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

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

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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 examining 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 trials 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

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

6 The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by
7 office endometrial biopsy, dilation and curettage, or diagnostic hysteroscopy and directed
8 endometrial biopsy. Hysteroscopy can provide gynecologist with visualization of the uterine cavity
9 and is considered to be the most helpful tool for the evaluation of the endometrium in the
10 presentation of abnormal uterine bleeding[6]. According to the study of Garuti, hysteroscopy has
11 high sensitivity, specificity, negative predictive value and positive predictive values of
12 94.2%, 88.8%, 96.3% and 83.1% respectively, in predicting abnormal or normal endometrial
13 histopathology[6]. Due to its accuracy, hysteroscopy with endometrial biopsy is highly
14 recommended as the gold standard investigation for abnormal uterine bleeding and this procedure
15 is taking the place of the traditional fractional dilation and curettage[7, 8].

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

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

33 **Population**

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

36 **Exposures**

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

39 **Comparison**

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

42 **Outcomes**

43 Recurrence-free survival, disease-specific survival and overall survival, defined as the period
44 from the date of the diagnosis to the date of recurrence or the last clinic visit (if alive) or the date of
45 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 participants, 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 participants, 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 trials, 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

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

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

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

18 19 **Ethics and dissemination**

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

24 25 **Patient and public involvement**

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

30 31 **Potential limitations**

32
33 There are a number of limitations predicted in this review. A degree of heterogeneity is
34 anticipated between studies. Differences in the length of follow-up and the study design are the main
35 reason for the heterogeneity, and differences in sampling frames are also likely to cause
36 heterogeneity. So, a random-effects model will be used for meta-analyses if there is moderate or high
37 heterogeneity among the included studies.

38
39 In all observational studies, the existence of selection bias and residual confounding is a
40 concern. Potential confounders may include age, race, socioeconomic status, degree of histological
41 differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-
42 aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy. Where possible, our
43 meta-analysis will show both crude and adjusted results, adjusted according to the definitions
44 outlined in each individual study. However, given that less adjusted effect estimates may distort the
45 overall results, a sensitivity analysis will be performed, where possible, to examine for more fully
46 adjusted effect estimates for confounders (ie, adjusted for, at a minimum, age, degree of histological
47 differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-
48 aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy).

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

53 54 **Discussion**

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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.

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Competing interests

None declared.

Patient consent for publication

Not required.

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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 examining 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 trials 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

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

6 The diagnosis of endometrial cancer is based on histologic results of endometrial sampling by
7 office endometrial biopsy, dilation and curettage, or diagnostic hysteroscopy and direct endometrial
8 biopsy. Hysteroscopy can provide gynecologist with visualization of the uterine cavity and is
9 considered to be the most helpful tool for the evaluation of the endometrium in the presentation of
10 abnormal uterine bleeding[6]. According to the study of Garuti, hysteroscopy has high sensitivity,
11 specificity, negative predictive value and positive predictive value of 94.2%, 88.8%, 96.3% and
12 83.1% respectively, in predicting abnormal or normal endometrial histopathology[7]. Due to its
13 accuracy, hysteroscopy with endometrial biopsy is highly recommended as the gold standard
14 investigation for abnormal uterine bleeding and this procedure is taking the place of the traditional
15 fractional dilation and curettage[8, 9].

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

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

33 **Population**

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

39 **Exposures**

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

42 **Comparison**

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

45 **Outcomes**

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3 Recurrence-free survival, disease-specific survival and overall survival, defined as the period
4 from the date of the diagnosis to the date of recurrence or the last clinic visit (if alive) or the date of
5 death.
6
7

8 **Review question**

9
10 Does hysteroscopy as a diagnostic procedure worsen the prognosis of cases with stage I
11 endometrial cancer?
12

13 **Methods and design**

14
15 This protocol was drafted using the Preferred Reporting Items for Systematic Reviews and
16 Meta-Analysis Protocols checklist[28]. The proposed systematic review and meta-analysis will be
17 conducted in accordance with the standard guideline of “Meta-analyses Of Observational Studies
18 in Epidemiology (MOOSE) guidelines[29]” and “Preferred Reporting Items for Systematic Reviews
19 and Meta-Analyses (PRISMA)[30]”.
20
21

22 **Search strategy**

23
24 The leading author (Xu Yu) and corresponding author (Zheng Ai) will search four electronic
25 bibliographic databases to identify qualifying studies published from database inception till July 30,
26 2020, including PubMed/Medline, EMBASE, Cochrane Library and Web of Science. Informed by
27 medical subject headings (MSH), the following keywords will be used to search the databases
28 mentioned: “endometrial neoplasm” , “cancer of the endometrium” , “carcinoma of the
29 endometrium” , “endometrial cancer” , “endometrial carcinoma” , “endometrium cancer” ,
30 “endometrium carcinoma” , “hysteroscopy” , “hysteroscopic surgery” , “uterine endoscopy” ,
31 “uteroscopy” , “diagnostic hysteroscopy” and “hysteroscopic surgical procedure” . The search terms
32 will be combined using Boolean Logic (AND, OR) where needed. We will restrict our search to
33 human studies and peer reviewed journal articles published in the English language. The precise
34 search strategies for one of the databases can be found in the supplementary file. In addition,
35 reference lists from the relevant reviews and retrieved papers will be manually searched for any
36 further potentially relevant studies. To ensure that the search is comprehensive, the search will be
37 re-checked by an epidemiologist (He YueDong).
38
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43 **Study selection**

44
45 Retrieved records from the databases will be entered into the Endnote reference manager
46 (version X9) in order to categorize, manage, remove duplicates, and record titles, abstracts, and full-
47 texts. Two independent review authors (Xu Yu and Zhang Qianwen) will screen all titles and
48 abstracts for potentially relevant studies. The full-texts of the relevant studies will then be retrieved
49 and screened for compliance with eligibility criteria by two reviewers (Xu Yu and Zhang Qianwen).
50 For unpublished studies and abstracts that full-texts are not available, we will contact the authors
51 by email to ask for the relevant data. If consensus on eligibility cannot be achieved, a third review
52 author (Qin ZhaoJuan) will be consulted. For any articles which do not meet the inclusion criteria,
53 the reasons for rejection will be noted. A MOOSE flow diagram documenting the process of study
54 selection will be completed.
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58 **Inclusion criteria**

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1. Case-control studies, cohort studies, or randomized controlled trials.
 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 participants, 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 participants, 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 trials, 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

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3 outcome data, selective reporting and other bias[32]. Possible sources of ‘other bias’ were
4 determined by consensus of the investigators.
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6 Where disagreement in quality appraisal arise, a third opinion from He YueDong will be
7 obtained.
8

9 **Data synthesis and assessment of heterogeneity**

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11 Separate meta-analyses will be undertaken for each of the outcomes if possible. Each meta-
12 analysis will be undertaken to calculate the pooled estimate of the relationship between the
13 diagnostic hysteroscopy and the outcomes. For example, for recurrence-free survival as one of the
14 outcomes of interest, a meta-analysis will be undertaken to investigate the association between the
15 recurrence-free survival and diagnostic hysteroscopy. We will stratify eligible studies into two
16 categories based on the study design: observational study and randomized controlled trial because
17 of the concern that there may be considerable heterogeneity between different types of studies. We
18 will perform subgroup analysis according to the type of studies and for all outcomes.
19

20
21 Both the crude and adjusted effect estimates will be displayed using the generic inverse
22 variance method. Adjustment will be based on the definition outlined in each of the individual
23 studies. Heterogeneity among the studies will be assessed by the χ^2 test and I^2 (<25% deemed low
24 heterogeneity, 25%–50% moderate, and >50% high) statistics. $P < 0.10$ or $I^2 > 50\%$ indicates that
25 heterogeneity existed among the studies, so a random-effects model (Mantel–Haenszel method)
26 will be used. If studies cannot be meaningfully combined in a meta-analysis, they will be presented
27 in tabular format.
28

29
30 Where ten or more studies are included in a meta-analysis, we will assess the publication bias.
31 The trim and fill method will be used to identify and correct for funnel plot asymmetry arising from
32 publication bias, if appropriate[33].
33

34 **Ethics and dissemination**

35
36 This systematic review and meta-analysis will be based on published data, and thus there is no
37 requirement for ethics approval. The results will be shared through publication in a peer reviewed
38 journal and through presentations at academic conferences.
39

40 **Patient and public involvement**

41
42 Patients were not involved in the design of this systematic review and meta-analysis. However,
43 the authors will communicate the study findings to patient and public groups with interest in this
44 area.
45

46 **Potential limitations**

47
48 There are a number of limitations we can predicted in this review. A degree of heterogeneity
49 is anticipated between studies. Differences in the length of follow-up and the study design are the
50 main reason for the heterogeneity, and differences in sampling frames are also likely to cause
51 heterogeneity. So, a random-effects model will be used for meta-analyses if there is moderate or
52 high heterogeneity among the included studies.
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54
55 In all observational studies, the existence of selection bias and residual confounding is a
56 concern. Potential confounders may include age, race, socioeconomic status, degree of histological
57 differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-
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3 aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy. Where possible,
4 our meta-analysis will show both crude and adjusted results, adjusted according to the definitions
5 outlined in each individual study. However, given that less adjusted effect estimates may distort the
6 overall results, a sensitivity analysis will be performed where possible, to examine for more fully
7 adjusted effect estimates for confounders (ie, adjusted for, at a minimum, age, degree of histological
8 differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-
9 aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy).

10
11
12 Due to limited resources, only studies which are published in the English language will be
13 included. Besides, considering that there are many challenges and difficulties to conduct
14 randomized control studies to investigate the oncological safety of hysteroscopy in the diagnosis of
15 stage I endometrial cancer in real clinical settings, the majority of included studies will be
16 observational studies, and this will compromise the results of our proposed study.
17
18

19 Discussion

20
21 There is a lack of consensus on whether diagnostic hysteroscopy deteriorates the prognosis of
22 the early stage endometrial cancer. This proposed systematic review and meta-analysis will
23 summarise the available evidence which has examined these associations, thus providing novel
24 information on the role of hysteroscopy in the evaluation of abnormal uterine bleeding and the
25 diagnosis of endometrial cancer.
26
27

28 Contributors

29
30 Xu Yu, Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai conceived and
31 designed the protocol, and Xu Yu drafted the protocol manuscript. Zhang QianWen developed the
32 search strategy, with input from Xu Yu, Du Yi and Qin ZhaoJuan. Xu Yu and Du Yi planned the
33 data extraction. Xu Yu and Du Yi planned the quality appraisal of all included studies. Xu Yu,
34 Zhang QianWen, Du Yi, Qin ZhaoJuan, He YueDong and Zheng Ai critically revised the manuscript
35 for methodological and intellectual content. All authors approved the final version.
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40
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43

44 Competing interests

45
46 None declared.
47

48 Patient consent for publication

49
50 Not required.
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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

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Primary Subject Heading:	Obstetrics and gynaecology
Secondary Subject Heading:	Obstetrics and gynaecology
Keywords:	Gynaecological oncology < GYNAECOLOGY, Minimally invasive surgery < GYNAECOLOGY, Gynaecological oncology < ONCOLOGY

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

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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 statistically 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 trials 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

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

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

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

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

40 Population

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

49 Exposures

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

54 Comparison

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

59 Outcomes

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

9
10 Does hysteroscopy as a diagnostic procedure worsen the prognosis of cases with stage I
11 endometrial cancer?
12

13 **Methods and design**

14
15 This protocol was drafted according to the Preferred Reporting Items for Systematic Reviews
16 and Meta-Analysis Protocols checklist[28]. The proposed systematic review and meta-analysis will
17 be conducted in accordance with the standard guideline of “Meta-analyses Of Observational Studies
18 in Epidemiology (MOOSE) guidelines[29]” and “Preferred Reporting Items for Systematic Reviews
19 and Meta-Analyses (PRISMA)[30]”.
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22 **Search strategy**

23
24 The leading author (Xu Yu) and corresponding author (Zheng Ai) will search four electronic
25 databases (PubMed/Medline, EMBASE, Cochrane Library and Web of Science) to identify
26 qualifying studies published from database inception till July 30, 2020. Informed by medical subject
27 headings (MSH), the following keywords will be used to search the databases mentioned:
28 “endometrial neoplasm” , “cancer of the endometrium” , “carcinoma of the endometrium” ,
29 “endometrial cancer” , “endometrial carcinoma” , “endometrium cancer” , “endometrium carcinoma”
30 , “hysteroscopy” , “hysteroscopic surgery” , “uterine endoscopy” , “uteroscopy” , “diagnostic
31 hysteroscopy” and “hysteroscopic surgical procedure” . The search terms will be combined using
32 Boolean Logic (AND, OR) where needed. We will restrict our search to human studies and peer
33 reviewed journal articles published in English. The precise search strategies for one of the databases
34 can be found in the supplementary material. In addition, reference lists of all included studies will
35 be manually searched for any further potentially relevant studies. To ensure that the search is
36 comprehensive, the search will be re-checked by an epidemiologist (He YueDong).
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42 **Study selection**

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

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

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3 outcome data, selective reporting and other bias[32]. Possible sources of 'other bias' were
4 determined by consensus of the investigators.
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6 Where disagreement in quality appraisal arise, a third opinion from He YueDong will be
7 obtained.
8

9 **Data synthesis and assessment of heterogeneity**

10
11 Separate meta-analysis will be undertaken for each of the outcomes if possible. Each meta-
12 analysis will be performed to calculate the pooled estimate of the relationship between the
13 diagnostic hysteroscopy and the outcomes. For example, for recurrence-free survival as one of the
14 outcomes of interest, a meta-analysis will be undertaken to investigate the association between the
15 recurrence-free survival and diagnostic hysteroscopy. We will stratify eligible studies into two
16 categories based on the study design: observational study and randomized controlled trial because
17 of the concern that there may be considerable heterogeneity between different types of study. We
18 will perform subgroup analysis according to the type of study and for all outcomes.
19

20
21 Both the crude and adjusted effect estimates will be displayed using the generic inverse
22 variance method. Adjustment will be based on the definition outlined in each of the eligible studies.
23 Heterogeneity among the studies will be assessed by the χ^2 test and I^2 (<25% deemed low
24 heterogeneity, 25%–50% moderate, and >50% high) statistics. $P < 0.10$ or $I^2 > 50\%$ indicates that
25 heterogeneity existed among the studies, so a random-effects model (Mantel–Haenszel method)
26 will be used. If studies cannot be meaningfully combined in a meta-analysis, they will be presented
27 in tabular format.
28

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

34 **Ethics and dissemination**

35
36 Our study will be based on published data, and thus there is no requirement for ethics approval.
37 The results will be shared through publication in a peer reviewed journal and presentations at
38 academic conferences.
39

40 **Patient and public involvement**

41
42 Patients were not involved in the design of this study. However, the authors will communicate
43 the study findings to patient and public groups with interest in this area.
44

45 **Potential limitations**

46
47 There are a number of limitations we can predict in this review. A degree of heterogeneity is
48 anticipated between studies. Differences in the length of follow-up and the study design are the main
49 source for the heterogeneity, and differences in sampling frames are also likely to cause
50 heterogeneity. So, a random-effects model will be used for meta-analyses if there is moderate or
51 high heterogeneity among the included studies.
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54 In all observational studies, the existence of selection bias and residual confounding is a
55 concern. Potential confounders may include age, race, socioeconomic status, degree of histological
56 differentiation, histologic type, lymphovascular space invasion, pelvic lymph node dissection, para-
57 aortic lymph node dissection, adjuvant chemotherapy and adjuvant radiotherapy. Where possible,
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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.

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Competing interests

None declared.

Patient consent for publication

Not required.

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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