BMJ Open

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer:a protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041981
Article Type:	Protocol
Date Submitted by the Author:	22-Jun-2020
Complete List of Authors:	Xu, Yu; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zhang, QianWen; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Du, Yi; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Qin, ZhaoJuan; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology He, YueDong; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zheng, Ai; Sichuan University West China Medical Center,
Keywords:	Gynaecological oncology < GYNAECOLOGY, Minimally invasive surgery < GYNAECOLOGY, Gynaecological oncology < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer:a protocol for a systematic review and meta-analysis

Xu Yu[1];Zhang QianWen[1];Du Yi[1];Qin ZhaoJuan[1];He YueDong[1];Zheng Ai[1]

1.Department of Obstetrics and Gynecology,West China Second University Hospital,Sichuan University,ChengDu,China.

Correspondence to:Dr Zheng Ai,West China Second University Hospital,Sichuan University, No. 20, Section 3, South Renmin Road, Chengdu, Sichuan Province,China,610041,Email address: ZhengAi_WestChina@163.com

Abstract

Background: The oncological safety of diagnostic hysteroscopy in the stage Ⅰ endometrial cancer remains uncertain and conflicting.The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examing the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer and to synthesise the results of relevant studies.

Methods and analysis:A systematic search of PubMed/Medline,EMBASE,Cochrane Library and Web of Science will be undertaken using a detailed prespecified search strategy.Two authors will independently review the titles and the abstracts of all studies,perform data extraction and appraise the quality of included studies.Original case-control studies,cohort studies and randomized controlled trails published in English will be considered for inclusion.The outcomes of interest will be 5-year recurrence-free survival,disease-specific survival and overall survival.Meta-analyses will be performed to calculate the overall pooled estimates.The systematic review will follow the Meta-analysis of Observational Studies in Epidemiology guidelines.

Ethics and dissemination: This systematic review and meta-analysis will be based on published data,and thus there is no requirement for ethics approval.The results will be shared through publication in a peer reviewed journal and through presentations at academic conferences.

Strengths and limitations of this study

1. This proposed systematic review and meta-analysis is the first one in this topic and will compare survival measures of women with stage Ⅰ endometrial cancer who underwent either hysteroscopy or a non-hysteroscopic procedure as a diagnostic procedure.
2. Hysteroscopy is widely used in the diagnosis of early endometrial cancer and the significantly prognostic importance of positive peritoneal cytology suggests that any potential associations would have momentous practical implications.
3. We minimise the potential reviewer bias by letting two independent reviewers to screen for eligible studies,extract the data and assess the quality of the included studies.
4. We only include published papers in the English language.
5. A considered heterogeneity is anticipated between studies because of differences in study method and length of follow-up.

Introduction

Endometrial cancer is the most common cancer of the female reproductive system in developed countries[1].Of the patients with endometrial cancer,the majority will be diagnosed at stage Ⅰ or stage Ⅱ ,and five-year survival rates are as high as 80%-90% in these women[2, 3].The main symptom of endometrial cancer is abnormal uterine bleeding,this is typically post-menopausal but

may also be intermenstrual or heavy/prolonged periods,and these clinical manifestations can be found in up to ninety percent of patients[4, 5].

The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by office endometrial biopsy,dilation and curettage,or diagnostic hysteroscopy and directed endometrial biopsy.Hysteroscopy can provide gynecologist with visualization of the uterine cavity and is considered to be the most helpful tool for the evaluation of the endometrium in the presentation of abnormal uterine bleeding[6].According to the study of Garuti,hysteroscopy has high sensitivity,specificity,negative predictive value and positive predictive values of 94.2%,88.8%,96.3% and 83.1% respectively,in predicting abnormal or normal endometrial histopathology[6].Due to its accuracy,hysteroscopy with endometrial biopsy is highly recommended as the gold standard investigation for abnormal uterine bleeding and this procedure is taking the place of the traditional fractional dilation and curettage[7, 8].

However,concern exists that the use of distention media and increased intrauterine pressure may facilitate the intraperitoneal spread of cancer cells into peritoneal cavity though the fallopian tubes,and thereby,a potential deleterious effect on staging and prognosis in cases of endometrial cancer.Although positive peritoneal cytology no longer changes endometrial cancer FIGO staging[9],FIGO still recommends obtaining peritoneal cytology washings during surgery because of the potential for positive peritoneal cytology to compound the effects of other risk factors in early stage endometrial cancer[10].There is some evidence to suggest that diagnostic hysteroscopy increase the risk of positive peritoneal cytology[11-15].Nevertheless,whether or not the positive peritoneal cytology following a diagnostic hysteroscopy is associated with increased mortality or worsened prognosis in patients of endometrial cancer is inconclusive[16-26].

To our knowledge,there is no systematic review has been made in this topic.The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examing the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer.The outcomes of interest will be 5-year recurrence-free survival,disease-specific survival and overall survival.

Population

women with stage Ⅰ endometrial cancer who underwent either hysteroscopy or a non-hysteroscopic procedure as a diagnostic procedure.

Exposures

Hysteroscopy with endometrial biopsy as a preoperative diagnostic procedure for the early stage of endometrial cancer.

Comparison

Patients with the stage Ⅰ endometrial cancer diagnosed by non-hysteroscopy procedures,for example curettage and office endometrial biopsy.

Outcomes

Recurrence-free survival,disease-specific survival and overall survival,defined as the period from the date of the diagnosis to the date of recurrence or the last clinic visit (if alive) or the date of death.

Review question

Does the hysteroscopy as a diagnostic procedure worsen the prognosis of stage Ⅰ endometrial cancer?

Methods and design

This protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist[27].The proposed systematic review and meta-analysis will be conducted in accordance with the standard guideline of "Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines[28]" and "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[29]".

Search strategy

The lead author (Xu Yu) and corresponding author (Zheng Ai) will search numerous electronic bibliographic databases to identify qualifying studies published from database inception till July 2020,including PubMed/Medline,EMBASE,Cochrane Library and Web of Science.Informed by medical subject headings (MSH),the following keywords will be used to search the databases mentioned: "endometrial neoplasm","cancer of the endometrium","carcinoma of the endometrium","endometrial cancer", "endometrial carcinoma","endometrium cancer","endometrium carcinoma","hysteroscopy", "hysteroscopic surgery","uterine endoscopy","uteroscopy" , "diagnostic hysteroscopy"and "hysteroscopic surgical procedure".The search terms will be combined using Boolean Logic (AND,OR) where needed.We will restrict our search to human studies and peer reviewed journal articles published in the English language.In addition,reference lists from the relevant reviews and retrieved papers will be manually searched for any further potentially relevant studies.To ensure that the search is comprehensive,the search will be re-checked by an epidemiologist (He YueDong).

Study selection

Retrieved records from the databases will be entered into the Endnote reference manager (version X9) in order to categorize,manage,remove duplicates,and record titles,abstracts,and full-texts.Two independent review authors(Xu Yu and Zhang Qianwen) will screen all titles and abstracts for potentially relevant studies.The full text of the relevant studies will then be retrieved and screened for compliance with eligibility criteria by two reviewers(Xu Yu and Zhang Qianwen) . If consensus on eligibility cannot be achieved,a third review author (Qin ZhaoJuan) will be consulted.For any articles which do not meet the inclusion criteria,the reasons for rejection will be noted.A MOOSE flow diagram documenting the process of study selection will be completed.

Inclusion criteria

1. Case-control studies,cohort studies,or randomized controlled trails.
2. Only English language studies from inception of databases to July 2020 will be considered.
3. Data must be from an original study.
4. Peer reviewed papers only will be included.
5. Studies that provides measures of association between diagnostic hysteroscopy and prognosis of the stage Ⅰ endometrial cancer.

Exclusion criteria

1. Non-human studies.
2. Studies that are not in English.
3. Case reports,case series,letters,commentaries,notes and editorials.
4. Studies that have include patients of stage Ⅱ,Ⅲ and Ⅳ endometrial cancer.
5. Only the latest or the most informative study will be included when there are multiple studies that report on the same study population.

Data extraction

Data from all eligible studies will be independently extracted by two reviewers (Xu Yu and Du Yi) using a standardised data collection form,including the name of the primary author,year of publication,geographic location,study style,number of centers,number of particitants,study period,the duration of follow-up,the outcome(s) of interest, the definition used for each outcome,the confounders adjusted for (if any) and the crude and adjusted measures of association.In the cases of relevant papers in which the required data were not reported,the corresponding authors of these studies will be contacted by e-mail to obtain any information needed relating to effect estimates.If discrepancies arise in data extraction,these will be discussed between reviewers,and where necessary,a third reviewer (Zheng Ai) will be consulted to achieve consensus.

Quality appraisal of included studies

The quality of all included studies will be independently assessed by two reviewers (Xu Yu and Du Yi) using the Risk of Bias Instrument for Non-Randomized Studies of Exposures (ROBINS-E) or the Cochrane collaboration's tool for assessing risk of bias according to the style of the included studies.For each included study,the overall likelihood of bias will be assessed and reported.

The ROBINS-E has seven domains evaluating the source of bias:confounding,selection of particitants,classification of the expose,deviation from intended exposures,missing data,measurement of outcomes and selection of the reported result[30].Each domain will be assessed as at low,moderate,serious,or critical risk of bias, and the study will be rated overall as at least the same level of severity of the highest risk of bias of an individual domain[30].

For the randomized controlled trails,the risk of bias was assessed by answering the questions about the following features of studies with "Yes"(low risk of bias), "No" (high risk of bias) or "Unclear"(lack of information or uncertainty over the potential bias): random sequence generation, allocation concealment,blinding of participants,blinding of outcome assessment,incomplete outcome data,selective reporting and other bias[31].Possible sources of 'other bias' were determined by consensus of the investigators.

Where disagreement in quality appraisal arise,a third opinion from He YueDong will be obtained.

Data synthesis and assessment of heterogeneity

Separate meta-analyses will be undertaken for each of the outcomes where possible.Each meta-analysis will be undertaken to calculate the pooled estimate of the relationship between the diagnostic hysteroscopy and the outcomes.For example,for recurrence-free survival as one of the outcomes of interest,a meta-analysis will be undertaken to investigate the association between the

recurrence-free survival and diagnostic hysteroscopy.Two subgroup analyses will be conducted，these will be by the study design and by the risk of bias.

Both the crude and adjusted effect estimates will be displayed using the generic inverse variance method.Adjustment will be based on the definition outlined in each of the individual studies.Heterogeneity among the studies will be assessed by the x^2 test and I^2 (<25% deemed low heterogeneity,25%–50% moderate,and >50% high) statistics.P<0.10 or I^2>50% indicates that heterogeneity existed among the studies,so a random-effects model (Mantel–-Haenszel method) will be used.If studies cannot be meaningfully combined in a meta-analysis,they will be presented in tabular format.

Where ten or more studies are included in a meta-analysis,we will assess the publication bias. The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from publication bias,if appropriate[32].

Ethics and dissemination

This systematic review and meta-analysis will be based on published data,and thus there is no requirement for ethics approval.The results will be shared through publication in a peer reviewed journal and through presentations at academic conferences.

Patient and public involvement

Patients were not involved in the design of this systematic review and meta-analysis.However, the authors will communicate the study findings to patient and public groups with interest in this area.

Potential limitations

There are a number of limitations predicted in this review.A degree of heterogeneity is anticipated between studies.Differences in the length of follow-up and the study design are the main reason for the heterogeneity,and differences in sampling frames are also likely to cause heterogeneity.So,a random-effects model will be used for meta-analyses if there is moderate or high heterogeneity among the included studies.

In all observational studies,the existence of selection bias and residual confounding is a concern.Potential confounders may include age,race,socioeconomic status,degree of histological differentiation,histologic type,lymphovascular space invasion,pelvic lymph node dissection,para-aortic lymph node dissection,adjuvant chemotherapy and adjuvant radiotherapy.Where possible, our meta-analysis will show both crude and adjusted results,adjusted according to the definitions outlined in each individual study.However,given that less adjusted effect estimates may distort the overall results,a sensitivity analysis will be performed,where possible,to examine for more fully adjusted effect estimates for confounders (ie,adjusted for,at a minimum,age,degree of histological differentiation,histologic type,lymphovascular space invasion,pelvic lymph node dissection,para-aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy).

Due to limited resources,only studies which are published in the English language will be included.Predictably,few randomized controlled trials will be included in the proposed meta-analysis,the studies to be included will be lacked randomization,and will be not very powerful.

Discussion

There is a lack of consensus on whether diagnostic hysteroscopy deteriorates the prognosis of the early stage endometrial cancer.This proposed systematic review and meta-analysis will summarise the available evidence which has examined these associations,thus providing novel information on the role of hysteroscopy in the evaluation of abnormal uterine bleeding and the diagnosis of endometrial cancer.

Contributors

Xu Yu,Zhang QianWen,Du Yi,Qin ZhaoJuan,He YueDong and Zheng Ai conceived and designed the protocol,and Xu Yu drafted the protocol manuscript.Zhang QianWen developed the search strategy,with input from Xu Yu,Du Yi and Qin ZhaoJuan.Xu Yu and Du Yi planned the data extraction.Xu Yu and Du Yi planned the quality appraisal of all included studies. Xu Yu,Zhang QianWen,Du Yi,Qin ZhaoJuan,He YueDong and Zheng Ai critically revised the manuscript for methodological and intellectual content.All authors approved the final version.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent for publication

Not required.

Reference

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2018.* CA Cancer J Clin, 2018. **68**(1): p. 7-30.

2. Lewin, S.N., et al., *Comparative performance of the 2009 international Federation of gynecology and obstetrics' staging system for uterine corpus cancer.* Obstet Gynecol, 2010. **116**(5): p. 1141-9.

3. Creasman, W.T., et al., *Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.* Int J Gynaecol Obstet, 2006. **95 Suppl 1**: p. S105-43.

4. Seebacher, V., et al., *The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study.* BMC

Cancer, 2009. **9**: p. 460.

5. Kimura, T., et al., *Abnormal uterine bleeding and prognosis of endometrial cancer.* Int J Gynaecol Obstet, 2004. **85**(2): p. 145-50.

6. Garuti, G., et al., *Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women.* J Am Assoc Gynecol Laparosc, 2001. **8**(2): p. 207-13.

7. Revel, A. and A. Shushan, *Investigation of the infertile couple: hysteroscopy with endometrial biopsy is the gold standard investigation for abnormal uterine bleeding.* Hum Reprod, 2002. **17**(8): p. 1947-9.

8. de Wit, A.C., M.P. Vleugels, and J.H. de Kruif, *Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma?. Six years of experience with non-clinical diagnostic hysteroscopy.* Eur J Obstet Gynecol Reprod Biol, 2003. **110**(1): p. 79-82.

9. Pecorelli, S., *Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium.* Int J Gynaecol Obstet, 2009. **105**(2): p. 103-4.

10. Wethington, S.L., et al., *Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: Unraveling a mystery.* Gynecol Oncol, 2009. **115**(1): p. 18-25.

11. Chang, Y.N., et al., *Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis.* Fertil Steril, 2011. **96**(4): p. 957-61.

12. Polyzos, N.P., et al., *Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis.* Int J Gynecol Cancer, 2010. **20**(2): p. 261-7.

13. Obermair, A., et al., *Does hysteroscopy facilitate tumor cell dissemination? Incidence of peritoneal cytology from patients with early stage endometrial carcinoma following dilatation and curettage (D & C) versus hysteroscopy and D & C.* Cancer, 2000. **88**(1): p. 139-43.

14. Zerbe, M.J., et al., *Retrograde seeding of malignant cells during hysteroscopy in presumed early endometrial cancer.* Gynecol Oncol, 2000. **79**(1): p. 55-8.

15. Bradley, W.H., et al., *Hysteroscopy and cytology in endometrial cancer.* Obstet Gynecol, 2004. **104**(5 Pt 1): p. 1030-3.

16. Ben-Arie, A., et al., *Does hysteroscopy affect prognosis in apparent early-stage endometrial cancer?* Int J Gynecol Cancer, 2008. **18**(4): p. 813-9.

17. Cicinelli, E., et al., *Risk of long-term pelvic recurrences after fluid minihysteroscopy in women with endometrial carcinoma: a controlled randomized study.* Menopause, 2010. **17**(3): p. 511-5.

18. Gu, M., et al., *Association between initial diagnostic procedure and hysteroscopy and abnormal peritoneal washings in patients with endometrial carcinoma.* Cancer, 2000. **90**(3): p. 143-7.

19. Juhasz-Böss, I., et al., *Number of hysteroscopies and the time interval between hysteroscopy and surgery: influence on peritoneal cytology in patients with endometrial cancer.* Anticancer Res, 2010. **30**(6): p. 2425-30.

20. Kudela, M. and R. Pilka, *Is there a real risk in patients with endometrial carcinoma undergoing diagnostic hysteroscopy (HSC)?* Eur J Gynaecol Oncol, 2001. **22**(5): p. 342-4.

21. Sáinz de la Cuesta, R., et al., *Does fluid hysteroscopy increase the stage or worsen the prognosis in patients with endometrial cancer? A randomized controlled trial.* Eur J Obstet Gynecol Reprod Biol, 2004. **115**(2): p. 211-5.

22. Chen, J., et al., *Does hysteroscopy worsen prognosis in women with type II endometrial carcinoma?* PLoS One, 2017. **12**(3): p. e0174226.

23. Zhu, H.L., et al., *Hysteroscopy and directed biopsy in the diagnosis of endometrial carcinoma.* Chin Med J (Engl), 2010. **123**(24): p. 3524-8.

24. Namazov, A., et al., *The oncological safety of hysteroscopy in the diagnosis of early-stage endometrial cancer: An Israel gynecologic oncology group study.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2019. **243**: p. 120-124.

25. Soucie, J.E., et al., *The risk of diagnostic hysteroscopy in women with endometrial cancer.* Am J Obstet Gynecol, 2012. **207**(1): p. 71.e1-5.

26. Obermair, A., et al., *Impact of hysteroscopy on disease-free survival in clinically stage I endometrial cancer patients.* Int J Gynecol Cancer, 2000. **10**(4): p. 275-279.

27. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Syst Rev, 2015. **4**(1): p. 1.

28. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* Jama, 2000. **283**(15): p. 2008-12.

29. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Ann Intern Med, 2009. **151**(4): p. W65-94.

30. Hinneburg, I., *ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions.* Med Monatsschr Pharm, 2017. **40**(4): p. 175-7.

31. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.

32. Weinhandl, E.D. and S. Duval, *Generalization of trim and fill for application in meta-regression.* Res Synth Methods, 2012. **3**(1): p. 51-67.

BMJ Open

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041981.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Sep-2020
Complete List of Authors:	Xu, Yu; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zhang, QianWen; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Du, Yi; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Qin, ZhaoJuan; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology He, YueDong; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zheng, Ai; Sichuan University West China Medical Center,
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Gynaecological oncology < GYNAECOLOGY, Minimally invasive surgery < GYNAECOLOGY, Gynaecological oncology < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer: protocol for a systematic review and meta-analysis

Xu Yu[1]; Zhang QianWen[1]; Du Yi[1]; Qin ZhaoJuan[1]; He YueDong[1]; Zheng Ai[1]

1.Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, ChengDu,China.

Correspondence to: Dr Zheng Ai, West China Second University Hospital, Sichuan University, No. 20, Section 3, South Renmin Road, Chengdu, Sichuan Province, China, 610041, Email address: ZhengAi_WestChina@163.com

Abstract

Background: The oncological safety of diagnostic hysteroscopy in the stage Ⅰ endometrial cancer remains uncertain and conflicting. The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examing the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer and to synthesise the results of relevant studies.

Methods and analysis: A systematic search of PubMed/Medline, EMBASE, Cochrane Library and Web of Science will be undertaken using a detailed prespecified search strategy. Two authors will independently review the titles and the abstracts of all studies, perform data extraction and appraise the quality of included studies. Original case-control studies, cohort studies and randomized controlled trails published in English will be considered for inclusion. The outcomes of interest will be 5-year recurrence-free survival, disease-specific survival and overall survival. Meta-analyses will be performed to calculate the overall pooled estimates. The systematic review will follow the Meta-analysis of Observational Studies in Epidemiology guidelines.

Ethics and dissemination: This systematic review and meta-analysis will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer reviewed journal and through presentations at academic conferences.

PROSPERO registration number: CRD42020193696.

Strengths and limitations of this study

1. This proposed systematic review and meta-analysis is the first one in this topic and will compare survival measures of women with stage Ⅰ endometrial cancer who underwent either hysteroscopy or non-hysteroscopic procedures as diagnostic procedures.
2. Hysteroscopy is widely used in the diagnosis of early endometrial cancer and the significantly prognostic importance of positive peritoneal cytology suggests that any potential associations would have momentous practical implications.
3. We minimise the potential reviewer bias by letting two independent reviewers to screen for eligible studies, extract the data and assess the quality of the included studies.
4. We only include published papers in the English language.
5. A considered heterogeneity is anticipated between studies because of differences in study design and length of follow-up.

Introduction

Endometrial cancer is the most common cancer of the female reproductive system in developed countries[1]. Of the patients with endometrial cancer, the majority will be diagnosed at stage Ⅰ or stage Ⅱ, and five-year survival rates are as high as 80%-90% in these women[2, 3]. The main symptom of endometrial cancer is abnormal uterine bleeding, this is typically post-menopausal but

may also be intermenstrual or heavy/prolonged periods, and these clinical manifestations can be found in up to ninety percent of patients[4, 5].

The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by office endometrial biopsy, dilation and curettage, or diagnostic hysteroscopy and direct endometrial biopsy. Hysteroscopy can provide gynecologist with visualization of the uterine cavity and is considered to be the most helpful tool for the evaluation of the endometrium in the presentation of abnormal uterine bleeding[6]. According to the study of Garuti, hysteroscopy has high sensitivity, specificity, negative predictive value and positive predictive value of 94.2%, 88.8%, 96.3% and 83.1% respectively, in predicting abnormal or normal endometrial histopathology[7]. Due to its accuracy,hysteroscopy with endometrial biopsy is highly recommended as the gold standard investigation for abnormal uterine bleeding and this procedure is taking the place of the traditional fractional dilation and curettage[8, 9].

However, concern exists that the use of distention media and increased intrauterine pressure may facilitate the intraperitoneal spread of cancer cells into peritoneal cavity though the fallopian tubes, and thereby, a potential deleterious effect on staging and prognosis in cases of endometrial cancer. Although positive peritoneal cytology no longer changes endometrial cancer FIGO staging[10], FIGO still recommends obtaining peritoneal washings during surgery because of the potential for positive peritoneal cytology to compound the effects of other risk factors in early stage endometrial cancer[11]. There is some evidence to suggest that diagnostic hysteroscopy increase the risk of positive peritoneal cytology[12-16]. Nevertheless, whether or not the positive peritoneal cytology following a diagnostic hysteroscopy is associated with increased mortality or worsened prognosis in patients of endometrial cancer is inconclusive[17-27].

To our knowledge, there is no systematic review and/or meta-analysis available on this topic. The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examing the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer. The outcomes of interest will be 5-year recurrence-free survival, disease-specific survival and overall survival.

Population

Women with stage Ⅰ endometrial cancer diagnosed by hysteroscopy and direct endometrium sampling or by non-hysteroscopic procedures. The final pathologic diagnosis of endometrial cancer was made by pathologic examination of the specimen after total hysterectomy, the stage of the disease was determined by results of comprehensive staging surgery and pathological examination according to the FIGO staging for the corresponding period.

Exposures

Hysteroscopy with endometrial biopsy as a preoperative diagnostic procedure for stage Ⅰ endometrial cancer.

Comparison

Patients with the stage Ⅰ endometrial cancer diagnosed by non-hysteroscopy procedures, for example curettage and office endometrial biopsy.

Outcomes

Recurrence-free survival, disease-specific survival and overall survival, defined as the period from the date of the diagnosis to the date of recurrence or the last clinic visit (if alive) or the date of death.

Review question

Does hysteroscopy as a diagnostic procedure worsen the prognosis of cases with stage Ⅰ endometrial cancer?

Methods and design

This protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist[28]. The proposed systematic review and meta-analysis will be conducted in accordance with the standard guideline of "Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines[29]" and "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30]".

Search strategy

The leading author (Xu Yu) and corresponding author (Zheng Ai) will search four electronic bibliographic databases to identify qualifying studies published from database inception till July 30, 2020, including PubMed/Medline, EMBASE, Cochrane Library and Web of Science. Informed by medical subject headings (MSH), the following keywords will be used to search the databases mentioned: "endometrial neoplasm" , "cancer of the endometrium" , "carcinoma of the endometrium" , "endometrial cancer" , "endometrial carcinoma" , "endometrium cancer" , "endometrium carcinoma" , "hysteroscopy" , "hysteroscopic surgery" , "uterine endoscopy" , "uteroscopy" , "diagnostic hysteroscopy" and "hysteroscopic surgical procedure" . The search terms will be combined using Boolean Logic (AND, OR) where needed. We will restrict our search to human studies and peer reviewed journal articles published in the English language. The precise search strategies for one of the databases can be found in the supplementary file. In addition, reference lists from the relevant reviews and retrieved papers will be manually searched for any further potentially relevant studies. To ensure that the search is comprehensive, the search will be re-checked by an epidemiologist (He YueDong).

Study selection

Retrieved records from the databases will be entered into the Endnote reference manager (version X9) in order to categorize, manage, remove duplicates, and record titles, abstracts, and full-texts. Two independent review authors (Xu Yu and Zhang Qianwen) will screen all titles and abstracts for potentially relevant studies. The full-texts of the relevant studies will then be retrieved and screened for compliance with eligibility criteria by two reviewers (Xu Yu and Zhang Qianwen). For unpublished studies and abstracts that full-texts are not available, we will contact the authors by email to ask for the relevant data. If consensus on eligibility cannot be achieved, a third review author (Qin ZhaoJuan) will be consulted. For any articles which do not meet the inclusion criteria, the reasons for rejection will be noted. A MOOSE flow diagram documenting the process of study selection will be completed.

Inclusion criteria

1. Case-control studies,cohort studies,or randomized controlled trails.
2. Only English language studies published from inception of databases to July 30, 2020 will be considered.
3. Data must be from an original study.
4. Peer reviewed papers only will be included.
5. Studies that provide measures of association between diagnostic hysteroscopy and prognosis of the patients with stage Ⅰ endometrial cancer.

Exclusion criteria

1. Non-human studies.
2. Studies that are not in English.
3. Case reports, case series, letters, commentaries, notes and editorials.
4. Studies that have include patients of stage Ⅱ, Ⅲ and Ⅳ endometrial cancer.
5. Only the latest or the most informative study will be included when there are multiple studies that report on the same study population.
6. Abstracts and unpublished studies for which the attempts to contact the authors to get relevant data failed.

Data extraction

Data from all eligible studies will be independently extracted by two reviewers (Xu Yu and Du Yi) using a standardised data collection form, including the name of the primary author, year of publication, geographic location, study style, number of centers, number of particitants, study period, the duration of follow-up, the outcome(s) of interest, the definition used for each outcome, the confounders adjusted for (if any) and the crude and adjusted measures of association. In cases of relevant papers in which the required data were not reported, the corresponding authors of these studies will be contacted by email to obtain any information needed relating to effect estimates. If discrepancies arise in data extraction, these will be discussed between reviewers, and where necessary, a third reviewer (Zheng Ai) will be consulted to achieve consensus.

Quality appraisal of included studies

The quality of all included studies will be independently assessed by two reviewers (Xu Yu and Du Yi) using the Risk of Bias Instrument for Non-Randomized Studies of Exposures (ROBINS-E) or the Cochrane collaboration's tool for assessing risk of bias according to the style of the included studies. For each included study, the overall likelihood of bias will be assessed and reported.

The ROBINS-E has seven domains evaluating the source of bias: confounding, selection of particitants, classification of the exposures, deviation from intended exposures, missing data, measurement of outcomes and selection of the reported result[31]. Each domain will be assessed as low, moderate, serious, or critical risk of bias, and the study will be rated overall as at least the same level of severity of the highest risk of bias of an individual domain[31].

For the randomized controlled trails, the risk of bias was assessed by answering the questions about the following features of studies with "Yes" (low risk of bias), "No" (high risk of bias) or "Unclear" (lack of information or uncertainty over the potential bias): random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete

outcome data, selective reporting and other bias[32]. Possible sources of 'other bias' were determined by consensus of the investigators.

Where disagreement in quality appraisal arise, a third opinion from He YueDong will be obtained.

Data synthesis and assessment of heterogeneity

Separate meta-analyses will be undertaken for each of the outcomes if possible. Each meta-analysis will be undertaken to calculate the pooled estimate of the relationship between the diagnostic hysteroscopy and the outcomes. For example, for recurrence-free survival as one of the outcomes of interest, a meta-analysis will be undertaken to investigate the association between the recurrence-free survival and diagnostic hysteroscopy. We will stratify eligible studies into two categories based on the study design: observational study and randomized controlled trail because of the concern that there may be considerable heterogeneity between different types of studies. We will perform subgroup analysis according to the type of studies and for all outcomes.

Both the crude and adjusted effect estimates will be displayed using the generic inverse variance method. Adjustment will be based on the definition outlined in each of the individual studies. Heterogeneity among the studies will be assessed by the x^2 test and I^2 (<25% deemed low heterogeneity, 25%–50% moderate, and >50% high) statistics. $P<0.10$ or $I^2>50\%$ indicates that heterogeneity existed among the studies, so a random-effects model (Mantel–-Haenszel method) will be used. If studies cannot be meaningfully combined in a meta-analysis, they will be presented in tabular format.

Where ten or more studies are included in a meta-analysis, we will assess the publication bias. The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from publication bias, if appropriate[33].

Ethics and dissemination

This systematic review and meta-analysis will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer reviewed journal and through presentations at academic conferences.

Patient and public involvement

Patients were not involved in the design of this systematic review and meta-analysis. However, the authors will communicate the study findings to patient and public groups with interest in this area.

Potential limitations

There are a number of limitations we can predicted in this review. A degree of heterogeneity is anticipated between studies. Differences in the length of follow-up and the study design are the main reason for the heterogeneity, and differences in sampling frames are also likely to cause heterogeneity. So, a random-effects model will be used for meta-analyses if there is moderate or high heterogeneity among the included studies.

In all observational studies, the existence of selection bias and residual confounding is a concern. Potential confounders may include age, race, socioeconomic status, degree of histological differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-

aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy. Where possible, our meta-analysis will show both crude and adjusted results, adjusted according to the definitions outlined in each individual study. However, given that less adjusted effect estimates may distort the overall results, a sensitivity analysis will be performed where possible, to examine for more fully adjusted effect estimates for confounders (ie, adjusted for, at a minimum, age, degree of histological differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy).

Due to limited resources, only studies which are published in the English language will be included. Besides, considering that there are many challenges and difficulties to conduct randomized control studies to investigate the oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer in real clinical settings, the majority of included studies will be observational studies, and this will compromise the results of our proposed study.

Discussion

There is a lack of consensus on whether diagnostic hysteroscopy deteriorates the prognosis of the early stage endometrial cancer. This proposed systematic review and meta-analysis will summarise the available evidence which has examined these associations, thus providing novel information on the role of hysteroscopy in the evaluation of abnormal uterine bleeding and the diagnosis of endometrial cancer.

Contributors

Xu Yu, Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai conceived and designed the protocol, and Xu Yu drafted the protocol manuscript. Zhang QianWen developed the search strategy, with input from Xu Yu, Du Yi and Qin ZhaoJuan. Xu Yu and Du Yi planned the data extraction. Xu Yu and Du Yi planned the quality appraisal of all included studies. Xu Yu, Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent for publication

Not required.

Reference

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2018.* CA Cancer J Clin, 2018. **68**(1): p. 7-30.

2. Lewin, S.N., et al., *Comparative performance of the 2009 international Federation of*

gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol, 2010. **116**(5): p. 1141-9.

3. Creasman, W.T., et al., *Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.* Int J Gynaecol Obstet, 2006. **95 Suppl 1**: p. S105-43.

4. Seebacher, V., et al., *The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study.* BMC Cancer, 2009. **9**: p. 460.

5. Kimura, T., et al., *Abnormal uterine bleeding and prognosis of endometrial cancer.* Int J Gynaecol Obstet, 2004. **85**(2): p. 145-50.

6. Clark, T.J., et al., *Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review.* Jama, 2002. 288(13): p. 1610-21.

7. Garuti, G., et al., *Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women.* J Am Assoc Gynecol Laparosc, 2001. **8**(2): p. 207-13.

8. Revel, A. and A. Shushan, *Investigation of the infertile couple: hysteroscopy with endometrial biopsy is the gold standard investigation for abnormal uterine bleeding.* Hum Reprod, 2002. **17**(8): p. 1947-9.

9. de Wit, A.C., M.P. Vleugels, and J.H. de Kruif, *Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma?. Six years of experience with non-clinical diagnostic hysteroscopy.* Eur J Obstet Gynecol Reprod Biol, 2003. **110**(1): p. 79-82.

10. Pecorelli, S., *Revised FIGO staging for carcinoma of the vulva, cervix, and*

endometrium. Int J Gynaecol Obstet, 2009. **105**(2): p. 103-4.

11. Wethington, S.L., et al., *Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: Unraveling a mystery.* Gynecol Oncol, 2009. **115**(1): p. 18-25.

12. Chang, Y.N., et al., *Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis.* Fertil Steril, 2011. **96**(4): p. 957-61.

13. Polyzos, N.P., et al., *Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis.* Int J Gynecol Cancer, 2010. **20**(2): p. 261-7.

14. Obermair, A., et al., *Does hysteroscopy facilitate tumor cell dissemination? Incidence of peritoneal cytology from patients with early stage endometrial carcinoma following dilatation and curettage (D & C) versus hysteroscopy and D & C.* Cancer, 2000. **88**(1): p. 139-43.

15. Zerbe, M.J., et al., *Retrograde seeding of malignant cells during hysteroscopy in presumed early endometrial cancer.* Gynecol Oncol, 2000. **79**(1): p. 55-8.

16. Bradley, W.H., et al., *Hysteroscopy and cytology in endometrial cancer.* Obstet Gynecol, 2004. **104**(5 Pt 1): p. 1030-3.

17. Ben-Arie, A., et al., *Does hysteroscopy affect prognosis in apparent early-stage endometrial cancer?* Int J Gynecol Cancer, 2008. **18**(4): p. 813-9.

18. Cicinelli, E., et al., *Risk of long-term pelvic recurrences after fluid minihysteroscopy in women with endometrial carcinoma: a controlled randomized study.* Menopause, 2010. **17**(3): p. 511-5.

19. Gu, M., et al., *Association between initial diagnostic procedure and hysteroscopy and abnormal peritoneal washings in patients with endometrial carcinoma.* Cancer, 2000. **90**(3): p. 143-7.

20. Juhasz-Böss, I., et al., *Number of hysteroscopies and the time interval between hysteroscopy and surgery: influence on peritoneal cytology in patients with endometrial cancer.* Anticancer Res, 2010. **30**(6): p. 2425-30.

21. Kudela, M. and R. Pilka, *Is there a real risk in patients with endometrial carcinoma undergoing diagnostic hysteroscopy (HSC)?* Eur J Gynaecol Oncol, 2001. **22**(5): p. 342-4.

22. Sáinz de la Cuesta, R., et al., *Does fluid hysteroscopy increase the stage or worsen the prognosis in patients with endometrial cancer? A randomized controlled trial.* Eur J Obstet Gynecol Reprod Biol, 2004. **115**(2): p. 211-5.

23. Chen, J., et al., *Does hysteroscopy worsen prognosis in women with type II endometrial carcinoma?* PLoS One, 2017. **12**(3): p. e0174226.

24. Zhu, H.L., et al., *Hysteroscopy and directed biopsy in the diagnosis of endometrial carcinoma.* Chin Med J (Engl), 2010. **123**(24): p. 3524-8.

25. Namazov, A., et al., *The oncological safety of hysteroscopy in the diagnosis of early-stage endometrial cancer: An Israel gynecologic oncology group study.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2019. **243**: p. 120-124.

26. Soucie, J.E., et al., *The risk of diagnostic hysteroscopy in women with endometrial cancer.* Am J Obstet Gynecol, 2012. **207**(1): p. 71.e1-5.

27. Obermair, A., et al., *Impact of hysteroscopy on disease-free survival in clinically stage*

l endometrial cancer patients. Int J Gynecol Cancer, 2000. **10**(4): p. 275-279.

28. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Syst Rev, 2015. **4**(1): p. 1.

29. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* Jama, 2000. **283**(15): p. 2008-12.

30. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Ann Intern Med, 2009. **151**(4): p. W65-94.

31. Hinneburg, I., *ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions.* Med Monatsschr Pharm, 2017. **40**(4): p. 175-7.

32. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.

33. Weinhandl, E.D. and S. Duval, *Generalization of trim and fill for application in meta-regression.* Res Synth Methods, 2012. **3**(1): p. 51-67.

search strategies for PubMed

#1 (((((((endometrial neoplasm[Title/Abstract]) OR (cancer of the endometrium[Title/Abstract])) OR (carcinoma of the endometrium[Title/Abstract])) OR (endometrial cancer[Title/Abstract])) OR (endometrial carcinoma[Title/Abstract])) OR (endometrium cancer[Title/Abstract])) OR (endometrium carcinoma[Title/Abstract]))

#2 (((((hysteroscopy[Title/Abstract]) OR (hysteroscopic surgery[Title/Abstract])) OR (uterine endoscopy[Title/Abstract])) OR (uteroscopy[Title/Abstract])) OR (diagnostic hysteroscopy[Title/Abstract])) OR (hysteroscopic surgical procedure[Title/Abstract])

#3 ("1900/01/01"[Date - Publication] : "2020/07/30"[Date - Publication])

#4 #1 and #2 and #3

BMJ Open

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-041981.R2
Article Type:	Protocol
Date Submitted by the Author:	14-Nov-2020
Complete List of Authors:	Xu, Yu; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zhang, QianWen; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Du, Yi; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Qin, ZhaoJuan; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology He, YueDong; Sichuan University West China Second University Hospital, Department of Obstetrics and Gynecology Zheng, Ai; Sichuan University West China Medical Center,
Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Gynaecological oncology < GYNAECOLOGY, Minimally invasive surgery < GYNAECOLOGY, Gynaecological oncology < ONCOLOGY

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer: protocol for a systematic review and meta-analysis

Xu Yu[1]; Zhang QianWen[1]; Du Yi[1]; Qin ZhaoJuan[1]; He YueDong[1]; Zheng Ai[1]

1.Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, ChengDu,China.

Correspondence to: Dr Zheng Ai, West China Second University Hospital, Sichuan University, No. 20, Section 3, South Renmin Road, Chengdu, Sichuan Province, China, 610041, Email address: ZhengAi_WestChina@163.com

Abstract

Background: The oncological safety of diagnostic hysteroscopy in patients with stage Ⅰ endometrial cancer remains uncertain and conflicting. The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examining the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer and to statistical synthesise the results of relevant studies.

Methods and analysis: systematic searches of PubMed/Medline, EMBASE, Cochrane Library and Web of Science will be undertaken using prespecified search strategies. Two authors will independently conduct eligible studies selection process, perform data extraction and appraise the quality of included studies. Original case-control studies, cohort studies and randomized controlled trails published in English will be considered for inclusion. The outcomes of interest will be 5-year recurrence-free survival, disease-specific survival and overall survival. Meta-analyses will be performed to calculate pooled estimates.

Ethics and dissemination: Our study will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer reviewed journal and presentations at academic conferences.

PROSPERO registration number: CRD42020193696.

Strengths and limitations of this study

1. This proposed systematic review and meta-analysis is the first one on this topic and will compare survival measures of women with stage Ⅰ endometrial cancer who underwent either diagnostic hysteroscopy or non-hysteroscopic diagnostic procedures.
2. Hysteroscopy is widely used in the diagnosis of early endometrial cancer, any potential associations between diagnostic hysteroscopy and prognosis of patients would have significantly practical implications.
3. We minimise the potential reviewer bias by letting two independent reviewers to screen for eligible studies, extract the data and assess the quality of the included studies.
4. We only include papers published in English.
5. A considered heterogeneity is anticipated between studies because of differences in study design and length of follow-up.

Introduction

Endometrial cancer is the most common malignancy of the female reproductive system in developed countries[1]. Of the patients with endometrial cancer, the majority will be diagnosed at stage Ⅰ or stage Ⅱ, and five-year survival rate is as high as 80%-90% in these women[2, 3]. The main symptom of endometrial cancer is abnormal uterine bleeding, this is typically post-menopausal

but may also be intermenstrual or heavy/prolonged periods, and these clinical manifestations can be found in up to ninety percent of patients[4, 5].

The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by office endometrial biopsy, dilation and curettage, or diagnostic hysteroscopy and direct endometrial biopsy. Hysteroscopy can provide gynaecologist with visualization of the uterine cavity and is considered to be the most helpful tool for the evaluation of endometrium in presentation of abnormal uterine bleeding[6]. According to the study of Garuti, hysteroscopy has high sensitivity, specificity, negative predictive value and positive predictive value of 94.2%, 88.8%, 96.3% and 83.1% respectively, in predicting abnormal or normal endometrial histopathology[7]. Due to its accuracy, hysteroscopy with endometrial biopsy is highly recommended as the gold standard investigation for abnormal uterine bleeding and this procedure is taking the place of the traditional fractional dilation and curettage[8, 9].

However, concern exists that the use of distention media and increased intrauterine pressure may facilitate the spread of cancer cells into peritoneal cavity though the fallopian tubes, and thereby, a potential deleterious effect on staging and prognosis in cases of endometrial cancer. Although positive peritoneal cytology no longer changes the International Federation of Gynecology and Obstetrics(FIGO) stages of endometrial cancer[10], FIGO still recommends obtaining peritoneal washings during surgery because of the potential for positive peritoneal cytology to compound the effects of other risk factors in early stage endometrial cancer[11]. There was some evidence to suggest that diagnostic hysteroscopy increase the risk of positive peritoneal cytology[12-16]. Nevertheless, whether or not the positive peritoneal cytology following a diagnostic hysteroscopy is associated with increased mortality or worsened prognosis in patients of endometrial cancer is inconclusive[17-27].

To our knowledge, there is no systematic review and/or meta-analysis available on this topic. The aim of the proposed systematic review and meta-analysis is to summarise the available evidence examining the association between diagnostic hysteroscopy and the prognosis of stage Ⅰ endometrial cancer. The outcomes of interest will be 5-year recurrence-free survival, disease-specific survival and overall survival.

Population

Women with stage Ⅰ endometrial cancer diagnosed by hysteroscopy and direct endometrium sampling or by non-hysteroscopic procedures. The final pathologic diagnosis of endometrial cancer was made by pathologic examination of the specimen after total hysterectomy, the stage of the disease was determined by results of comprehensive staging surgery and pathological examination according to the FIGO staging for the corresponding period.

Exposures

Hysteroscopy with endometrial biopsy as a preoperative diagnostic procedure for stage Ⅰ endometrial cancer.

Comparison

Patients with the stage Ⅰ endometrial cancer diagnosed by non-hysteroscopic procedures, for example curettage and office endometrial biopsy.

Outcomes

Recurrence-free survival, disease-specific survival and overall survival, defined as the period from the date of the diagnosis to the date of recurrence or the last clinic visit (if alive) or the date of death.

Review question

Does hysteroscopy as a diagnostic procedure worsen the prognosis of cases with stage Ⅰ endometrial cancer?

Methods and design

This protocol was drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist[28]. The proposed systematic review and meta-analysis will be conducted in accordance with the standard guideline of "Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines[29]" and "Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[30]".

Search strategy

The leading author (Xu Yu) and corresponding author (Zheng Ai) will search four electronic databases (PubMed/Medline, EMBASE, Cochrane Library and Web of Science) to identify qualifying studies published from database inception till July 30, 2020. Informed by medical subject headings (MSH), the following keywords will be used to search the databases mentioned: "endometrial neoplasm" , "cancer of the endometrium" , "carcinoma of the endometrium" , "endometrial cancer" , "endometrial carcinoma" , "endometrium cancer" , "endometrium carcinoma" , "hysteroscopy" , "hysteroscopic surgery" , "uterine endoscopy" , "uteroscopy" , "diagnostic hysteroscopy" and "hysteroscopic surgical procedure" . The search terms will be combined using Boolean Logic (AND, OR) where needed. We will restrict our search to human studies and peer reviewed journal articles published in English. The precise search strategies for one of the databases can be found in the supplementary material. In addition, reference lists of all included studies will be manually searched for any further potentially relevant studies. To ensure that the search is comprehensive, the search will be re-checked by an epidemiologist (He YueDong).

Study selection

Retrieved records from literature searches will be entered into the Endnote reference manager (version X9) in order to categorize, manage, remove duplicates, and record titles, abstracts, and full-texts. Two independent authors (Xu Yu and Zhang Qianwen) will screen all titles and abstracts for potentially relevant studies. The full-texts of the relevant studies will then be retrieved and screened for compliance with eligibility criteria by the same two reviewers. For unpublished studies and abstracts that full-texts are not available, we will contact the authors by email to ask for the relevant data. If consensus on eligibility cannot be achieved, a third author (Qin ZhaoJuan) will be consulted. For any articles which do not meet the inclusion criteria, the reasons for rejection will be noted. A MOOSE flow diagram documenting the process of study selection will be completed.

Inclusion criteria

1. Case-control studies, cohort studies, or randomized controlled trails.

2. Only English language studies published from inception of databases to July 30, 2020 will be considered.
3. Data must be from an original study.
4. Peer reviewed papers only will be included.
5. Studies that provide measures of association between diagnostic hysteroscopy and prognosis of patients with stage Ⅰ endometrial cancer.

Exclusion criteria

1. Non-human studies.
2. Paper that are not in English.
3. Case reports, case series, letters, commentaries, notes and editorials.
4. Studies that have include patients of stage Ⅱ, Ⅲ and Ⅳ endometrial cancer.
5. Only the latest or the most informative study will be included when there are multiple studies that report on the same study population.
6. Abstracts and unpublished studies for which the attempts to contact the authors to get relevant data failed.

Data extraction

Data from all eligible studies will be independently extracted by two reviewers (Xu Yu and Du Yi) using a standardised data collection form, including the name of the first author, year of publication, geographic location, study style, number of center, number of participant, study span, the duration of follow-up, the outcome(s) of interest, the definition used for each outcome, the confounders adjusted for (if any) and the crude and adjusted measures of association. In cases of relevant papers in which the required data were not reported, the corresponding authors of these studies will be contacted by email to obtain information needed relating to effect estimates. If discrepancies arise in data extraction, these will be discussed between reviewers, and when necessary, a third reviewer (Zheng Ai) will be consulted to achieve consensus.

Quality appraisal of included studies

The quality of all included studies will be independently assessed by two reviewers (Xu Yu and Du Yi) using the Risk of Bias Instrument for Non-Randomized Studies of Exposures (ROBINS-E) or the Cochrane collaboration's tool for assessing risk of bias according to the style of the included studies. For each included study, the overall likelihood of bias will be appraised and reported.

The ROBINS-E has seven domains evaluating the source of bias: confounding, selection of participant, classification of the exposures, deviation from intended exposures, missing data, measurement of outcomes and selection of the reported result[31]. Each domain will be assessed as low, moderate, serious, or critical risk of bias, and the study will be rated overall as at least the same level of severity of the highest risk of bias of an individual domain[31].

For the randomized controlled trails, the risk of bias was assessed by answering the questions about the following features of studies with "Yes" (low risk of bias), "No" (high risk of bias) or "Unclear" (lack of information or uncertainty over the potential bias): random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete

outcome data, selective reporting and other bias[32]. Possible sources of 'other bias' were determined by consensus of the investigators.

Where disagreement in quality appraisal arise, a third opinion from He YueDong will be obtained.

Data synthesis and assessment of heterogeneity

Separate meta-analysis will be undertaken for each of the outcomes if possible. Each meta-analysis will be performed to calculate the pooled estimate of the relationship between the diagnostic hysteroscopy and the outcomes. For example, for recurrence-free survival as one of the outcomes of interest, a meta-analysis will be undertaken to investigate the association between the recurrence-free survival and diagnostic hysteroscopy. We will stratify eligible studies into two categories based on the study design: observational study and randomized controlled trail because of the concern that there may be considerable heterogeneity between different types of study. We will perform subgroup analysis according to the type of study and for all outcomes.

Both the crude and adjusted effect estimates will be displayed using the generic inverse variance method. Adjustment will be based on the definition outlined in each of the eligible studies. Heterogeneity among the studies will be assessed by the x^2 test and I^2 (<25% deemed low heterogeneity, 25%–50% moderate, and >50% high) statistics. $P<0.10$ or $I^2>50\%$ indicates that heterogeneity existed among the studies, so a random-effects model (Mantel–-Haenszel method) will be used. If studies cannot be meaningfully combined in a meta-analysis, they will be presented in tabular format.

Where ten or more studies are included in a meta-analysis, we will assess the publication bias. The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from publication bias, if appropriate[33].

Ethics and dissemination

Our study will be based on published data, and thus there is no requirement for ethics approval. The results will be shared through publication in a peer reviewed journal and presentations at academic conferences.

Patient and public involvement

Patients were not involved in the design of this study. However, the authors will communicate the study findings to patient and public groups with interest in this area.

Potential limitations

There are a number of limitations we can predict in this review. A degree of heterogeneity is anticipated between studies. Differences in the length of follow-up and the study design are the main source for the heterogeneity, and differences in sampling frames are also likely to cause heterogeneity. So, a random-effects model will be used for meta-analyses if there is moderate or high heterogeneity among the included studies.

In all observational studies, the existence of selection bias and residual confounding is a concern. Potential confounders may include age, race, socioeconomic status, degree of histological differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy. Where possible,

our meta-analysis will show both crude and adjusted results, adjusted according to the definitions outlined in each individual study. However, given that less adjusted effect estimates may distort the overall results, a sensitivity analysis will be performed where possible, to examine for more fully adjusted effect estimates for confounders (ie, adjusted for, at a minimum, age, degree of histological differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy).

Due to limited resources, only studies which were published in English will be included. Besides, considering that there are many challenges and difficulties to conduct randomized control studies to investigate the oncological safety of hysteroscopy in the diagnosis of stage Ⅰ endometrial cancer in real clinical settings, the majority of included studies will be observational studies, and this will compromise the results of our proposed study.

Discussion

There is a lack of consensus on whether diagnostic hysteroscopy deteriorates the prognosis of the early stage endometrial cancer. This proposed systematic review and meta-analysis will summarise the available evidence which has examined these associations, thus providing novel information on the role of hysteroscopy in the evaluation of abnormal uterine bleeding and the diagnosis of endometrial cancer.

Contributors

Xu Yu, Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai conceived and designed the protocol, and Xu Yu drafted the protocol manuscript. Zhang QianWen developed the search strategy, with input from Xu Yu, Du Yi and Qin ZhaoJuan. Xu Yu and Du Yi planned the data extraction. Xu Yu and Du Yi planned the quality appraisal of all included studies. Xu Yu, Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai critically revised the manuscript for methodological and intellectual content. All authors approved the final version.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests

None declared.

Patient consent for publication

Not required.

Reference

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2018.* CA Cancer J Clin, 2018. **68**(1): p. 7-30.

2. Lewin, S.N., et al., *Comparative performance of the 2009 international Federation of*

gynecology and obstetrics' staging system for uterine corpus cancer. Obstet Gynecol, 2010. **116**(5): p. 1141-9.

3. Creasman, W.T., et al., *Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer.* Int J Gynaecol Obstet, 2006. **95 Suppl 1**: p. S105-43.

4. Seebacher, V., et al., *The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study.* BMC Cancer, 2009. **9**: p. 460.

5. Kimura, T., et al., *Abnormal uterine bleeding and prognosis of endometrial cancer.* Int J Gynaecol Obstet, 2004. **85**(2): p. 145-50.

6. Clark, T.J., et al., *Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review.* Jama, 2002. 288(13): p. 1610-21.

7. Garuti, G., et al., *Accuracy of hysteroscopy in predicting histopathology of endometrium in 1500 women.* J Am Assoc Gynecol Laparosc, 2001. **8**(2): p. 207-13.

8. Revel, A. and A. Shushan, *Investigation of the infertile couple: hysteroscopy with endometrial biopsy is the gold standard investigation for abnormal uterine bleeding.* Hum Reprod, 2002. **17**(8): p. 1947-9.

9. de Wit, A.C., M.P. Vleugels, and J.H. de Kruif, *Diagnostic hysteroscopy: a valuable diagnostic tool in the diagnosis of structural intra-cavital pathology and endometrial hyperplasia or carcinoma?. Six years of experience with non-clinical diagnostic hysteroscopy.* Eur J Obstet Gynecol Reprod Biol, 2003. **110**(1): p. 79-82.

10. Pecorelli, S., *Revised FIGO staging for carcinoma of the vulva, cervix, and*

endometrium. Int J Gynaecol Obstet, 2009. **105**(2): p. 103-4.

11. Wethington, S.L., et al., *Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: Unraveling a mystery.* Gynecol Oncol, 2009. **115**(1): p. 18-25.

12. Chang, Y.N., et al., *Effect of hysteroscopy on the peritoneal dissemination of endometrial cancer cells: a meta-analysis.* Fertil Steril, 2011. **96**(4): p. 957-61.

13. Polyzos, N.P., et al., *Intraperitoneal dissemination of endometrial cancer cells after hysteroscopy: a systematic review and meta-analysis.* Int J Gynecol Cancer, 2010. **20**(2): p. 261-7.

14. Obermair, A., et al., *Does hysteroscopy facilitate tumor cell dissemination? Incidence of peritoneal cytology from patients with early stage endometrial carcinoma following dilatation and curettage (D & C) versus hysteroscopy and D & C.* Cancer, 2000. **88**(1): p. 139-43.

15. Zerbe, M.J., et al., *Retrograde seeding of malignant cells during hysteroscopy in presumed early endometrial cancer.* Gynecol Oncol, 2000. **79**(1): p. 55-8.

16. Bradley, W.H., et al., *Hysteroscopy and cytology in endometrial cancer.* Obstet Gynecol, 2004. **104**(5 Pt 1): p. 1030-3.

17. Ben-Arie, A., et al., *Does hysteroscopy affect prognosis in apparent early-stage endometrial cancer?* Int J Gynecol Cancer, 2008. **18**(4): p. 813-9.

18. Cicinelli, E., et al., *Risk of long-term pelvic recurrences after fluid minihysteroscopy in women with endometrial carcinoma: a controlled randomized study.* Menopause, 2010. **17**(3): p. 511-5.

19. Gu, M., et al., *Association between initial diagnostic procedure and hysteroscopy and abnormal peritoneal washings in patients with endometrial carcinoma.* Cancer, 2000. **90**(3): p. 143-7.

20. Juhasz-Böss, I., et al., *Number of hysteroscopies and the time interval between hysteroscopy and surgery: influence on peritoneal cytology in patients with endometrial cancer.* Anticancer Res, 2010. **30**(6): p. 2425-30.

21. Kudela, M. and R. Pilka, *Is there a real risk in patients with endometrial carcinoma undergoing diagnostic hysteroscopy (HSC)?* Eur J Gynaecol Oncol, 2001. **22**(5): p. 342-4.

22. Sáinz de la Cuesta, R., et al., *Does fluid hysteroscopy increase the stage or worsen the prognosis in patients with endometrial cancer? A randomized controlled trial.* Eur J Obstet Gynecol Reprod Biol, 2004. **115**(2): p. 211-5.

23. Chen, J., et al., *Does hysteroscopy worsen prognosis in women with type II endometrial carcinoma?* PLoS One, 2017. **12**(3): p. e0174226.

24. Zhu, H.L., et al., *Hysteroscopy and directed biopsy in the diagnosis of endometrial carcinoma.* Chin Med J (Engl), 2010. **123**(24): p. 3524-8.

25. Namazov, A., et al., *The oncological safety of hysteroscopy in the diagnosis of early-stage endometrial cancer: An Israel gynecologic oncology group study.* European Journal of Obstetrics & Gynecology and Reproductive Biology, 2019. **243**: p. 120-124.

26. Soucie, J.E., et al., *The risk of diagnostic hysteroscopy in women with endometrial cancer.* Am J Obstet Gynecol, 2012. **207**(1): p. 71.e1-5.

27. Obermair, A., et al., *Impact of hysteroscopy on disease-free survival in clinically stage*

l endometrial cancer patients. Int J Gynecol Cancer, 2000. **10**(4): p. 275-279.

28. Moher, D., et al., *Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.* Syst Rev, 2015. **4**(1): p. 1.

29. Stroup, D.F., et al., *Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.* Jama, 2000. **283**(15): p. 2008-12.

30. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* Ann Intern Med, 2009. **151**(4): p. W65-94.

31. Hinneburg, I., *ROBINS-1: A tool for asssessing risk of bias in non-randomised studies of interventions.* Med Monatsschr Pharm, 2017. **40**(4): p. 175-7.

32. Higgins, J.P., et al., *The Cochrane Collaboration's tool for assessing risk of bias in randomised trials.* Bmj, 2011. **343**: p. d5928.

33. Weinhandl, E.D. and S. Duval, *Generalization of trim and fill for application in meta-regression.* Res Synth Methods, 2012. **3**(1): p. 51-67.

search strategies for PubMed

#1 (((((((endometrial neoplasm[Title/Abstract]) OR (cancer of the endometrium[Title/Abstract])) OR (carcinoma of the endometrium[Title/Abstract])) OR (endometrial cancer[Title/Abstract])) OR (endometrial carcinoma[Title/Abstract])) OR (endometrium cancer[Title/Abstract])) OR (endometrium carcinoma[Title/Abstract]))

#2 (((((hysteroscopy[Title/Abstract]) OR (hysteroscopic surgery[Title/Abstract])) OR (uterine endoscopy[Title/Abstract])) OR (uteroscopy[Title/Abstract])) OR (diagnostic hysteroscopy[Title/Abstract])) OR (hysteroscopic surgical procedure[Title/Abstract])

#3 ("1900/01/01"[Date - Publication] : "2020/07/30"[Date - Publication])

#4 #1 and #2 and #3