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# BROMOCRIPTINE NOT YET A THERAPEUTIC OPTION IN PERIPARTUM CARDIOMYOPATHY

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The idea of late pregnancy hormones causing peripartum Cardiomyopathy (PPCM) was put forward in 1985.[1] Reduced expression of STAT 3 (signal transduction and activation of transcription) was found in the left ventricles from patients with end-stage heart failure due to PPCM compared with non-failing control subjects.[2] This triggered research on STAT 3 knockout murine hearts. A landmark article in 2007 substantiated this idea. Loss of STAT3 in murine hearts led to reduced expression of manganese superoxide dismutase (MnSOD), which neutralizes superoxides generated by highly active cardiomyocytes. Superoxides accumulation stimulate cathepsin D secretion which cleaves prolactin into a 16-kDa fragment that promotes apoptosis in endothelial cells causing PPCM. Blocking prolactin secretion from pituitary with bromocriptine in STAT3 knockout mice completely reversed the PPCM.[3]

The 16 kDa fragment exerts its action through micro RNAs (miRNA 146a) by causing endothelial and myocyte damage. Circulating levels of miRNA-146a are very high in women with PPCM which drop significantly with bromocriptine treatment. Prolactin thus qualify as causal agent for PPCM. The therapeutic targets can be either blocking prolactin secretion with bromocriptin or blocking miRNA 146a through antisense oligonucleotides.[4]

In a proof of concept study in 2010 bromocriptine was highlighted to improve the LVEF and composite clinical outcomes. In this small study, comprised of only 10 patients in each arm, ethnicity was not clearly mentioned in the baseline characteristics. Moreover on further analysis of the data by me, bromocriptine group presented significantly earlier after delivery than the standard treatment group (12.5+10.4 days vs. 20.5+ 6.7 days p=0.019).[5] In the IPAC study early recruitment after delivery or at delivery was associated with better outcomes. Time since delivery was a significant predictor of LV function recovery in univariate analysis. The late recruitment may have omitted those patients with good prospects to recover early or bromocriptine would have been really effective if instituted early.

After an exhaustive and convincing research on the causative role of prolactin in a murine model of PPCM in 2007 by Hilfiker et al, their clinical research in Germany in July 2017 was not very convincing.[6] The term multicentre randomized in its title is misleading. There was no placebo group in the study for comparison with bromocriptine group. Both the groups received bromociptine rather. The comparison with IPAC study is having a profound racial bias. Black women were 30% in the IPAC US study versus 1.6% in the recent German study. Moreover selecting those with LVEF less than 30% from the IPAC subjects further biased the

study to represent blacks than whites because the mean LVEF in blacks was 31% compared to 36% in whites. The black race significantly predicted the poor recovery in LV function in both univariate and multivariate analyses.[7] Four fold higher incidence of and fatality from PPCM in black versus white women was observed by Harper et al.[8] Till the availability of convincing data from ethnically matched population, bromociptine cannot be considered as a therapeutic option in peripartum cardiomyopathy.

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