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Chinese Herbal Medicine for induced abortion in early pregnancy (before 14 weeks' gestation) (Protocol)

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[Intervention Protocol]

Chinese Herbal Medicine for induced abortion in early pregnancy (before 14 weeks' gestation)

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To evaluate the efficacy and safety of Chinese herbal medicine for induced abortion in early pregnancy (before 14 weeks' gestation).

BACKGROUND

Description of the condition

Induced abortion is the interruption of a pregnancy in early gestation. Using 1990 to 2019 data, the worldwide incidence of induced abortion is estimated to be about 3.9% (Bearak 2020), although the prevalence is not precise.

Using 1990 to 2019 data, 73.3 million induced abortions are performed globally, of which about 82% are from low- and middle-income countries (Bearak 2020). In more recent years, due to the advancement of antenatal diagnosis for early detection of aneuploidy pregnancies or abnormal foetuses and the popularisation of abortion medication use, induced abortion has been carried out mostly in early pregnancy rather than late pregnancy (Henkel 2021). In addition, women in early gestational age (a measure of the age of pregnancy) take fewer risks of induced abortion. Using 2009 to 2010 data, the incidence of major complications such as haemorrhage, infection and uterine perforation was 1.3% in first-trimester aspiration abortion (Upadhyay 2015). Spontaneous abortion, also referred to miscarriage, in early pregnancy seldom causes long-term risk of infertility, ectopic pregnancy, subsequent spontaneous abortion and breast cancer (Biggs 2016).

Induced abortion can be achieved by either drugs or surgery (Ajmal 2020). The common medications for drug-induced abortion include mifepristone and misoprostol. Drugs are simpler and required fewer resources than surgical abortion and provide women with a choice of intervention (Oppegaard 2015). These methods are very effective, but drawbacks include uncertainty of duration and completeness of the abortion. Surgical induced abortion includes negative pressure uterine suction or vacuum aspiration, and manual dilation and forceps curettage, which is of short duration, and completion can be assessed at the point of care. However, women prefer to terminate pregnancy quickly and would like few visits to clinical if possible (Kopp Kallner 2010). Therefore, it is vital to provide a method that is both effective and convenient for induced abortion.

Description of the intervention

Chinese herbal medicine (CHM) has been widely used for induced abortion in China and some Asian countries since the 16th century (Cheng 2006). Most CHM is purely of herbal origin, such as plants, parts of plants and products made of plants (Commission CP 2020); however, some CHM also includes substances from animal and mineral origins (Li 2012). Some CHMs have been claimed to induce abortion with high therapeutic effects and minimal adverse outcomes and effects (He 2010). *Flos Genkwa* (lilac daphne flower bud, YuanHua) is a common traditional Chinese medicine (TCM) used to induce abortion. Yuanhua diterpene, the active ingredient of *Flos Genkwa*, in doses ranging from 60 µg to 80 µg is administered into the amniotic cavity or extramurally to achieve medication abortion (Chi 2016).

How the intervention might work

According to the records in the ancient book "Compendium of Materia Medica", *Radix Trichosanthis* (Snakegourd Root, TianHuaFen) can be used to induce abortion, and its efficacy and mechanism have been studied on mice and women (SIBS 1976). In addition, 31 CHMs contraindicated for wanted pregnancy could also be used to induce abortion, such as *Andrographis Paniculata* (Common Andrographis Herb, ChuanXinLian), *Radix Lithospermi* (Arnebia Root, ZiCao), etc. (Cheng 2006). Studies had been conducted to determine the pharmacology of herbal medicines. For example, *trichosanthin* (TCS), of which the main component of *Radix Trichosanthis*, has obvious therapeutic effects on inducing abortion (Xia 2000); *Radix Lithospermi* (Arnebia Root, ZiCao) could terminate a pregnancy and assist induced abortion by destroying the growth of embryonic villi, reducing human chorionic gonadotropin (hCG) production and interrupting the corpus luteum (Ren 2011).

Why it is important to do this review

Induced abortion can be performed surgically or medically, and requires safe, effective options. As an alternative and complementary medicine, the evidence of effectiveness and safety of CHMs for induced abortion in high-quality systematic reviews are lacking. In this review, we aim to provide background information, and clarify the clinical evidence of CHM as a treatment for induced abortion.

OBJECTIVES

To evaluate the efficacy and safety of Chinese herbal medicine for induced abortion in early pregnancy (before 14 weeks' gestation).

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised clinical trials (RCT) including those randomised at the individual or cluster level. We will include trials reported in abstract format if the data are sufficient for analysis. We will exclude cross-over trials because this is not feasible or ethical for studies of the intervention evaluated in this review. We will also exclude observational, cohort, case report, case-control and case series studies.

We will include studies irrespective of their publication status and language of publication.

Types of participants

Women seeking induced abortion, who have an ultrasound documented intrauterine pregnancy of less than 14 weeks' gestation.

We will exclude women presenting for follow-up care related to incomplete abortion when testing efficacy. No other treatments given before the trial interventions will be permitted. We will exclude women with gestational trophoblastic disease and other gynaecological disorders, and with pregnancies at or after 14 weeks' gestation.

Types of interventions

All types of CHMs (such as decoctions, tablets, powders, capsules and herbal plasters). There will be no restrictions on the formula, dose, frequency, duration of administration and TCM syndrome (the clinical symptom of people diagnosed by TCM principle, such as observation, listening, interrogation, and pulse examination). We will exclude formulae with individual herbs that have been identified as teratogens.

The comparisons for this review will be:

- CHMs combined with western medicine compared with placebo/sham control/no treatment;
- CHMs combined with western medicine compared with other pharmaceuticals alone (mostly western medicines);
- CHMs combined with western medicine compared with surgery alone;
- CHMs combined with western medicine compared with other pharmaceuticals combined with surgery.

Types of outcome measures

Primary outcomes

- Complete abortion rate (defined as complete abortion without surgical intervention within 30 days of taking the medication).
  - Complete abortion rate = complete abortion cases/ incomplete abortion cases × 100%.
- Pain (measured by visual analogue scale (VAS) or usage of analgesics).
- Participant satisfaction (measured by satisfaction rating scale during follow-up).

Secondary outcomes

- Haemorrhage:
  - total blood loss (vaginal bleeding volume measured by trial authors or decreased haemoglobin level measured by blood test);
  - duration of vaginal bleeding;
  - requirement for blood transfusion.
- Incidence of extra-surgical abortion (such as uterine aspiration and curettage) due to incomplete medical abortion.
- Incidence of severe adverse effects which are severely debilitating or life-threatening (ICH S5(R3) Guideline 2020), such as death, infection, uterine rupture, etc.
- Time to complete abortion. The investigator determines that abortion is complete when the participant excretes the gestational sac. (Cunningham 2014).

Search methods for identification of studies

The Fertility Regulation Group Information Specialist will conduct the non-Chinese language searches for all published, unpublished and ongoing studies, with no restrictions on language or publication status. A librarian on the review author team (AZ) will conduct Chinese language searches.

We will model the search strategies for non-Chinese language databases on the search strategy designed for PubMed and MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily) in Appendix 1. The search strategies for Chinese language databases will be modelled on the search strategy (China Journal Net (CJN, China Journals Full-text Database), WanFang Database (Chinese Ministry of Science & Technology) and VIP Database) in Appendix 2.

Electronic searches

We will search the following databases from their inception to date of search:

- EBM Reviews Ovid – Cochrane Central Register of Controlled Trials (CENTRAL; year and issue);
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily; from 1946);
- Embase.com (from 1974);
- CINAHL (EBSCOHost; from 1982);
- LILACs (lilacs.bvsalud.org/en/);
- Global Health Ovid (from 1973);
- Scopus (conference abstracts only) (from 2004).

We will search the following trials registries:

- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- ClinicalTrials.gov (www.clinicaltrials.gov).

We will search the following grey literature sites:

- Guttmacher Institute (www.guttmacher.org/united-states/abortion);
- International Planned Parenthood Federation (www.ippf.org/);
- Ibis Reproductive Health (ibisreproductivehealth.org/);
- Women on Waves (www.womenonwaves.org/);
- Marie Stopes International (www.mariestopes.org/);
- Population Council (www.popcouncil.org/);
- Population Services International (www.psi.org/);
- Ipas (www.ipas.org/).

Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews for further studies. We will contact experts/organisations in the field to obtain additional information on relevant studies. If necessary, we will contact authors of included studies for data clarification and further information. We will consider adverse effects described in included studies only.

Data collection and analysis

Selection of studies

We will download all titles and abstracts retrieved by electronic searching to a reference management database and remove duplicates. Two review authors (AZ, YS) will independently screen titles and abstracts for inclusion. We will retrieve the full-text study reports/publications and two review authors (AZ, LL) will independently screen the full-text and identify studies for inclusion and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreements through discussion or, if required, consult a third review author (CC). We will list studies that initially appeared to meet the inclusion criteria but that we later excluded in the 'Characteristics of excluded studies' table. We will collate multiple reports of the same study, so that each study rather than each report is the unit of interest in the review. We will provide any information we obtain about ongoing studies in the 'Characteristics of ongoing studies' table. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Liberati 2009).

Data extraction and management

We will use a standard data collection form for study characteristics and outcome data; we will pilot the form on at least one study in the review. Two review authors (LL, AZ) will independently extract the following characteristics from the included studies.

- Methods: study design, number of study centres and location, study setting, withdrawals, date of study, follow-up, approach to adjustment for design effects or confounding.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, inclusion criteria, exclusion criteria, other relevant characteristics.
- Interventions: intervention components, comparison, fidelity assessment.
- Outcomes: events, means, relative effects, time points reported, adjusted effect estimates and information about the confounders and design effects accounted for.
- Notes: funding for trial, notable conflicts of interest of trial authors, ethical approval.

Two review authors (AZ, LL) will independently extract outcome data from included studies. We will note in the 'Characteristics of included studies' table if outcome data were reported in an unusable way. We will resolve disagreements by consensus or by involving a third review author (XF).

We will not translate Chinese language publications into English; instead, two review authors with good command of both Chinese and English will independently extract data and information. All results will be reported in English.

Assessment of risk of bias in included studies

Three review authors (LL, AZ, XL) will independently assess risk of bias for each study. We will resolve any disagreements by discussion or by involving another review author (XF).

We will assess the risk of bias in randomised trials using the Cochrane RoB 2 tool for the following domains (Higgins 2020a).

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

We will judge each potential source of bias as high, low or unclear and provide a quote from the study report with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from a participant-reported pain scale).

Measures of treatment effect

We will report the effects of interventions for dichotomous outcomes as risk ratios (RR) with 95% confidence intervals (CI) and for continuous data as mean difference (MD) or standardised mean difference (SMD) with 95% CIs. Outcomes adjusted for confounders or design effects will be reported and, where possible, used for meta-analysis.

We will use SMDs when studies use different scales to measure the same outcomes, necessitating the standardisation of the results of the studies to a uniform scale before they can be combined. We will present data ensuring consistency in the direction of effects. The SMD expresses the size of the intervention effect in each study relative to the variability observed in that study, thus studies for which the difference in means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to make the measurements. To interpret the SMD, we will use the Cohen's effect size rubric where 0.2 represents a small effect, 0.5 a moderate effect and 0.8 a large effect (Cohen 1988). If possible, we will express the study SMDs using a recognisable and standard metric used by some included studies or employ other strategies to aid interpretability outlined in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

For studies reporting results that are not provided in a format that can be directly entered into meta-analysis, we will use guidance provided in the *Cochrane Handbook for Systematic Reviews of Interventions* to convert the data to the necessary format (Higgins 2020b).

Unit of analysis issues

We will perform the primary analysis per participant randomised. We will abstract information on the study design and unit of analysis for each study, indicating whether clustering of observations is present due to allocation to the intervention at the group level or clustering of individually randomised observations (e.g. women within clinics). Available statistical information needed to account for the implications of clustering on the estimation of outcome variances will be abstracted, such as design effects or intracluster correlations (ICC), and whether the study adjusted results for the correlations in the data. In cases where the study does not account for clustering, we will ensure that appropriate adjustments are made to the effective sample size following guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b). Where possible, we will derive the ICC for these adjustments from the trial itself, or from a similar trial. If an appropriate ICC is unavailable, we will conduct sensitivity analyses to investigate the potential effect of clustering by imputing a range of values of ICC.

If any trials have multiple arms that are compared against the same control condition that will be included in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or select one pair of interventions and exclude the others. We will list any interventions that are not relevant to the review in the 'Characteristics of included studies' table.

Dealing with missing data

We will contact investigators or study sponsors to verify key study characteristics and obtain missing numerical outcome data for those studies identified as abstract only.

We will calculate missing standard deviations or other necessary data using other data from the trial, such as CIs, based on methods outlined in *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020b).

We will examine the possibility of selective non-reporting or under-reporting by noting the number of included studies that did not report key outcomes and therefore could not be included in our synthesis for key outcomes.

We will report all responses and data provided by investigators or study sponsors in the 'Characteristics of included studies' table. Where we make any assumptions about missing data, we will report the potential impact in the 'Discussion' of the review.

Assessment of heterogeneity

We will describe the clinical diversity and methodological variability of the evidence in the review text and the 'Characteristics of included studies' table, including design features, population characteristics and intervention details.

To assess statistical heterogeneity, we will visually inspect forest plots and describe the direction and magnitude of effects and the degree of overlap of CIs. We will also consider the statistics generated in forest plots that measure statistical heterogeneity. We will use the I^2 statistic to quantify inconsistency among the trials in each analysis. We will also consider the P value from the Chi^2 test to assess if this heterogeneity is significant ($P < 0.1$). If we identify substantial heterogeneity, we will report the finding and explore possible explanatory factors using prespecified subgroup analysis.

We will use an approximate guideline to interpret the I^2 value rather than a simple threshold, and our interpretation will take into account an understanding that measures of heterogeneity (I^2 statistic and Tau) are estimated with high uncertainty when the number of studies is small (Deeks 2020):

- 0% to 40%: heterogeneity might not be important;
- 30% to 60%: may represent moderate heterogeneity*;
- 50% to 90%: may represent substantial heterogeneity*;
- 75% to 100%: considerable heterogeneity*.

*The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects, and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or a CI for the I^2 statistic: uncertainty in the value of the I^2 statistic is substantial when the number of studies is small).

Assessment of reporting biases

If we have enough studies available for meta-analysis to support a funnel plot (at least 10), we will create and visually inspect the funnel plot and run a formal statistical test for asymmetry, as proposed by Egger 1997. We plan to provide a funnel plot for the complete evacuation rate, data permitting. For reviews with fewer studies eligible for meta-analysis, the ability to detect publication bias will be largely diminished, and we will note the difficulty excluding the presence of publication bias. In the event that there is funnel plot asymmetry in the evidence, we will discuss the potential for this to be attributed to small-study effects and not just non-reporting bias.

Data synthesis

We will undertake meta-analyses to estimate pooled effects when adequate comparable data are reported that can support statistical pooling.

When skewed data are suspected based on the reporting of median and interquartile ranges, we will note the skewness and discuss the implication, but will not pool medians with means. For outcomes that cannot be statistically pooled, we will present descriptive forest plots showing the individual study results to illustrate the range of effects reported.

We will base the meta-analysis approach taken on an evaluation of the clinical and methodological diversity of the included studies, as well as the statistical heterogeneity. We will generate pooled analyses of outcomes with sufficient data using the Dersimonian and Laird random-effects technique. We will consider a fixed-effect estimate using the Mantel-Haenszel approach if the included studies can be assumed to estimate the same intervention effect, if the intervention effects are relatively consistent in direction and magnitude, and heterogeneity is low. We will also consider the Mantel-Haenszel approach if there is evidence of potential variation in outcome effects by study size (i.e. small-study effects). For rare outcomes or trials with zero-count events, we will consider analyses using the Peto odds ratios and other analytic approaches for the main analysis or to evaluate the stability of results in sensitivity analyses.

We will illustrate meta-analyses using forest plots displaying effect estimates and 95% CIs for both individual study effects and pooled effects.

If it is not possible to quantitatively summarise the study data, we will follow guidance available for synthesis without meta-analysis outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (McKenzie 2020). Our synthesis will avoid enumerating the statistical significance of effects of individual studies or focus only on individual studies that report statistically significant findings.

Subgroup analysis and investigation of heterogeneity

We will interpret tests for subgroup differences in effects with caution given the potential for confounding with other study characteristics and the observational nature of the comparisons. In particular, subgroup analyses with fewer than five studies per category are likely to be inadequate to ascertain valid differences in effects and will not be highlighted in our results. Subgroup comparisons will not be undertaken when there are fewer than 10 studies available for meta-analysis. When subgroup comparisons are possible, we will conduct a stratified meta-analysis and a formal statistical test for interaction to examine subgroup differences that could account for effect heterogeneity (e.g. Cochran's Q test, meta-regression) (Borenstein 2013; Higgins 2020b).

Given the potential differences in the intervention effectiveness related to pregnancy stage, duration of menolipsis, parity, routes of interventions and differences in CHM formulae discussed in the Background section, we will conduct subgroup comparisons to see if the intervention is more effective for induced abortion.

We will conduct the following subgroup analyses of factors that may contribute to heterogeneity in the effects of the intervention:

- before seven weeks' gestation versus after seven weeks' gestation;
- duration of menolipsis (the absence of a menstrual period in a woman of reproductive age);

- parity;
- standard or non-standard CHM formula.

We will use the following outcomes in subgroup analyses if there are enough studies reporting to support valid subgroup comparisons:

- complete abortion rate;
- pain (by VAS or usage of analgesics);
- participant satisfaction.

Sensitivity analysis

Given that there is no formal statistical test that can be used for sensitivity analysis, we will provide informal comparisons between the different ways of estimating the effect under different assumptions. Changes in the P values should not be used to judge whether there is a difference between the main analysis and sensitivity analysis, since statistical significance may be lost with fewer studies included.

We will report sensitivity analysis results in tables rather than forest plots.

We will use the following outcomes in sensitivity analysis:

- complete abortion rate;
- pain (by VAS or usage of analgesics);
- participant satisfaction.

Summary of findings and assessment of the certainty of the evidence

We will evaluate the evidence on the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the certainty of the body of evidence as it relates to the studies that contribute data to the meta-analyses for the prespecified outcomes.

We will follow the methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2020) and use GRADEpro software (GRADEpro GDT).

We will provide a separate summary of findings table for each of the following comparisons to be evaluated in this review:

- CHMs combined with western medicine compared with placebo/sham control/no treatment;
- CHMs combined with western medicine compared with other pharmaceuticals alone (mostly western medicines);
- CHMs combined with western medicine compared with surgery alone;
- CHMs combined with western medicine compared with other pharmaceuticals combined with surgery.

We will include the following outcomes in the summary of findings tables.

- Complete abortion rate.
- Haemorrhage.
- Incidence of extrauterine aspiration due to incomplete medical abortion.
- Incidence of severe adverse effects.

We will justify decisions to downgrade the certainty of studies using footnotes and provide comments to aid reader's understanding of the review where necessary.

Two review authors (LL and XL) will independently judge the certainty of the evidence, with disagreements resolved by discussion or involving a third review author (XF). We will justify, document and incorporate judgements into reporting of results for each outcome.

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APPENDICES

Appendix 1. Model search strategy (non-Chinese language)

PubMed Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

1 (Abortion, Induced) OR (Abortion, Eugenic) OR (Abortion, Legal) OR (Abortion, Therapeutic) OR (“Dilatation and Curettage”) OR (Vacuum Curettage) (55575)
2 (abortion* or pre-abort* or preabort* or post-abort* or postabort* or "D&C" or "D & C" or "D/C" or ((interrupt* or terminat*) AND(gestation or pregnan*)) OR ((dilation or dilatation or electric or gestation or manual or pregnan* or sharp or suction or surgical or uterine or uterus or vacuum) AND (aspiration* or curettage or evacuation* or terminat*))) (231725)

3 (Abortifacient Agents) OR (Abortifacient Agents, Nonsteroidal) OR (Abortifacient Agents, Steroidal) (63182)

4 (((mifepristone or misoprostol or methotrexate or dinoprost* or carboprost or sulprostone or gemeprost or meteneprost or lilopristone or onapristone or epostane or oxytocin) AND (abortion* or interrupt* or terminat*)) or abortifacient* or Abo-pill or Colestone or Cytotec or Elmif or GyMiso or Korlym or Medabon or Mefeprin or Mefipil or Mifebort or Mifegest or Mifeprex or Miferiv or Mifty or Mtpill or Pitocin or RU-486 or RU486 or Syntocinon or T-Pill or Termipil) (94573)
5 or/1-4 (319570)

6 Pregnancy Trimester, First (38154)

7 ("1st trimester" or "first trimester" or ((early) AND (abortion* or pregnan*)) or (("9" or nine or "10" or ten or "11" or eleven or "12" or twelve or "13" or thirteen or "14" or fourteen) AND (weeks))) (764699)
8 or/6-7 (771988)
9 (Drugs, Chinese Herbal) OR (Medicine, Chinese Traditional) (122616)
10 ((Chinese) AND (botanical* or decoction* or extract* or formula or herb* or medic* or pill or pills or plant* or powder or powders or capsule or capsules or phytomedicine* or phyto- medicine* or plaster or plasters or soup or soups or tablet* or teas or tincture* or tradition*)) (556761)
11 ("Largehead Atractylodes" or "Chinese Dodder" or "Himalayan Teasel" or "Donkey-hide" or "Chinese Taxillus" or "Liquorice" or "Mongolian Milkcetch" or "White Paeony" or "white peony" or "Chinese Angelica" or "Baical Skullcap" or "Eucommia" or "Steamed Rehmannia" or "Pilose Asiabell" or "Szechwon Tangshen" or "Common Yam" or "Wingde Yan" or "Villous Amomrum" or "Rehmannia" or "Szechuan Lovage" or "Chinese Mugwort" or "Motherwort" or "Tangerine" or "Danshen" or "Heterophylly Falsestarwort" or "St.John's wort" or "Perilla" or "Ramie" or "Gin Seng" or "Ginseng" or "Indian Buead" or "Largetrifoliolious Bugbane" or "Chinese Thorowax" or "Red Peony" or "red paeony" or "Glossy Privet" or "Hairyvein Agrimonia" or "Bamboo" or "Common Macrocarpium" or "Cattail" or "Glutinous Rice" or "Turmeric Root" or "Malaytea Scurfpea" or "Hiraute Shiny Bugleweed" or "Barbary Wolfberry" or "Nutgrass Galingale"

or "Suberect Spatholobus" or "India Madder" or "Cassia" or "Deerhorn" or "Spina Date" or "Yan Hu Suo" or "Fennel" or "Indian mulberry" or "Garden Burnet" or "Dwarf Lilyturf" or "Fineleaf Schizonepeta" or "Cape Jasmine" or "Citron Fruit" or "Sharpleaf Galangal" or "Trogopterus Dung" or "Szechwan Chinaberry" or "Chinese Magnoliavine" or "Pinellia" or "Round Cardamom" or "Java Amomum" or "Oyster Shell" or "Tuber Fleeceflower" or "Peach" or "Cuttlefish" or "Amur Corktree" or "Epimedium" or "Tree Peony" or "tree paeony" or "San Chi" or "Desertliving Cistanche" or "Fortune Windmillpalm" or "Costustoot" or "Dark Plum" or "Wrinkled Gianthyssop" or "Safflower" or "Incised Notopterygium" or "Forbes Notopterygium" or "Common Anemarrhena" or "East Asian Tree Fern" or "Lotus" or "Yerbadetajo" or "Dragon's Bones" or "Indian Bread" or "Tuckahoe" or "Capillary Wormwood" or "Dried Ginger" or "Chinese Hawthorn" or "Indigowoad" or "Chinese Date" or "Grassleaf Sweelflag" or "Dried Longan" or "Figwort" or "Chinese Wolfberry" or "Silktree Albizzia" or "Malt" or "Thinleaf Milkwort" or "Swordlike Atractylodes Rhizome" or "Chinese Atractylodes" or "Gordon Enryale Seed" or "Reed Rhizome" or "Japanese Honeysuckle" or "Loquat" or "Chinese Arborvitae" or "Honeysuckle" or "Heartleaf Houttuynia" or "Oriental Waterplantain" or "Nacre" or "Bittet Orange" or "Officinal Magnolia" or "Gambir" or "Mantis Egg-case" or "Manyflower Solomonseal Rhizome / Siberian Solomonseal Rhizome / King Solomonseal" or "Cyrtomium Rhizome" or "Perilla Leaf" or "Redroot Gromwell" or "Mongolian Dandelion" or "Tree-of-heaven Ailanthus" or "Palmleaf Raspberry" or "Coastal Glehnia" or Ladybell or "Dahurian Patrinia" or "Whiteflower Patrinia" or "India Madder" or Hemp or "Whiteflower Cacalia" or "Finger Citron" or Dendrobium or "Human Placenta" or "Cherokee Rose" or Platycladi or "Hyacinth Bletilla" or Mulberry) (1875589)
12 ("Atractylodis Macrocephalae" or "Semen Cuscutae" or "Dipsaci" or "Colla Corii Asini" or "Taxilli" or "Glycyrrhizae" or "Astragali" or "Paeoniae Alba" or "Angelicae Sinensis" or "Scutellariae" or "Cortex Eucommiae" or "Rehmanniae" or "Codonopsis" or "Diosscoreae" or "Amomi" or "Rehmanniae" or "Chuanxiong" or "Folium Artemisiae Argyi" or "Leonuri" or "Pericarpium Citri Reticulatae" or "Miltiorrhizae" or "Pseudostellariae" or "Ecliptae Eclipta prostrala" or "Caulis Perillae" or "Boehmeriae" or "Ginseng" or "Poria" or "Cimicifugae" or "Bupleuri" or "Paeoniae Rubra" or "Ligustri Lucidi" or "Agrimoniae" or "Caulis Bambusae in Taenia" or "Corni" or "Pollen Typhae" or "Semen Oryzae Glutinosae" or "Curcumae" or "Psoraleae" or "Lycopi" or "Lycii" or "Cyperi" or "Caulis Spatholobi" or "Et Rubiae" or "Ramulus Cinnamomi" or "Colla Cornu Cervi" or "Cornu Cervi Degelatinatum" or "Semen Ziziphi Spinosae" or "Corydalis" or "Foeniculi" or "Morindae Officinalis" or "Sanguisorbae" or "Ophiopogonis" or "Schizonepetae" or "Gardeniae" or "Citri" or "Receptaculum Nelumbinis" or "Alpiniae Oxyphyllae" or "Faeces Trogopterori" or "Toosendan" or "Schisandrae Chinensis" or "Pinelliae" or "Amomi Rotundus" or "Concha Ostreae" or "Polygoni Multiflori" or "Semen Persicae" or "Endoconcha Sepiae" or "Cortex Phellodendri Chinensis" or "Epimedii" or "Nodus Nelumbinis Rhizomatis" or "Moutan Cortex" or "Et Notoginseng" or "Cistanches" or "Petiolus Trachycarpi" or "Aucklandiae" or "Mume" or "Herha Agastaches" or "Flos Carthami" or "Cortex Moutan" or "Et Notopterygii" or "Anemarrhenae" or "Cibotii" or "Semen Nelumbinis" or "Ecliptae" or "Os Draconis" or "Poriacocos Wolf" or "Artemisiae Scopariae" or "Zingiberis" or "Crataegi" or "Folium Isatidis" or "Jujubae" or "Acori Tatarinowii" or "Arillus Longan" or "Scrophulariae" or "Cortex Lycii" or "Cortex Albiziae" or "Gordei Germinatus" or "Polygalae" or "Atractylodis" or "Semen Euryales" or "Phragmitis" or "Caulis Lonicerae Japonicae" or "Folium Eriobotryae" or "Cacumen Platycladi" or "Flos Lonicerae Japonicae" or "Houttuyniae" or "Alismatis" or "Concha Margaritifera" or "Aurantii" or "Cortex Magnoliae Officinalis" or "Ramulus Uncariae Cum Uncis" or "Folium Mori" or "Ootheca Mantidis" or "Polygonati" or "Cyrtomii" or "Folium Perillae" or "Arnebiae" or "Taraxaci" or "Cortex Ailanthi" or "Rubi" or "Glehniae" or "Adenophorae" or "Patriniae" or "Rubiac Cordifoliae" or "Cannabis" or "Semen Caesalpiniae Minacis" or "Citri Sarcodactylis" or "Dendrobii Nobilis" or "Placenta Hominis" or "Rosae Laevigatae" or "Semen Platycladi" or "Platantherae Chloranthae" or "Mori") (148,949)
13 or/9-12 (557953)
14 and/5,8,13 (887)
15 (randomized controlled trial) OR (controlled clinical trial) (816031)
16 (random* or trial) OR (groups or placebo) (6265875)
17 or/15-16 (6265875)
18 17 NOT ((exp Animals/ not Humans/) or (mice or mouse or murine or rat or rats)) (5632251)

19 and/14,18 (418)

MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily

1 Abortion, Induced/ or Abortion, Eugenic/ or Abortion, Legal/ or Abortion, Therapeutic/ or "Dilatation and Curettage"/ or Vacuum Curettage/ (57059)
2 (abortion* or pre-abort* or preabort* or post-abort* or postabort* or "D&C" or "D & C" or "D/C" or ((interrupt* or terminat*) adj2 (gestation or pregnan*)) or ((dilation or dilatation or electric or gestation or manual or pregnan* or sharp or suction or surgical or uterine or uterus or vacuum) adj3 (aspiration* or curettage or evacuation* or terminat*))).ti,ab,kf. (162606)
3 Abortifacient Agents/ or Abortifacient Agents, Nonsteroidal/ or Abortifacient Agents, Steroidal/ (5320)
4 (((mifepristone or misoprostol or methotrexate or dinoprost* or carboprost or sulprostone or gemeprost or meteneprost or lilopristone or onapristone or epostane or oxytocin) adj10 (abortion* or interrupt* or terminat*)) or abortifacient* or Abo-pill or Colestone or Cytotec or Elmif or GyMiso or Korlym or Medabon or Mefeprin or Mefipil or Mifebort or Mifegest or Mifeprex or Miferiv or Mifty or Mtpill or Pitocin or RU-486 or RU486 or Syntocinon or T-Pill or Termipil) (13003)
5 or/1-4 (168770)
6 Pregnancy Trimester, First (38812)
7 ("1st trimester" or "first trimester" or (early AND (abortion* or pregnan*)) or (("9" or nine or "10" or ten or "11" or eleven or "12" or twelve or "13" or thirteen or "14" or fourteen) AND weeks)) (820325)
8 or/6-7 (827911)
9 Drugs, Chinese Herbal/ or Medicine, Chinese Traditional (75122)

10 (Chinese AND (botanical* or decoction* or extract* or formula or herb* or medic* or pill or pills or plant* or powder or powders or capsule or capsules or phytomedicine* or phyto- medicine* or plaster or plasters or soup or soups or tablet* or teas or tincture* or tradition*)) (66967)
11 ("Largehead Atractylodes" or "Chinese Dodder" or "Himalayan Teasel" or "Donkey-hide" or "Chinese Taxillus" or "Liquorice" or "Mongolian Milkcetch" or "White Paeony" or "white peony" or "Chinese Angelica" or "Baical Skullcap" or "Eucommia" or "Steamed Rehmannia" or "Pilose Asiabell" or "Szechwon Tangshen" or "Common Yam" or "Wingde Yan" or "Villous Amomrum" or "Rehmannia" or "Szechuan Lovage" or "Chinese Mugwort" or "Motherwort" or "Tangerine" or "Danshen" or "Heterophylly Falsestarwort" or "St.John's wort" or "Perilla" or "Ramie" or "Gin Seng" or "Ginseng" or "Indian Buead" or "Largetrifoliolious Bugbane" or "Chinese Thorowax" or "Red Peony" or "red paeony" or "Glossy Privet" or "Hairyvein Agrimonia" or "Bamboo" or "Common Macrocarpium" or "Cattail" or "Glutinous Rice" or "Turmeric Root" or "Malaytea Scurfpea" or "Hiraute Shiny Bugleweed" or "Barbary Wolfberry" or "Nutgrass Galingale" or "Suberect Spatholobus" or "India Madder" or "Cassia" or "Deerhorn" or "Spina Date" or "Yan Hu Suo" or "Fennel" or "Indian mulberry" or "Garden Burnet" or "Dwarf Lilyturf" or "Fineleaf Schizonepeta" or "Cape Jasmine" or "Citron Fruit" or "Sharpleaf Galangal" or "Trogopterus Dung" or "Szechwan Chinaberry" or "Chinese Magnoliavine" or "Pinellia" or "Round Cardamom" or "Java Amomum" or "Oyster Shell" or "Tuber Fleeceflower" or "Peach" or "Cuttlefish" or "Amur Corktree" or "Epimedium" or "Tree Peony" or "tree paeony" or "San Chi" or "Desertliving Cistanche" or "Fortune Windmillpalm" or "Costustoot" or "Dark Plum" or "Wrinkled Gianthyssop" or "Safflower" or "Incised Notopterygium" or "Forbes Notopterygium" or "Common Anemarrhena" or "East Asian Tree Fern" or "Lotus" or "Yerbadetajo" or "Dragon's Bones" or "Indian Bread" or "Tuckahoe" or "Capillary Wormwood" or "Dried Ginger" or "Chinese Hawthorn" or "Indigowoad" or "Chinese Date" or "Grassleaf Sweelflag" or "Dried Longan" or "Figwort" or "Chinese Wolfberry" or "Silktree Albizzia" or "Malt" or "Thinleaf Milkwort" or "Swordlike Atractylodes Rhizome" or "Chinese Atractylodes" or "Gordon Enryale Seed" or "Reed Rhizome" or "Japanese Honeysuckle" or "Loquat" or "Chinese Arborvitae" or "Honeysuckle" or "Heartleaf Houttuynia" or "Oriental Waterplantain" or "Nacre" or "Bittet Orange" or "Officinal Magnolia" or "Gambir" or "Mantis Egg-case" or "Manyflower Solomonseal Rhizome / Siberian Solomonseal Rhizome / King Solomonseal" or "Cyrtomium Rhizome" or "Perilla Leaf" or "Redroot Gromwell" or "Mongolian Dandelion" or "Tree-of-heaven Ailanthus" or "Palmleaf Raspberry" or "Coastal Glehnia" or Ladybell or "Dahurian Patrinia" or "Whiteflower Patrinia" or "India Madder" or Hemp or "Whiteflower Cacalia" or "Finger Citron" or Dendrobium or "Human Placenta" or "Cherokee Rose" or Platycladi or "Hyacinth Bletilla" or Mulberry) (58273)
12 ("Atractylodis Macrocephalae" or "Semen Cuscutae" or "Dipsaci" or "Colla Corii Asini" or "Taxilli" or "Glycyrrhizae" or "Astragali" or "Paeoniae Alba" or "Angelicae Sinensis" or "Scutellariae" or "Cortex Eucommiae" or "Rehmanniae" or "Codonopsis" or "Diosscoreae" or "Amomi" or "Rehmanniae" or "Chuanxiong" or "Folium Artemisiae Argyi" or "Leonuri" or "Pericarpium Citri Reticulatae" or "Miltiorrhizae" or "Pseudostellariae" or "Ecliptae Eclipta prostrala" or "Caulis Perillae" or "Boehmeriae" or "Ginseng" or "Poria" or "Cimicifugae" or "Bupleuri" or "Paeoniae Rubra" or "Ligustri Lucidi" or "Agrimoniae" or "Caulis Bambusae in Taenia" or "Corni" or "Pollen Typhae" or "Semen Oryzae Glutinosae" or "Curcumae" or "Psoraleae" or "Lycopi" or "Lycii" or "Cyperi" or "Caulis Spatholobi" or "Et Rubiae" or "Ramulus Cinnamomi" or "Colla Cornu Cervi" or "Cornu Cervi Degelatinatum" or "Semen Ziziphi Spinosae" or "Corydalis" or "Foeniculi" or "Morindae Officinalis" or "Sanguisorbae" or "Ophiopogonis" or "Schizonepetae" or "Gardeniae" or "Citri" or "Receptaculum Nelumbinis" or "Alpiniae Oxyphyllae" or "Faeces Trogopterori" or "Toosendan" or "Schisandrae Chinensis" or "Pinelliae" or "Amomi Rotundus" or "Concha Ostreae" or "Polygoni Multiflori" or "Semen Persicae" or "Endoconcha Sepiae" or "Cortex Phellodendri Chinensis" or "Epimedii" or "Nodus Nelumbinis Rhizomatis" or "Moutan Cortex" or "Et Notoginseng" or "Cistanches" or "Petiolus Trachycarpi" or "Aucklandiae" or "Mume" or "Herha Agastaches" or "Flos Carthami" or "Cortex Moutan" or "Et Notopterygii" or "Anemarrhenae" or "Cibotii" or "Semen Nelumbinis" or "Ecliptae" or "Os Draconis" or "Poriacocos Wolf" or "Artemisiae Scopariae" or "Zingiberis" or "Crataegi" or "Folium Isatidis" or "Jujubae" or "Acori Tatarinowii" or "Arillus Longan" or "Scrophulariae" or "Cortex Lycii" or "Cortex Albiziae" or "Gordei Germinatus" or "Polygalae" or "Atractylodis" or "Semen Euryales" or "Phragmitis" or "Caulis Lonicerae Japonicae" or "Folium Eriobotryae" or "Cacumen Platycladi" or "Flos Lonicerae Japonicae" or "Houttuyniae" or "Alismatis" or "Concha Margaritifera" or "Aurantii" or "Cortex Magnoliae Officinalis" or "Ramulus Uncariae Cum Uncis" or "Folium Mori" or "Ootheca Mantidis" or "Polygonati" or "Cyrtomii" or "Folium Perillae" or "Arnebiae" or "Taraxaci" or "Cortex Ailanthi" or "Rubi" or "Glehniae" or "Adenophorae" or "Patriniae" or "Rubiac Cordifoliae" or "Cannabis" or "Semen Caesalpiniae Minacis" or "Citri Sarcodactylis" or "Dendrobii Nobilis" or "Placenta Hominis" or "Rosae Laevigatae" or "Semen Platycladi" or "Platantherae Chloranthae" or "Mori") (53444)
13 or/9-12 (178786)
14 and/5,8,13 (259)
15 (randomized controlled trial or controlled clinical trial) (567334)
16 (random* or trial) or (groups or placebo) (5650899)
17 or/15-16 (5650899)
18 17 not ((exp Animals not (Humans)) or (mice or mouse or murine or rat or rats)) (5081698)
19 and/14,18 (65)

Appendix 2. Model search strategy (Chinese language)

中国知网 **China Journal Net (CJN), China Journals Full-text Database**

1. 堕胎 /or 人工流产 /or 诱导性流产 /or “刮宫术” /or 真空刮除术 （16180）
2. 堕胎药 /or 非甾体类堕胎药 /or 甾体类堕胎药 （1896）
3. or/ 1-2 （16178）SU=(’堕胎‘+’人工流产‘+’诱导性流产‘+’“刮宫术”’+‘真空刮宫术’+‘堕胎药’+‘非甾体类堕胎药’+‘甾体类堕胎药’)
4. 妊娠初期 /or 怀孕3个月 （40）
5. 中药 /or 中草药 （236041）

6. or/ 4-5 （236081） SU=('妊娠初期'+'怀孕3个月'+'中药'+'中草药')
7. and/3，6 （57）
8. 随机对照试验 /or 临床对照试验 /or 安慰剂 （4653）
9. 8 not （动物试验 /or 小鼠 /or 大鼠） （4645） SU=（'随机对照试验'+'临床对照试验'+'安慰剂'） NOT SU=（'动物试验'+'小鼠'+'大鼠'）
10. and/ 7，9 (0)

万方数据库 **WanFang Database (Chinese Ministry of Science & Technology)**

1. 堕胎 /or 人工流产 /or 诱导性流产 /or "刮宫术" /or 真空刮除术 （2016）
2. 堕胎药 /or 非甾体类堕胎药 /or 甾体类堕胎药 （16）
3. or/ 1-2 （2016） 主题=("堕胎"or"人工流产"or"诱导性流产"or"刮宫术"or"真空刮宫术"or"堕胎药"or"非甾体类堕胎药"or"甾体类堕胎药")
4. 妊娠初期 /or 怀孕3个月 /or （怀孕9周，怀孕10周，怀孕11周，怀孕12周，怀孕13周，怀孕14周） （99）
5. 中药 /or 中草药 （31880）
6. or/ 4-5 （31977） 主题=("妊娠初期"or"怀孕3个月"or"中药"or"中草药")
7. and/3，6 （33）
8. 随机对照试验 /or 临床对照试验 /or 安慰剂 （7）
9. 8 not （动物试验 /or 小鼠 /or 大鼠） （7）
10. and/ 7，9 （0）

维普数据库 , **VIP database**

1. 堕胎 /or 人工流产 /or 诱导性流产 /or "刮宫术" /or 真空刮除术 （22102）
2. 堕胎药 /or 非甾体类堕胎药 /or 甾体类堕胎药 （52）
3. or/ 1-2 （22102） U=(堕胎 OR 人工流产 OR 诱导性流产 OR "刮宫术" OR 真空刮宫术 OR 堕胎药 OR 非甾体类堕胎药 OR 甾体类堕胎药)
4. 妊娠初期 /or 怀孕3个月 （2329）
5. 中药 /or 中草药 （1344437） U=(妊娠初期 OR 怀孕3个月 OR 中药 OR 中草药)
6. or/ 4-5 （1346694）
7. and/3，6 （260）
8. 随机对照试验 /or 临床对照试验 /or 安慰剂 （21042）
9. 8 not （动物试验 /or 小鼠 /or 大鼠） （20958） U=（随机对照试验 OR 临床对照试验 OR 安慰剂'） NOT U=（动物试验 OR 小鼠 OR 大鼠'）
10. and/ 7，9 (1)

WHAT'S NEW

Date	Event	Description
31 August 2021	Amended	protocol submission
20 August 2021	Amended	protocol revision
12 July 2019	Amended	First draft of protocol

CONTRIBUTIONS OF AUTHORS

LL and XF conceived the review question, developed, co-ordinated and completed the protocol.

LL and XF developed and completed the draft of the protocol.

AZ and YS performed part of editing the protocol and advised on part of the protocol.

CW and XL advised on part of the protocol.

All authors approved the final version of the protocol prior to submission.

DECLARATIONS OF INTEREST

AZ: none.

XF: none.

YS: none.

XL: none.

CW: none.

LL has been awarded two grants, Zhejiang Provincial Natural Science Foundation of China (LY20H180004) and Qianjiang Talents Fund of Zhejiang Province (grant number: QJD1602022), to financially support her research work including both basic sciences and clinical study papers. In the preparation of this protocol, she used part of these grants to pay for expert consultant fees and student labour fees/allowance.

SOURCES OF SUPPORT

Internal sources

- Zhejiang Provincial Natural Science Foundation of China (LY20H180004), China

  In the preparation of this protocol, Prof Lu LI used part of the grant to pay for expert consultant fees and student labour fees/allowance.
- Qianjiang Talents Fund of Zhejiang Province (grant number: QJD1602022), China

  In the preparation of this protocol, Prof Lu LI used part of the grant to pay for expert consultant fees and student labour fees/allowance.

External sources

- NA, Other

  NA