PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Anticoagulation regimens during pregnancy in patients with mechanical heart valves: a protocol for a systematic review and network meta-analysis
AUTHORS	He, Shiwei; Zou, Yue; Li, Juan; Liu, Jumei; Zhao, Li; Yang, Hua; Su, Zhiying; Ye, Huiming

VERSION 1 – REVIEW

REVIEWER	Offer Erez Ben-Gurion University of the Negev
REVIEW RETURNED	09-Nov-2019

GENERAL COMMENTS	The authors stated that no metaanalysis and systematic review were performed in this topic. However, Rohan D'Souza,1,2 Jackie Ostro,3 Prakesh S. Shah,2,4 Candice K. Silversides,5 Ann Malinowski,1 Kellie E. Murphy,1,2 Mathew Sermer,1 and Nadine Shehata2,6 published the exact metaanalysis in 2017 in the European heat journal. Please cite this paper and explain how is your metaanalysis different from that presented in this paper. Otherwise the English requier substential editing

REVIEWER	Hassan Mir McMaster University, Medicine
REVIEW RETURNED	24-Nov-2019

GENERAL COMMENTS	The authors reference three important reviews in this field of study (Reference 24,25,26). However, the results of these systematic reviews and meta analysis are not discussed. The results of these studies should be summarized and compared to one another in the introduction and/or discussion. It should be made clear how this current paper differs from those already done and what it hopes to add (ex network meta analysis, including newly reported studies/data, etc). Otherwise, interesting idea for an update using NMA.

VERSION 1 – AUTHOR RESPONSE

2.2 Responds to reviewer 1's comments:

2.2.1 Reviewer Name: Offer Erez

2.2.2 First comment:

The authors stated that no meta-analysis and systematic review were performed in this topic. However, Rohan D'Souza,1,2 Jackie Ostro,3 Prakesh S. Shah,2,4 Candice K. Silversides,5 Ann Malinowski,1 Kellie E. Murphy,1,2 Mathew Sermer,1 and Nadine Shehata2,6 published the exact meta-analysis in 2017 in the European heat journal.

Please cite this paper and explain how is your meta-analysis different from that presented in this paper.

2.2.3 Response to first comment:

Regarding the first comment, thank you for pointing this out and we have revised the Introduction section according to your comment. The revised Introduction has been inserted into the revised manuscript.

It is worth noting that network meta-analysis, which will be first used in our study to evaluate the comparative effects of multiple anticoagulation regimen in patients during pregnancy with mechanical heart valves, has obvious differences from traditional pairwise meta-analysis in terms of application conditions, statistical methods, and results reporting.(Reference 23 ,24) At the same time, there are many differences between the D'Souza et al.'s study(Reference 20) and our study.

Firstly, D'Souza et al.'s study(Reference 20) was conducted by traditional pairwise meta-analysis which did not allow for the inclusion of data from treatments that have not been compared head-to-head. For example, the different sequential treatments (LMWH and VKAs (INR target 2.5–3.5) compared with LMWH and VKAs (INR target 1.5–2.5) ,etc.) were unable to compared directly in D'Souza et al.'s study(Reference 20),which will be indirect compared by network meta-analysis in our study. Furthermore, the results from indirect combined with direct evidence in our study can improve precision for treatments that have been directly evaluated and a network meta-analysis can estimate the rank of these treatments. (Reference 23 ,24)

Secondly, some high-quality and latest studies (Reference 25-34) were not included in D'Souza et al.'s study, which will be included in our study to strengthen the trustworthiness and statistical power. Finally, more subgroups (e.g. type, location and number of mechanical heart valves) will be included in our studies to provide more information on the effectiveness and safety of subgroup patients, which were not considered in D'Souza et al.'s study (Reference 20).

These limitations of D'Souza et al.'s study (Reference 20) pose a urgently practical challenge to clinicians for choosing a suitable anticoagulation regimen because a direct comparison is rarely seen or not available for many anticoagulation regimens, thus, a Bayesian network meta-analysis is necessary.

2.2.4 Second comment:
Otherwise the English require substential editing

2.2.5 Response to second comment:

Considering the Reviewer's suggestion, we have revised the use of English in our report, and we will refine our report based on further comments.

2.3 Responds to reviewer 2's comments:

2.3.1 Reviewer Name: Hassan Mir

2.3.2 First comment:
The authors reference three important reviews in this field of study (Reference 24,25,26). However, the results of these systematic reviews and meta-analysis are not discussed. The results of these studies should be summarized and compared to one another in the introduction and/or discussion. It should be made clear how this current paper differs from those already done and what it hopes to add (ex network meta analysis, including newly reported studies/data, etc).

2.3.3 Response to first comment:

Regarding the first comment, it is really true as Reviewer suggested that the three reviews (Reference 24,25,26) need to be summarized and compared with our study in the Introduction section. We have re-write this part, which has been inserted into the revised manuscript. The revised part is as follows:

Although, several meta-analysis related to this research topic have been published previously, all of them are traditional pairwise meta-analyses which included some obvious limitations that need to be urgently improved.(Reference 13 20-22)Firstly, synthesising evidence using the traditional pairwise meta-analyses would not allow for the inclusion of data from treatments(e.g. the comparations of different sequential treatments) that have not been compared head-to-head in Xu et al.'s,D'Souza et al.'s, Steinberg et al.'s, and Chan et al.'s studies.(Reference 13 20-23) The results from indirect combined with direct evidence using network meta-analysis (NMA) allows for simultaneous consideration of the relative effectiveness and safety of all available anticoagulation treatments .(Reference 23) Furthermore, a network meta-analysis can estimate the rank of these treatments (Reference 23 ,24).Secondly, some high-quality and latest studies(one RCT (Reference 25) and nine observational studies (Reference 26-34)) in recent years were not included in these studies, which reduced trustworthiness and statistical power of these studies. Finally, some subgroups of anticoagulation treatments (e.g.different VKAs and heparin doses, different combinations of sequential treatments, and type, location and number of MHVs,etc.) were not considered in these studies, which led to the lack of results of effectiveness and safety by comparing these subgroups. These research gaps pose a urgently practical challenge to clinicians for choosing a suitable anticoagulation regimen because a direct comparison is rarely seen or not available for many anticoagulation regimens. Therefore, to address the challenge of clinicians to determine which anticoagulation regimen is more effective and safer during pregnancy in patients with MHVs, a Bayesian network meta-analysis is necessary.

2.3.4 Second comment:

Otherwise, interesting idea for an update using NMA.

2.3.5 Response to second comment:

Thank you for your comments, we also think this research topic is interesting, and our team will continue to modify and improve our research according to your comments.

3 Special thanks to you for your good comments

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate Editors/Reviewers' warm work earnestly, and hope the correction will meet with approval. Once again, thank you very much for your comments and suggestions.