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)	Prior surgical uterine evacuation of pregnancy and infertility: protocol for systematic review and meta-analysis
AUTHORS	Tu, Pengcheng; Pei, Kaiyan

VERSION 1 – REVIEW

REVIEWER	Bassel H.Al Wattar University of Warwick
REVIEW RETURNED	20-Nov-2019

GENERAL COMMENTS	Thank you for asking me to review this submitted protocol for a planned systematic review and meta-analysis aiming to examine the effect of uterine evacuation on future subfertility. Overall, I do not perceive high merits for publishing this manuscript for the following reasons: 1- I do not see a protocol published for this ''simple'' in peer-reviewed journals to be of benefit to the medical literature, in contrast to protocols for like IPD meta-analyses, prospective interventional studies etc.. A registered protocol on PROSPERO is sufficient. 2- The research question is clear, but I am not confident the authors will be able to answer it with the study design they plan to meta-analyse. Are they including case-control studies (women with diagnosed subfertility and previous exposure) or cohort studies (women with evacuation followed to check their subfertility)? Either way, the comparison the authors are stating is useless (any other women!). Specifically, subfertility is a multi-factorial condition that involved both couples. What is the couple have subfertility due to male factors?! 3- The outcomes planned are vague and not well defined. What does (newborn) mean? Are those outcomes really of clinical value to this question? 4- The statistical methods need revising, any planned meta-regression? How about adjusting for the inherent risk of bias in those observational studies? How about a GRADE approach. 5- The discussion needs improvement. Why is this question important? How are we likely to deal with the results? Are we going to advocate medical management of miscarriage and abortion instead of surgery? The authors need to add much more clinical input to this section. 6- The language needs improvement, too many spelling and grammar mistakes.

REVIEWER	Salvatore Giovanni Vitale Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania (Italy)

REVIEW RETURNED	08-Dec-2019

GENERAL COMMENTS	I read with great interest the Protocol titled “Prior uterine evacuation of pregnancy and infertility: protocol for systematic review and meta-analysis” (bmjopen-2019-034837), which falls within the aim of BMJ Open. In my honest opinion, the topic is interesting, and the methodology is accurate. Nevertheless, the authors should clarify some points and improve the discussion citing relevant and novel critical articles about the topic. Authors should consider the following recommendations: - A native English speaker should further revise the manuscript. - Authors should stress the possibility of concomitant causes of infertility/subfertility, such as endometriosis (PMID: 20801404), PCOS (PMID: 30311070) and chronic endometritis and/or adhesions that need hysteroscopic investigation (PMID 28948169). In this scenario, these populations should be excluded from the proposed analysis, regardless of the inclusion criteria of previous D&C. - Since D&C is known to cause high risk subsequent intrauterine adhesions (Asherman’s syndrome) and so infertility, I would suggest to further stress the possibility to use pharmacological treatment (i.e., misoprostol and mifepristone) for the management of missed abortions: PMID 31784973.

REVIEWER	Lucian Puscasiu University of Medicine, Pharmacy, Science and Technology Târgu Mures, Romania
REVIEW RETURNED	16-Jan-2020

GENERAL COMMENTS	1. Please better define the control group- are cases managed by medical abortion included? Are cases with expectant management included - please clarify! 2. Please define the stratification by gestational age 3. Typo on R43 ...the effect ...and 296 4. Please revise the entire REFERENCES section for typo and format

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Reviewer Name: Bassel H.Al Wattar
Institution and Country: University of Warwick
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you for asking me to review this submitted protocol for a planned systematic review and meta-analysis aiming to examine the effect of uterine evacuation on future subfertility.
Overall, I do not perceive high merits for publishing this manuscript for the following reasons:
1- I do not see a protocol published for this ‘‘simple’’ in peer-reviewed journals to be of benefit to the medical literature, in contrast to protocols for like IPD meta-analyses, prospective interventional studies etc.. A registered protocol on PROSPERO is sufficient.

Response: We have registered this protocol on Prospero（registration number CRD42019117266）. However, we still hope to publish on BMJ OPEN because we think protocols for a study design should not be the limitation for publishing this manuscript. According to BMJ Open's guides for authors (https://bmjopen.bmj.com/pages/authors/#protocol), publishing study protocols enables researchers and funding bodies to stay up to date in their fields by providing exposure to research activity that may not otherwise be widely publicised. This can help prevent unnecessary duplication of work and will hopefully enable collaboration. Publishing protocols in full also makes available more information than is currently required by trial registries and increases transparency, making it easier for others (editors, reviewers and readers) to see and understand any deviations from the protocol that occurs during the conduct of the study. BMJ Open will consider for publication protocols for any study design. And when we search term "protocol for systematic review and meta-analysis" on BMJ OPEN's website, we can see 8,377 results so far and many protocols for systematic review and meta-analysis have been published.

2- The research question is clear, but I am not confident the authors will be able to answer it with the study design they plan to meta-analyese. Are they including case-control studies (women with diagnosed subfertility and previous exposure) or cohort studies (women with evacuation followed to check their subfertility)? Either way, the comparison the authors are stating is useless (any other women!). Specifically, subfertility is a multi-factorial condition that involved both couples. What is the couple have subfertility due to male factors?!
Response: We regret that the comparison that we defined was more ambiguous than intended, and we have adjusted to better define the control group to make it clearer. According to your suggestion, we intended to include case-control studies (women with diagnosed subfertility and previous exposure, e.g. PMID: 8436890) and cohort studies (women with evacuation followed to check their subfertility, e.g. PMID: 30075608). And we agree that subfertility is a multi-factorial condition that involved both couples. However, we are unaware of any observational studies that assessed male factors at the same time. Thus we have added relevant discussion into the potential limitations in this manuscript. This is a valid and important question. Actually, we are conducting a prospective cohort study on effects of prior induced termination of pregnancy on complications and pregnancy outcomes (NCT number: NCT04183829). We appreciate your suggestion and will take male factors into consideration in our own study.

3- The outcomes planned are vague and not well defined. What does (newborn) mean? Are those outcomes really of clinical value to this question?
Response: Newborn is mentioned in the search strategy of this manuscript, as one of the key words of search terms. Newborn means an infant during the first 28 days after birth. We appreciate your suggestion and 'newborn' has been deleted from key words. And we have optimized our search strategy to make it more clinical value to this question. A supplementary file has been added including an example of the full search strategy.

4- The statistical methods need revising, any planned meta-regression? How about adjusting for the inherent risk of bias in those observational studies? How about a GRADE approach.
Response: We have revised statistical methods. We appreciate your suggestion since a meta-regression is an extension to subgroup analyses that allows the effect of continuous, as well as categorical, characteristics to be investigated, and in principle allows the effects of multiple factors to be investigated simultaneously. In our original manuscript, we have planned to perform a subgroup analysis of the risk of infertility according to the number of prior uterine evacuation. We will consider a meta-regression when there are more than ten studies in our meta-analysis. The quality of all included studies will be independently assessed by two reviewers using an established quality assessment tool for observational studies. This tool has been described in detail elsewhere (PMID: 19577836) and used in some protocols published on BMJ OPEN（e.g. BMJ Open Oct 2017, 7 (10)

e018313; DOI: 10.1136/bmjopen-2017-018313 and BMJ Open May 2019, 9 (5) e027180; DOI: 10.1136/bmjopen-2018-027180）. In summary, this tool uses a checklist to assess common features of the six types of bias most often associated with observational studies (selection, exposure, outcome, analytic, attrition and confounding). For each study, each component will be assigned a risk of bias category: minimal, low, moderate, high or not reported. For example, selection bias will be minimised if the sample was taken from a 'consecutive unselected population', while conversely a study with high selection bias will arise if sample selection is ambiguous and the sample is not likely representative. GRADE approach is valid and important. The quality of the findings on each outcome of interest across studies will be assessed using GRADE approach.

5- The discussion needs improvement. Why is this question important? How are we likely to deal with the results? Are we going to advocate medical management of miscarriage and abortion instead of surgery? The authors need to add much more clinical input to this section.
Response: Thank you for your advice. This section requires much more clinical input and we have revised the discussion. Although male infertility contributes to more than half of all cases of global childlessness, infertility remains a woman's social burden. In China, the number of induced abortions recently is reported over 9 million per year with more than half being repeated abortions. This systematic review and meta-analysis will summarize the available evidence examining the association between prior surgical uterine evacuation and the risk of infertility. The results would enhance our understanding of the decision support available to women choosing between medical and surgical early abortion. More importantly, we hope to urge women to realize the risk of surgical uterine evacuation and use contraceptive methods correctly and continually in order to reduce the rate of repeat abortions.

6- The language needs improvement, too many spelling and grammar mistakes.
Response: We apologize for these mistakes, and our manuscript has been reviewed by a native English speaker and revised to improve readability.

Reviewer: 2
Reviewer Name: Salvatore Giovanni Vitale
Institution and Country: Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania (Italy)
Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below
I read with great interest the Protocol titled "Prior uterine evacuation of pregnancy and infertility: protocol for systematic review and meta-analysis" (bmjopen-2019-034837), which falls within the aim of BMJ Open.
In my honest opinion, the topic is interesting, and the methodology is accurate. Nevertheless, the authors should clarify some points and improve the discussion citing relevant and novel critical articles about the topic.

Authors should consider the following recommendations:

- A native English speaker should further revise the manuscript.
Response: We appreciate your suggestion, and our manuscript has been reviewed by a native English speaker and revised to improve readability.

- Authors should stress the possibility of concomitant causes of infertility/subfertility, such as endometriosis (PMID: 20801404), PCOS (PMID: 30311070) and chronic endometritis and/or adhesions that need hysteroscopic investigation (PMID 28948169). In this scenario, these populations should be excluded from the proposed analysis, regardless of the inclusion criteria of previous D&C.

Response: Thanks a lot for providing so many critical articles. We have stressed the possibility of concomitant causes of infertility and revised our exclusion criteria. Populations undergoing endometriosis, PCOS and chronic endometritis and/or adhesions will be excluded from the proposed analysis.

- Since D&C is known to cause high risk subsequent intrauterine adhesions (Asherman's syndrome) and so infertility, I would suggest to further stress the possibility to use pharmacological treatment (i.e., misoprostol and mifepristone) for the management of missed abortions: PMID 31784973.
Response: The suggestion is important and would provide additional information so we have modified our review question and added relevant discussion in our manuscript. However, this manuscript is only a protocol for a planned systematic review and a meta-analysis and we can not draw a conclusion yet before we finish this study.

Reviewer: 3
Reviewer Name: Lucian Puscasiu
Institution and Country: University of Medicine, Pharmacy, Science and Technology Tărgu Mures, Romania
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
1. Please better define the control group- are cases managed by medical abortion included? Are cases with expectant management included - please clarify !
Response: We regret that the control group that we defined was more ambiguous than intended, and we have adjusted to better define the control group to make it clearer. Specifically, we intended to include case-control studies (women with diagnosed subfertility and previous exposure, e.g. PMID: 8436890) and cohort studies (women with evacuation followed to check their subfertility, e.g. PMID: 30075608). Cases managed by medical abortion will be included in the control group but cases with expectant management will be excluded.

2. Please define the stratification by gestational age
Response: We appreciate your suggestion, and we have defined the stratification by gestational age and sub-group analysis will be performed on basis of gestational weeks (＜6 vs. 6-9 vs. 9-12 vs. ≥12 gestational weeks).

3. Typo on R43 ...the effect ...and 296
Response: We apologize for this error, and we have corrected the text as suggested.

4. Please revise the entire REFERENCES section for typo and format
Response: We appreciate your suggestion, and we have revised the entire REFERENCES section for typo and format.

Looking forward to hearing from you. Thank you and best regards.

VERSION 2 – REVIEW

REVIEWER	Bassel H.Al Wattar University of Warwick - UK
REVIEW RETURNED	02-Mar-2020

GENERAL COMMENTS	The authors have addressed all raised comments adequately. This protocol can be published to increase transparency and reproducibility of the findings.

REVIEWER	Salvatore Giovanni Vitale Obstetrics and Gynecology Unit, Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy.
REVIEW RETURNED	18-Feb-2020

GENERAL COMMENTS	The authors have adequately addressed the critical points highlighted by the Reviewers. The overall quality of the manuscript is satisfactory now. For these reasons, no further changes are needed.

REVIEWER	Lucian Puscasiu University of Medicine, Pharmacy, Sciences and Technology Târgu Mures, Romania
REVIEW RETURNED	22-Feb-2020

GENERAL COMMENTS	Please revise for minor English language issues (e.g. R62) ... infertility are (!) associated