PROTOCOL

Efficacy and Safety of Ayurvedic Interventions in Female Infertility: Protocol for Systematic Review

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Abstract

Introduction: The purpose of this systematic review is to investigate the efficacy and safety of Ayurveda interventions for female infertility through analyzing trial data.

Materials and methods: A systematic review of randomized controlled trials (RCTs), non-RCT (NRCT), randomized/nonrandomized placebo control trials, quasi-RCTs (QRCTs), controlled clinical trials (CCTs), parallel arm comparative trials, and multiple arms clinical trials would be conducted through electronic search of the following databases: PubMed, AYUSH Research Portal, Google Scholar, the Cochrane Library [the Cochrane database of systematic reviews, digital helpline for ayurveda research articles (DHARA), the Cochrane central register of controlled trials (CENTRAL), and the Cochrane methodology register] without any restriction of the publication year. Hand search, snowballing of studies will also be performed to fetch the complete literature. The selection of the studies, data abstraction, and validations will be performed independently by two teams of reviewers. Conclusion will be derived with the consensus of complete review team. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. If sufficient data are available, a meta-analysis will be conducted.

Discussion: This review will help to develop strategies for the management of female infertility using Ayurveda intervention with support from evidence compiled from various clinical studies in this area.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. The review will be updated to inform and guide healthcare practice and policy.

Trial registration number: PROSPERO 2019 CRD42019139503.

Keywords: Efficacy, Infertility, *Shamana*, *Shodhana*, Systematic review, *Vandhyatva*.

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Background

Female infertility has been considered as a major complaint of the women in the reproductive age group. Infertility is defined in specific terms as the failure to conceive after a year of regular intercourse without contraception, according to modern science. It affects an estimated 48 million women, with the highest prevalence of infertility in South Asia, sub-Saharan Africa, North Africa/Middle East, and Central/Eastern Europe and Central Asia.[1] Causes of infertility include ovulation problems, tubal blockage, age-related factors, uterine problems, previous tubal ligation, and endometriosis. Infertility may not cause any serious illness but results in psychological upset. Female infertility varies widely by geographic location around the world. In 2010, there was an estimated 48.5 million infertile couples worldwide; and from 1990 to 2010, there was little change in the levels of infertility in most of the world.[2] Treatment options for female infertility depend on the cause but may include surgery, ovulation induction (using hormone therapy), and assisted reproductive technologies including *in vitro* fertilization. Infertility affects women around the world, and the cultural and social stigma surrounding it varies.

In Ayurveda, this condition is considered as *Vandhyatva*. According to Ayurveda, four factors, viz., *Ritu*, *Ambu*, *Kshetra*, and *Beeja*, are responsible for conception.[3] *Ritu* is the appropriate time for conception, *Kshetra* is healthy reproductive tract of mother, *Ambu* is nutrition for proper growth of conception, and the *Beeja* are healthy sperm and ovum of parents. Any deformity in these factors may lead to *Vandhyatva*. Both *Shamana* and *Shodhana Chikitsa* is mentioned for infertility in Ayurvedic texts. Especially Panchakarma, such as *Basti*, *Virechana*, and *Nasya*, plays a very important role in treating female infertility. Ayurveda also offers a wide range of formulations in the treatment of female infertility. Proper selection of drugs and the time of administration are very essential for getting the desired results. Along with efficacy, the safety of these modalities and the quality of these trials should also be analyzed, critically evaluated and highlighted in public domain.

This study aims at thorough review of the published data of Ayurvedic interventions as in the management of *Vandhyatva* (female infertility). This will provide most reliable source of evidence

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Conflict of interest: None

to guide for both clinical practice and public health decision-making.

Objectives

Primary

- Systematic review of the published clinical data in view of the safety, efficacy, and effectiveness of Ayurvedic interventions in the management of female infertility.

Secondary

- Meta-analysis of the published clinical data in view of safety and efficacy and effectiveness in the management of female infertility.

Materials and Methods

Eligibility Criteria

Population or Participants and Conditions of Interest

- Participants diagnosed as cases of female infertility of any type.

Interventions or Exposures

- Ayurveda treatment (*Shamana* or/and *Shodhana*) with any dose, type, schedule, drug, dosage form.

Comparators/control

- Ayurveda treatment (*Shamana* or/and *Shodhana*) with different dose, type, schedule, medicine, medicine form as compared to intervention(s)/exposure(s).
- Placebo control
- No treatment.

Outcomes of Interest

Primary outcomes:

- Response to treatment (improvement in subjective and/or objective criteria of assessment of female infertility)
- *Timing and effect measures:* No restrictions will be made in inclusion of study in review on the basis of outcomes mentioned above.

Secondary outcomes:

- Serious adverse events (resulting in death, disability, or incapacity, life-threatening complications, led to hospitalization, or prolongation of hospitalization)
- Reported improvement in the patient's health-related quality of life.
- Withdrawals due to adverse events or lack of efficacy or inconvenience of therapy/treatment.
- Timing and effect measures: During the study period or up to 1 month after completion study.

Study to be Considered for Review Process

- Randomized controlled trials (RCTs), non-RCT (NRCT), randomized/nonrandomized placebo control trials, quasi-RCTs (QRCTs), controlled clinical trials (CCTs), parallel-arm comparative trials, multiple arms clinical trials, case studies, and case series would be included for the review.

Study Characteristic: Exclusion Criteria

Criteria for Excluding Studies Not Covered in Inclusion Criteria

- Animal trials
- Observational studies with case–control, cross-sectional, or cohort design
- Lack of sufficient information on baseline
- Editorials and opinions, qualitative studies, those published as dissertation and meeting, abstracts only, where insufficient methodological details are reported.

Information Sources (Search Methods)

We will use a predefined search strategy to search studies in the following manner:

Electronic Search

We will search the following electronic databases:

Language: English language

Sources:

- PubMed
- Cochrane library
- Google Scholar
- Digital helpline for ayurveda research articles (DHARA)
- AYUSH Research Portal (Government of India)
- For ongoing trials – clinical trial registry of India – ctri.nic.in
- World Health Organizations International Clinical Trials Registry Platform –http://apps.who.int/trialsearch
- For dissertations in public domain: http://shodhganga.inflibnet.ac.in/simple-search

Search Strategy

Ayurveda OR Ayurvedic therapy OR Ayurvedic treatment OR Herbal Ayurveda OR Polyherbal OR Panchakarma OR Rasaushadhi OR Herbo-mineral OR Traditional Medicine OR Alternative Medicine OR Complementary Medicine Ayurveda OR Uttarbasti OR Nasya OR Virechana OR Vamana OR Taila OR Oil OR Vati OR Guggul OR Kwath OR AND Female Infertility OR Vandhyatva, Beeja, Kshetra, Ambu, Ritu, Shamana, Shodhana Chikitsa, Ghrita, AND Clinical trial. All terms will be searched in the fields "Abstract" and "Article Title" and in MeSH/ Subject Headings/Thesaurus when available. No filters or limitations will be applied in order to retrieve the best possible result and to avoid excluding preindexed materials.

Method of Review

Details of methods	Two main reviewers and a third to resolve any disagreements.
Quality assessment	RCTs will be assessed with the help of Cochrane tool of risk of bias and that of nonrandomized trials will be assessed with Risk of Bias in Non-Randomized Studies - of Interventions tool (ROBINS-I).
Data extraction	A predesigned form to extract data from the included studies for assessment of study quality and data analysis would be prepared. Data extraction will be done independently by two reviewers. Disagreements will be resolved by discussion. If necessary, additional information will be obtained from the contact person (authors) of that study through e-mail or telephone.

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	The data extraction form will include the following points: (1) first author's name; (2) year of publication; (3) country where the study was performed; (4) study design; (5) number of participants in the intervention and control/placebo groups; (6) intervention assigned to the control group, if any; (7) type of intervention; (8) treatment duration; (9) age, gender, and body mass index (BMI) of study participants; and (9) data regarding baseline and follow-up visit.
Meta-analysis	Meta-analysis will only become apparent when we see what data are extracted and made available from the systematic review.

Presentation of Results

Additional material	Flowchart of the whole process Protocol Data extraction form and tables Forest plots of studies included in the final review
Outputs from review	Papers and target journals, conference presentations, reports, etc.

Data Analysis

Two investigators including statistician will analyze data by using appropriate software. Dichotomous data will be presented and combined using relative risks, continuous data will be summarized by arithmetic means and standard deviations data will be combined by using weighted mean differences; both will be accompanied by 95% confidence intervals. Medians and ranges will be reported in tables. Arithmetic means and standard deviations will be used to summarize continuous data, when the data are assumed to be normally distributed. Separate summary effect estimates will also be generated for studies that meet and do not meet the individual quality criterion. Heterogeneity among trials will be assessed by inspecting forest plots, to look for overlapping confidence intervals, applying the chi-square test, with a p value of 0.05, indicating statistical significance, and using the I^2 test with a value of 50%, used to denote moderate levels of heterogeneity. If heterogeneity is detected and it is still considered clinically meaningful to combine studies, then a random-effect model will be used. A sensitivity analysis, to investigate the robustness of the results to the quality components, will be done, provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality.

Risk of Bias in Individual Studies/Risk of Bias (Quality) Assessment

Two authors will independently assess the risk of bias in included studies.

The RCTs will be assessed with the help of Cochrane tool of risk of bias and that of nonrandomized trials will be assessed with ROBINS-I tool. Disagreements between these review authors will be resolved by discussion, with involvement of a third review author if necessary and the results will be interpreted.

Data Synthesis

The results of the studies will be analyzed by using appropriate software. We will summarize the data of clinically homogeneous studies in a meta-analysis. A random-effect model will be used when heterogeneity is present. Data will not be pooled if significant heterogeneity exists.

Discussion

The systematic review after completion will be published in a peer-reviewed journal. The review may be updated after a definite period of time through Grading of Recommendations Assessment, Development and Evaluation (GRADE) evaluation[4] of the quality of evidence of new studies of this disease condition utilizing Ayurveda management. The study might open avenues of further introduction of Ayurveda management of infertility into public health.

Study Registration

The protocol for this systematic review has been registered with PROSPERO, the international prospective register of systematic reviews (PROSPERO 2019 CRD42019139503).

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Author's Contribution

All the authors have significantly contributed in development of protocol.

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हिन्दी सारांश

महिला वंध्यत्व मे आयुर्वेद चिकित्साओं की प्रभावकारिता और सुरक्षा का सिस्टेमेटीक रिव्यू प्रोटोकॉल

मनीषा तलेकर, बबीता यादव, सुमित गोयल, ललिता शर्मा, भोगवल्ली चन्द्रशेखर राव, नारायणम् श्रीकान्त

परिचय: इस सिस्टेमेटीक रिव्यू का उद्देश्य डेटा विश्लेषण के माध्यम से महिला वंध्यत्व के लिए आयुर्वेद के चिकित्साओं की प्रभावकारिता और सुरक्षा की जांच करना है।

तरीके और विश्लेषण: रेन्डमाइजड् कन्ट्रोल्ड ट्रायल (RCTs), नौन रेन्डमाइजड् कन्ट्रोल्ड ट्रायल (NRCT), रेन्डमाइजड्/नौनरेन्डमाइजड् प्लासिबो कन्ट्रोल्ड ट्रायल, क्वासी रेन्डमाइजड् कन्ट्रोल्ड ट्रायल (QRCT), कन्ट्रोल्ड क्लिनिकल ट्रायल (CCTs), पेरेलल आर्म कंपेरेटीव ट्रायल, मल्टीपल आर्म क्लिनिकल ट्रायल को प्रस्तुत अध्ययन मे सिस्टेमेटीक रिव्यू मे शामिल किया जायेगा। प्राथमिक परिणामों में उपचार में प्रतिक्रिया (सब्जेक्टिव में सुधार और / या मूल्यांकन के वस्तुनिष्ठ मापदंड अर्थात वंध्यत्व से संबंधित लक्षण) और गंभीर प्रतिकूल घटनाओं (परिणाम स्वरूप मृत्यु, विकलांगता या अक्षमता, अस्पताल में भर्ती होना) इनका समावेश किया जाएगा। यदि पर्याप्त डेटा उपलब्ध हैं तो, एक मेटा-विश्लेषण आयोजित किया जाएगा।

प्रसार: सिस्टेमेटीक रिव्यू एक शोध पत्रिका में प्रकाशित किया जाएगा। इस रिव्यू को इलेक्ट्रॉनिक और प्रिंट में भी प्रसारित किया जाएगा। स्वास्थ्य सेवा अभ्यास और नीति को सूचित करने और मार्गदर्शन करने के लिए इस रिव्यू को पुन: संशोधित किया जाएगा।

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