INPLASY PROTOCOL

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None.

Comparative the clinical effectiveness and safety of controlled ovarian hyperstimulation for poor ovarian responders undergoing IVF/ICSI：a systematic review and bayesian network meta-analysis

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ABSTRACT

Review question / Objective: **What is the clinical effectiveness and safety of controlled ovarian hyperstimulation (COH) protocols for poor ovarian responders undergoing IVF/ICSI? We aim to assess the clinical effectiveness and safety of COH protocols, and to generate treatment rankings of these COH protocols on the most clinically-important and commonly-reported events of outcomes.**

Rationale: **For a complex process such as COH with multiple possible treatment options, not all of which have been directly compared, a network meta-analysis may be better able to allow for comparisons and conclusions about which protocol is most effective.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 03 April 2020 and was last updated on 03 April 2020 (registration number INPLASY202040009.

INTRODUCTION

Review question / Objectives: **What is the clinical effectiveness and safety of controlled ovarian hyperstimulation (COH) protocols for poor ovarian responders undergoing IVF/ICSI? We aim to assess the clinical effectiveness and safety of COH protocols, and to generate treatment rankings of these COH protocols on the most clinically-important and commonly-reported events of outcomes.**

Condition being studied: **Since the introduction of COH for IVF/ICSI, many trials have compared different regimens.**

There are eight separate Cochrane reviews (Al-Inany 2016; Albuquerque 2013; Gibreel 2012; Mochtar 2007; Pouwer 2012; Siristatidis 2015; Smulders 2010; Van Wely 2011) including an aggregate total of over 200 trials and 40,000 participants, that have compared one COH protocol to another.

Rationale: For a complex process such as COH with multiple possible treatment options, not all of which have been directly compared, a network meta-analysis may be better able to allow for comparisons and conclusions about which protocol is most effective.

METHODS

Participant or population: Poor ovarian responders undergoing COH during IVF/ICSI.

Intervention: COH protocols included long GnRH agonist protocol, short GnRH agonist protocol, Minimal ovarian stimulation protocol, GnRH antagonist protocol, natural cycle protocol, stop GnRH agonist protocol, flare up GnRH agonist protocol, delay start GnRH antagonist protocol,and so on.

Comparator: Comparing a COH protocol.

Study designs to be included: Randomized controlled trials (RCTS).

Eligibility criteria: Trials using gonadotrophins for ovulation induction that do not involve IVF, and studies using antioestrogens or aromatase inhibitors alone without gonadotropins, will be excluded. We will include poor responder women regardless of age or expected response to the COH protocol.

Information sources: We will search PubMed, Embase, Cochrane Library, Web of Science, and the Chinese databases SinoMed (formerly Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), Wanfang Data and VIP Database for Chinese Technical Periodicals. We will search trial registers for ongoing and registered trials and OpenGrey (www.opengrey.eu) for unpublished literature. We will search for the full texts of relevant studies identified as abstracts. We will seek information from primary authors to investigate whether these studies meet eligibility criteria, and to obtain outcome and study data. Trials that compare at least two of the proposed protocols are eligible and we shall search for all possible comparisons. We will check the reference lists of published reviews and retrieved studies for additional trials.

Main outcome(s): Live birth rate. The number of OHSS events.

Additional outcomes: Clinical pregnancy rate; Ongoing pregnancy rate; Number of oocytes retrieved; Multiple pregnancy rate; Miscarriage rate; Cycle cancellation.

Data management: Two independent reviewers (H.Yang and C. Zheng) screened the literatures and extracted data separately. The basic information in the literatures was extracted according to the predefined "Data Extraction Form", including study characteristics (the title, author, year of publication, source of study, country, multi-center or not) and participant details (sample size, age, Body Mass Index [BMI], duration of infertility, time of previous IVF treatments in experimental and control groups), dosage, regimen, and route of drug administration, etc.

Quality assessment / Risk of bias analysis: We assessed the risk of bias as "low risk", "unclear risk" or "high risk", in accordance with the Cochrane Collaboration's Risk of bias tool (RoB) described in the Cochrane Hand book for Systematic Reviews of Interventions.

Strategy of data synthesis: The outcomes of the review are dichotomous data, so we will present results as a summary risk ratio with 95% (CrIs). The NMA will be conducted in a Bayesian hierarchical framework using the Markov Chain Monte Carlo (MCMC) framework and fitted in R 3.6.3 software via the BUGSnet and gemtc packages (https://cran.r-project.org) Global

Deviance Information Criterion (DIC) statistics and Leverage plots were both used to compare fixed and random effect models and to ensure that the overall fit was adequate. Clinical and methodological heterogeneity will be assessed through examining the characteristics and design of included studies. The transitivity assumption underlying NMA was evaluated by comparing the distribution of clinical and methodological variables which could act as effect modifiers across treatment comparisons. The statistical heterogeneity of entire NMAs will be investigated by the magnitude of heterogeneity variance (τ2) estimated from the NMAs model. Global I2 >50% denotes considerable heterogeneity. Additionally, we assumed that the amount of heterogeneity was the same for all treatment comparisons. We will conduct a statistical evaluation of consistency by separating direct evidence from indirect evidence on a specific comparison. For each outcome, the treatment hierarchy was summarized and reported as surface under the cumulative ranking curve (SUCRA), which is a percentage by accumulating each iteration of the Markov chain, interpreted as the probability of a treatment is the most effective without uncertainty in every ranking position, which is equal to 1 when the treatment is certain to be the best and 0 when it is certain to be the worst. Comparison-adjusted funnel plots were performed to investigate whether the integrated results have difference between imprecise trials and precise trials.

Search strategy: We will search PubMed, Embase, Cochrane Library, Web of Science, and the Chinese databases SinoMed (formerly Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), Wanfang data and VIP Database for Chinese Technical Periodicals, from inception to March 31, 2020. The free text or keyword search strategy was ("IVF" OR "ICSI" OR "ET" OR "intracytoplasmic sperm injection techniques" OR "intracytoplasmic sperm injection" OR "in vitro fertilization" OR "Embryo Transfer" OR "ovarian stimulation" OR "ovarian stimulation controlled ovarian stimulation" OR "ovulation induction" OR "ovulation stimulation" OR "superovulation" OR "superovulation induction" OR "controlled ovarian hyperstimulation" OR "controlled ovarian stimulation" OR "COH") combined with ("long agonist protocol" OR "long-long protocol" OR "long protocol" OR "short protocol" OR "stimulated cycle" OR "Stimulation techniques" OR "stop protocol" OR "flare-down" OR "flare-up" OR "flare-up GnRH agonist" OR "flare-up protocol" OR "micro-dose GnRH-a flare" OR "micro-dose HCG" OR "flexible protocol" OR "multidose antagonist protocol" OR "GnRH agonist short protocol" OR "gonadotrophin stimulation" OR "mild ovarian stimulation" OR "mild protocol" OR "mild stimulated" OR "mild stimulation" OR "GnRH a" OR "GnRH agonist" OR "GnRH agonists" OR "GnRH analog" OR "GnRH analogue" OR "GnRH analogues" OR "GnRH antagonist" OR "GnRH antagonists" OR "GnRHa" OR "GnRHa-gonadotropin" OR "gonadotropin releasing hormone agonist" OR "Gonadotrophin releasing agonist" OR "natural cycle" OR "natural cycles" OR "modified natural cycle" OR "luteal support" OR " luteal phase support" OR "Luteal phase ovulation" OR "Luteal-phase ovarian stimulation") for the above databases. In addition to these searches, we obtained relevant references from published reviews, systematic reviews or meta-analyses, clinical trials, and conference abstracts. The search strategy was developed and adapted for each database, without language or sample size restrictions.

Subgroup analysis: We will also evaluate whether treatment effects for the each outcome will be robust in subgroup analyses and network meta-regression using sample size, mean year, Body Mass Index (BMI), baseline pregnancy rate, duration of infertility, bFSH, the protocol of COH , and so on.

Sensibility analysis: To assess the robustness of the results obtained by the primary model, we will do sensitivity analyses. Furthermore, we will adjust the results of each outcome.

Language: Without language restrictions.

Coutries involved: China.

Keywords: controlled ovarian hyperstimulation; poor ovarian responders; IVF/ICSI; systematic review; bayesian network meta-analysis.

Dissemination plans: The findings of the NMA will be published in peer-reviewed journals for dissemination.

Contributions of each author:
Author 1 - The author conceived the network meta-analysis and will draft the manuscript.
Author 2 - The author will participate in literature quality assessment, data extraction and analysis.
Author 3 - The author will participate in literature quality assessment, data extraction and analysis.
Author 4 - The author conceived the network meta-analysis and will drafted the manuscript.
Author 5 - The author will revise the manuscript.