PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Outcomes and complications of peripartum cardiomyopathy: protocol for a systematic review and meta-analysis
AUTHORS	Hoevelmann, Julian; Muller, Elani; Hohlfeld, Ameer; Bohm, Michael; Sliwa, Karen; Engel, Mark; Viljoen, Charle

VERSION 1 – REVIEW

REVIEWER	Jha, Nivedita Jawaharlal Institute of Postgraduate Medical Education and Research, Department of Obstetrics and Gynaecology
REVIEW RETURNED	28-Jul-2021

GENERAL COMMENTS	Comments to Authors This protocol is well written, methodologically sound with well-defined objectives. However, I do have a few suggestions. Since the majority of studies would be retrospective or case series spanning several years data, how the authors planning to deal with such patients which were diagnosed before 2000. How definition of PPCM changed over time (before 2000 and after 2000). How the authors planning to segregate obstetric complications from medical complications? Denominator may vary across the studies. Therefore, pooling of data may be challenging. Are the authors planning to analyze the pooled rate of complication based on treatment, interventions, time of diagnosis? Are the authors also planning to analyze complications related to anesthetic management of labor? Long term outcomes may also be different in those who received different types of heart failure medications, bromocriptine, serelaxin, pentoxifylline and so on.

REVIEWER	Honigberg, Michael Massachusetts General Hospital, Cardiology Division, Department of Medicine
REVIEW RETURNED	07-Aug-2021

GENERAL COMMENTS	Thanks for the opportunity to review this protocol. The protocol appears to be well conceived and presented. I would expect

	heterogeneity in findings based on the published literature to date, as noted in the Introduction of this protocol; some of this heterogeneity may stem from differences in diagnostic modalities and therapeutics available in different countries/regions. The authors note a plan to include "control" arms of randomized controlled trials. It would be worthwhile to clarify this plan further: Do they plan to include only placebo arms of RCTs, or would non-placebo control arms qualify? For example, Hilfiker-Kleiner et al., Eur Heart J 2017, did not include a placebo arm in their randomized trial of bromocriptine in PPCM. Given the relative paucity of RCTs in PPCM, the authors might consider also including and separately reporting intervention arms of RCTs (potentially in narrative review fashion).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1:

1. Since the majority of studies would be retrospective or case series spanning several years data, how the authors planning to deal with such patients which were diagnosed before 2000. How definition of PPCM changed over time (before 2000 and after 2000).

Thank you for raising this important aspect. We have decided to only include articles published after the year 2000, in which the first universal definition of PPCM was used. We plan to exclude articles prior to this date, as these might have included patients that did not fulfil the diagnostic criteria of PPCM and will thus not be comparable in a meta-analysis.

We have specified this in the eligibility criteria:
"The year 2000 was the year that the first unified definition of PPCM was used by National Heart, Lung and Blood Institute and Office of Rare Diseases.17 Therefore, articles published since 2000 will be considered for this systematic review and meta-analysis."

2. How the authors planning to segregate obstetric complications from medical complications?

Thank you for this comment. We do not plan to segregate medical from obstetric complications. We intend to report on all maternal outcomes around the time of diagnosis as well as at six- and/or twelve-month follow-up.

3. Denominator may vary across the studies. Therefore, pooling of data may be challenging.

Thank you for this comment. We acknowledge that the dominator will vary across the different studies. The Freeman-Tukey transformation double arcsine (FTT) procedure has been specifically included to prevent undue weighting given to smaller studies.

We mentioned in the manuscript: "The pooled rates will be estimated using the Freeman-Tukey double arcsine transformation method to stabilise the variance of proportion within each study."

4. Are the authors planning to analyze the pooled rate of complication based on treatment, interventions, time of diagnosis? Are the authors also planning to analyze complications related to anesthetic management of labor? Long term outcomes may also be different in those who received

different types of heart failure medications, bromocriptine, serelaxin, pentoxifylline and so on.

Thank you for raising this very important aspect. We acknowledge that outcomes may be affected by the different treatment regimens used. We will therefore report on the treatment used in the different studies. As not all studies that will be included in the systematic review and meta-analysis will be prospective clinical trials, it will not be possible to determine causality between treatment/interventions and outcomes. However, we will report on associations between these, if any.

We will calculate pooled prevalence estimates for all reported maternal complications and outcomes in our meta-analysis.

Reviewer 2:

The authors note a plan to include “control” arms of randomized controlled trials. It would be worthwhile to clarify this plan further: Do they plan to include only placebo arms of RCTs, or would non-placebo control arms qualify? For example, Hilfiker-Kleiner et al., Eur Heart J 2017, did not include a placebo arm in their randomized trial of bromocriptine in PPCM. Given the relative paucity of RCTs in PPCM, the authors might consider also including and separately reporting intervention arms of RCTs (potentially in narrative review fashion).

Thank you very much for this appreciated comment. We plan to only include placebo control arms of RCTs and exclude non-placebo control arms (such as in Hilfiker-Kleiner et al., Eur Heart J 2017) and intervention arms of RCTs. The rationale for this decision is that we would like to determine the pooled estimates of complications/outcomes and not compare different treatment modalities and their effects on outcome.

We have elaborated on this aspect in Table 1 under inclusion and exclusion criteria, as well as in the methods section: “In case of randomised control trials (RCTs) we will only include the placebo control arm and exclude non-placebo control arm or interventions arms.”