiate effective treatment for the prevention or moderation of relapse of heart failure or subsequent deterioration of LVEF.

7) Effective treatment [16,17] is available if there is pending relapse during pregnancy; this treatment consists of:

   a. Use of beta-blockers (BB), which are safe to use during pregnancy. Some prefer to keep BB in the picture from the time of beginning the subsequent pregnancy.

   b. Hydralazine, in tolerable dosages, can take the place of ACEIARB, which are not safe to take during pregnancy. If the hydralazine gives unacceptable increase of heart rate, this side-effect may be off-set by the use of nitrates, which are also safe to take during pregnancy. Hydralazine is more a "second-class" medication, with more potential side-effects; so closer monitoring is necessary.

8) Completion of pregnancy, with safe maturity of the infant, is the best measure to eliminate any further risk for relapse of heart failure. In completing the pregnancy, there are important considerations:

   a. If there has been any suggestion of beginning relapse, use of pitocin stimulation of labor should be avoided because it increases stress on the left ventricle [18]. This is reinforced by the author's case file which includes 5 additional PPCM mothers experiencing worsening heart failure after/during pitocin drip induction/stimulation of labor.

   b. If there is no suggestion of relapse, then earlier onset of labor may be encouraged by induction methods of stripping the membranes through the beginning cervical dilatation; and pitocin stimulation of labor contractions appears to be safe when no pending/developing relapse.

   c. Consideration for elective Caesarean section with maturity of baby is a safe alternative when quality anesthesia services are available.

After the post-PPCM pregnancy

1) If there has been no evidence for relapse of heart failure or trend towards relapse:

   a. It is important to continue to monitor for evidence of relapse up to approximately 5-6 months postpartum.

   b. An echocardiogram should be done 6 months postpartum in order to assure that no deterioration has occurred.

2) If there is evidence for relapse or trend towards relapse, treatment must be continued and intensified.

a. At this point, it is better to replace the hydralazine with ACEI or ARB;

b. However, if breastfeeding, the only ACEI that is safe to use is enalopril; and no ARB is deemed safe to use while breastfeeding.

c. It has not yet been determined if lactate hormone inhibition with use of bromocriptine or cabergoline is safe and effective [4,19-21].

"What is the best combination of treatment for the heart failure of PPCM?"

Of course, if there is excess fluid, then diuretics, such as lasix or furosemide are indicated. But they treat the symptom of the disease, not the underlying pathophysiology. For that, the most important medications are:

1) BB (beta-blocker), such as carvedilol or metoprolol long-acting;

2) ACEI (ACE-Inhibitor), such as lisinopril or enalopril;

3) ARB (angiotensin-receptor blocker), such as valsartan; and

4) NI (Neprilysin Inhibitor), as found in Sacubitril.

With those medications, one must find the best tolerable dosage. So for me, if the diagnostic LVEF is less that 40 %, it is ideal to use BB + ARB + NI (the combination of ARB + NI is found in Entresto). If the LVEF at diagnosis is 40 % or greater, then the ideal is to use BB + ACEI or ARB. Some would choose this option even for lower LVEF.

My adage on dosage is "Start low and go slow (on increases)". It is important to realize that the combination is very important and gives better recovery results than any of those classes of medication used alone. Hence, initial treatment of PPCM should always include a combination of BB + ACEI or ARB or the combination of BB + NI + ARB (start low dose Entresto, 2x/day, 49/51 mg, increase to 97/103 mg if needed after 2 to 4 weeks).

Never assume that a case of PPCM is "mild" and never assume that only one of those classes of medication is sufficient. The combinations described have a synergistic effect greater than any one has alone.

Figure 1. Recommendation for treatment of PPCM.

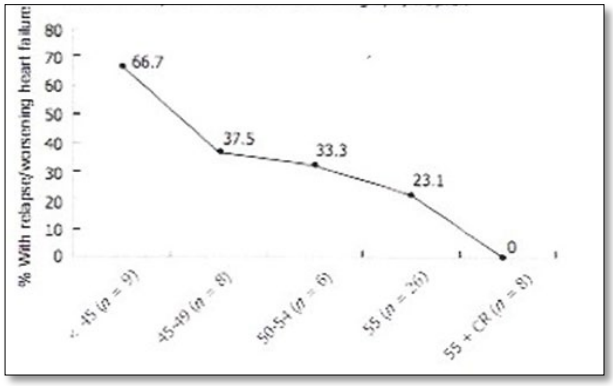

Figure 2. Risk for relapse of heart failure in a post-PPCM pregnancy, with emphasis of importance of contractile reserve on exercise stress echo.
Note: Relapse rate (%) decreases as the level of LVEF increases. The lowest relapse rate is for the subjects who have contractile reserve (CR) of at least 10% on exercise stress echocardiography

Weaning Process (Note: continue BB indefinitely if history of ventricular tachyarrhythmias or if LVEDD continues > 5.5 cm.)

a)Start with 1/3 to 1/2 reduction of ACEI/ARB. (Some prefer to stop entirely as a first step).
b)Within 3 months do echo for LVEF; if decreased by at least 5 absolute LVEF points, resume previous dosage.
c)If LVEF stable, discontinue ACEI/ARB.
d)Within 3 months do echo for LVEF; if EF decreased to LVEF < 0.50, resume previous dosage.
e) If stable consider start weaning BB in same manner.
f)Do not begin weaning process until after 6 months of treatment.
g)Minimum safe duration of treatment suggested conservatively as one year.
h)Some would do an exercise stress echo to assess adequate contractile reserve (looking for at least 10 % increased LVEF from resting to target exercise heart rate) before total discontinuation of Rx.

Figure 3. One strategy for phase out of treatment when evaluating full recovery of PPCM.

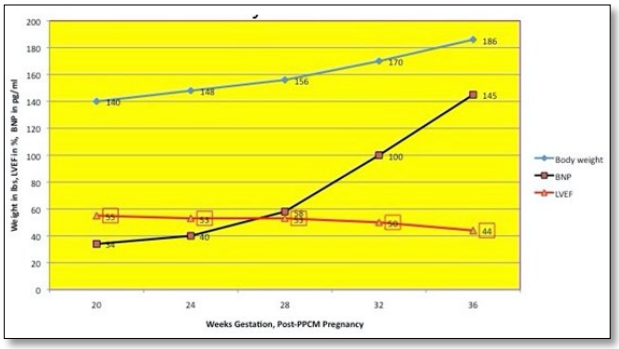

Figure 4. Monitoring serum B-type natriuretic peptide (BNP) during pregnancy.
Note: In this case example the serum BNP rises before significant fall in LVEF

CONCLUSION

From extensive experience with hundreds of PPCM subjects, I have seen this strategy work. It has helped to save the lives of mothers and children. Please consider some or all of these points in the management and treatment of those who experience or plan for subsequent pregnancy after having a diagnosis of PPCM.

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