BMJ Open

Controlled ovarian hyperstimulation for poor ovarian responders undergoing in vitro fertilisation/intracytoplasmic sperm injection: a protocol for systematic review and Bayesian network meta-analysis

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To cite: Yang H, Zheng C, Zheng Q, *et al*. Controlled ovarian hyperstimulation for poor ovarian responders undergoing in vitro fertilisation/intracytoplasmic sperm injection: a protocol for systematic review and Bayesian network meta-analysis. *BMJ Open* 2021;**11**:e039122. doi:10.1136/bmjopen-2020-039122

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2020-039122).

Received 04 April 2020
Revised 02 December 2020
Accepted 19 December 2020

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ABSTRACT

Introduction Controlled ovarian hyperstimulation (COH) is the routine regimen used to generate a sufficient number of follicles during in vitro fertilisation (IVF) or intracytoplasmic sperm injection (ICSI) treatment. Poor ovarian response is a challenge encountered by many clinicians during COH and poor ovarian responders (PORs) usually have higher follicle stimulating hormone levels, lower levels of anti-Mullerian hormone and few oocytes retrieved, which have been attributed mainly to advanced maternal age and poor follicle reserve or other reasons that could impair ovarian response during ovarian stimulation. Over the last few decades, researchers have proposed a series of strategies and ovarian stimulation protocols to improve pregnancy outcomes in patients with POR during their IVF/ICSI treatment. However, clinical decisions regarding COH protocols in PORs during IVF/ICSI treatment remain controversial. Traditional pairwise meta-analysis only allows the direct comparison of two protocols in COH for patients with POR. However, many of these COH protocols have not been compared directly in randomised controlled trials (RCTs). Thus, we aim to use network meta-analysis (NMA) to assess the clinical effectiveness and safety of COH protocols and to generate treatment rankings of these COH protocols for the most clinically important and commonly reported outcomes events.

Methods and analysis The PubMed, Embase, Cochrane Library, Web of Science, SinoMed, CNKI, WanFang database and Chongqing VIP information databases will be searched for all RCTs of COH for POR women during IVF/ICSI from inception to 31 March 2020. Primary outcomes will include live birth rate and number of oocytes retrieved. Secondary outcomes will include ongoing pregnancy rate, clinical pregnancy rate, miscarriage rate, ovarian hyperstimulation syndrome rate, multiple pregnancy rate and cycle cancellation rate. Pairwise meta-analysis and Bayesian NMA will be conducted for each outcome. Subgroup analysis, meta-regression, and sensitivity analysis will be performed to assess the robustness of the findings. The generation of NMA plots and subsequent results will be performed by using R V.4.0.1. The assessment of confidence in network estimates will use the Confidence in Network Meta-Analysis)web application (see https://cinema.ispm.unibe.ch/).

Ethics and dissemination This review does not require ethics approval and the results of the NMA will be submitted to a peer-review journal.

Strengths and limitations of this study

- ► Bayesian network meta-analysis (NMA) can integrate direct evidence with indirect evidence from currently applied controlled ovarian hyperstimulation protocols involving poor ovarian responder (POR) women undergoing in vitro fertilisation or intracytoplasmic sperm injection to generate a clinically useful ranking of these regimens.
- ► Only randomised controlled trials will be included.
- ► Evidence drawn from an NMA is limited and should be interpreted with caution.
- ► Different POR diagnostic criteria and various gonadotropin preparations may result in potential heterogeneity.
- ► The evidence of indirect comparison should be applied cautiously and reasonably in clinical practice.

In the 60 plus years between 1950 and 2017, the global total fertility rate has decreased by an estimated 49.4%.[1] As such, infertility may have become a global problem. Moreover, the absolute number of couples affected by infertility increased from 42.0 million in 1990 to 48.5 million in 2010.[2] In vitro fertilisation and embryo transfer (IVF-ET) and intracytoplasmic sperm injection (ICSI) are well-established infertility treatments. However, only 23.44% (90 618/386 632) of embryo transfers in in vitro fertilisation (IVF) or ICSI led to delivery based on data from 38

countries and 1169 clinics in Europe.[3] Furthermore, the cumulative live birth rate (LBR) among more than 3000 women who were poor ovarian responders (PORs) diagnosed according to the Bologna criteria[4] was 14.9% (95% CI 13.7% to 16.1%).[5] Generally, for IVF to be successful, adequate follicular recruitment and maturation are essential. POR is defined as the failure to develop a sufficient number of follicles after controlled ovarian hyperstimulation (COH) in women undergoing assisted reproductive technology treatment.[6] The incidence of POR varies worldwide and has been reported to range from 5.6% to 35.1%.[7]

COH is a routine regimen used to generate a sufficient number of follicles during IVF/ICSI treatment.[8] COH consists of three basic elements: exogenous gonadotropin (Gn) to stimulate multi follicular development; cotreatment with a Gn-releasing hormone (GnRH) agonist or antagonist to suppress pituitary function and prevent premature ovulation; and triggering of final oocyte maturation 36 hours–38 hours before oocyte retrieval. Complex endocrine changes occur while a woman undergoes ovarian stimulation as part of IVF/ICSI treatment. The primary aims of COH are to create a cohort of developing follicles and to prevent premature spontaneous ovulation.[9]

Poor ovarian response is a challenge encountered by many clinicians during COH, and PORs usually exhibit higher FSH levels, lower levels of anti-Mullerian hormone (AMH) and few oocytes retrieved, which are attributed to advanced maternal age and/or poor follicle reserve or other reasons that could impair the ovarian response during ovarian stimulation.[10 11] Therefore, PORs usually undergo multiple repeated cycles, incur high costs and experience IVF failure.[12 13] Various COH regimens and interventions have been proposed to improve pregnancy outcomes for patients with POR. Currently, the most frequently proposed COH protocols include delayed start GnRH antagonist protocol,[14] short GnRH agonist protocol,[15] mild ovarian stimulation protocol,[16] GnRH antagonist protocol,[17] natural cycle protocol,[18] long GnRH agonist protocol,[19] stop GnRH agonist protocol,[20] flare up GnRH agonist protocol,[21] luteal phase ovarian stimulation protocol[22] and progestin-primed ovarian stimulation protocol.[23]

Over the last few decades, researchers have proposed a series of strategies and ovarian stimulation protocols to improve pregnancy outcomes in patients with POR during their IVF/ICSI treatment. However, clinical decisions regarding COH protocols in PORs during IVF/ICSI treatment remain controversial. Traditional pairwise meta-analysis only allows the direct comparison of two protocols in COH for patients with POR.[24–37] However, many of these COH protocols have not been compared in randomised controlled trials (RCTs). Without direct evidence, it is difficult to identify the most effective COH protocol for patients with POR. As a useful tool that can rank the effectiveness of various treatments and subsequent guidance for clinical decision making, network meta-analysis (NMA) compares multiple various treatments in one statistical model.[38 39] The combination of direct and indirect evidence may improve the precision of the estimated effect sizes.[40] The major value of NMA is that it can rank each COH protocol according to its effectiveness, which is important for clinicians to make the best treatment choices. NMA can additionally be used to identify gaps in the evidence base for designing future trial(s) and may reduce uncertainty in treatment-effect estimates. Therefore, we aim to use NMA to assess the clinical effectiveness and safety of current COH protocols and to generate treatment rankings of these COH protocols for the most clinically important and commonly reported outcome events.

METHODS

Design

This study will be based on a Bayesian framework for NMA, and will be performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.[41]

Eligibility criteria

Study types

All RCTs of COH protocols in IVF/ICSI will be included. Non-randomised, cross-over design and quasi-randomised studies will be excluded.

Participants

The review will consider trials that include PORs undergoing COH during IVF/ICSI treatment. Ovarian stimulation protocols for IVF/ICSI will not be limited. POR women will be included regardless of age, patient's definition or expected response to the COH protocol.

Types of interventions

RCTs comparing one COH protocol to another will be included. Trials using Gns for ovulation induction that do not involve IVF/ICSI, studies using anti-oestrogens or aromatase inhibitors alone without Gns, and trials comparing different Gn doses in the same COH protocol, will be excluded. Gn preparations available for use include human menopausal Gn (hMG), a urinary product with FSH and luteinising hormone (LH) activity, purified FSH (p-FSH) and highly purified FSH (hp-FSH), and various recombinant FSH (rFSH) and LH (rFSH/rLH) preparations. From the relevant systematic reviews, at least 10 COH protocols for predicted PORs have been identified with multiple comparisons as depicted in the following network diagrams. If any other protocols are identified in the included studies, they will be considered as eligible and included in the NMA after assessing their comparability with those listed earlier. Table 1 lists the available COH protocols used in the network diagrams. An ideal network plot that is a fully connected network with all expected interventions has been generated (figure 1).

Table 1 Available controlled ovarian hyperstimulation protocols used in the network diagrams

COH protocol	Abbreviation	Description
Long GnRH agonist	Long	Down-regulation with GnRH agonist 0.1 mg/day is performed from day 21 of the previous cycle. It is reduced to 0.05 mg/day from the start of the following cycle and continued until hCG administration. Gn is started at day 2–3 of menses using a dose of 300 IU of rFSH. The Gn dose is adjusted from day 6 of stimulation according to the ovarian response monitored until the day of hCG administration.
Short GnRH agonist	Short	GnRH-a administration is commenced at the same time as starting stimulation and continued until the day of hCG administration. Women receive GnRH agonist 0.05 mg/day starting on day 1 until the hCG injection and 450 IU rFSH daily starting on day 2.
Stop GnRH agonist	Stop	Administration of GnRH agonist 0.1 mg/day starts in the mid-luteal phase in the previous cycle and stops at the time of menstruation before starting Gn stimulation on day 2 of the menstrual cycle. Gn at 300–450 IU/day is initiated, and careful monitoring of follicular growth is performed using transvaginal ultrasound until >1 follicle on both ovaries reaches a diameter of 14 mm, when GnRH antagonist is injected subcutaneously until the date of hCG trigger.
Flare up GnRH agonist	Flare	Administration of GnRH-a 0.05 mg/day starts from day 2 of the cycle. GnRH agonist is administered subcutaneously and continued daily up to and including the day of hCG administration.
GnRH antagonist	GnRH-A	Gn is administered daily from menstrual cycle day 3; follicle monitoring is performed 5 days later. When the dominant follicles reach a diameter of approximately 14 mm, GnRH antagonist 0.125–0.25 mg/day is administered up to the trigger day. The dose of Gn can be adjusted according to ovarian response.
Delayed start GnRH antagonist	Delay	Administration of GnRH antagonist starts on day 2 or 3 of the menstrual cycle and continues until the ninth day. Then, ovarian stimulation with Gn is started from day 9 of the menstrual cycle until the day of hCG administration.
Mild ovarian stimulation	Mild	(i) Lower dose and shorter duration of Gn administration; (ii) using GnRH- antagonist to desensitise the pituitary gland and (iii) administering clomiphene citrate or tamoxifen or aromatase inhibitors with or without Gn and GnRH-antagonists.
Natural cycle	Natural	Starting on day 8, 1 or 12 of their cycle, regular ultrasonic evaluation of the endometrium thickness and mean diameter of the dominant follicle is performed. When the endometrium thickness is >8 mm and the diameter of the dominant follicle is 16–20 mm, ovulation is induced using hCG injection.
Luteal phase ovarian stimulation	LPOS	Between 0 and 24 hours after spontaneous ovulation or oocyte retrieval, patients with at least one follicle measuring <8 mm are administered hMG injection until the day of hCG administration.
Progestin-primed ovarian stimulation	PPOS	Administration of hMG and MPA starts daily from cycle day 3. Follicles are monitored 5 days later, and the dose of hMG is adjusted according to ovarian response. MPA dose is consistent up to the trigger day.

COH, controlled ovarian hyperstimulation; FSH, follicle-stimulating hormone; Gn, gonadotropin; GnRH, gonadotropin-releasing hormone; hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; LPOS, Luteal phase ovarian stimulation; MPA, medroxyprogesterone acetate; PPOS, Progestin-primed ovarian stimulation; rFSH, recombinant follicle-stimulating hormone.

Outcome measures

Primary outcomes will include LBR (a baby born alive) and number of oocytes retrieved (NOR). Secondary outcomes will include clinical pregnancy rate (CPR, a gestational sac confirmed by ultrasound), ongoing pregnancy rate (OPR, a gestational sac with foetal heart motion, confirmed on ultrasound), miscarriage rate (MR, (CPR-OPR)/CPR), ovarian hyperstimulation syndrome (OHSS) rate (number of women experiencing OHSS events as defined by the trialists), multiple pregnancy rate (MPR, counted as one live birth event) and cycle cancellation rate (CCR, defined as cancelled cycle before oocyte retrieval). The longest follow-up time will be chosen as the measurement time point for all of the outcomes.

Data sources and search strategy

A systematic search of the PubMed, Embase, Cochrane Library and Web of Science databases, as well as the Chinese databases SinoMed (formerly Chinese Biomedical Database), CNKI (Chinese National Knowledge Infrastructure), Wanfang Data and VIP Database for Chinese Technical Periodicals, from their inception to 31 March 2020, will be performed. Trial registers of ongoing and registered trials (clinicaltrials.gov) and OpenGrey (www.

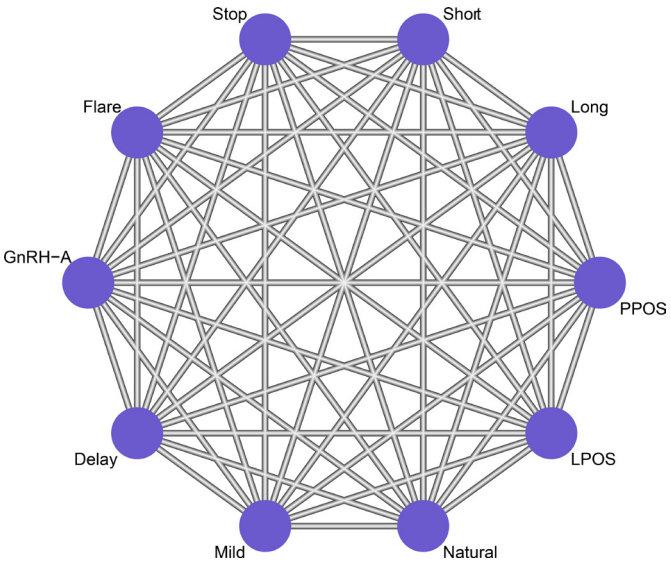

Figure 1 Network diagrams of possible comparisons of controlled ovarian hyperstimulation protocols for poor ovarian responder. Delay, delayed start; Flare, flare up GnRH agonist; GnRH-A, GnRH antagonist; Long, long GnRH agonist; Mild, mild ovarian stimulation; Natural, natural cycle; Short, short GnRH agonist; Stop, stop GnRH agonist; LPOS, Luteal phase ovarian stimulation; PPOS, Progestin-primed ovarian stimulation.

opengrey.eu) will be searched for unpublished literature. In addition, the proceedings of three major annual conferences on assisted reproduction technology will be searched: the American Society for Reproductive Medicine, the European Society for Human Reproduction and Embryology and the Pacific Coast Reproductive Society. The reference lists of published reviews and retrieved studies will be manually searched for additional trials. Search terms will be grouped into three blocks (table 2). The search strategy was developed and adapted for each database without language restrictions.

Study selection process

NoteExpress V.3.2 (Beijing Aegean Le Technology, Beijing, China) will be used to manage the citations retrieved from literature. After initial screening of titles and abstracts, the full text of all potentially eligible trials will be retrieved. Two authors (HY and CZ) will independently review these full-text articles for inclusion criteria and select the eligible RCTs. Disagreement between the reviewers will be resolved by discussion with the corresponding author (YF). For duplicate publications, more detailed and comprehensive literature that provides information and data will be retained. The reasons for study exclusion during this stage will be documented and reported, and the selection process will be illustrated in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart.

Data extraction

Two independent reviewers (XTL and MZH) will screen the eligible studies and extract the data separately. Basic information extracted from the eligible studies will be entered into a standardised data extraction form and will include the following: author; year of publication; trial setting; country; singlecentre or multicentre study; total number of cases; number of patients; POR diagnosis; age; body mass index (BMI); duration of infertility; COH protocol; type of antagonist; type of agonist; type of Gn; starting dose of Gn; type and dose of trigger medication;

Table 2 Search terms

Search block	Search terms
Participants	"poor responders" OR "poor responder" OR "poor prognostic patients" OR "poor ovarian responder" OR "poor ovarian response" OR "inappropriate ovarian response" OR "diminished ovarian reserve" OR " low prognosis" OR "poor prognosis"
Intervention	"IVF" OR "ICSI" OR "ET" OR "intracytoplasmic sperm injection techniques" OR "intracytoplasmic sperm injection" OR "in-vitro fertilisation" OR "in vitro fertilization" OR "Embryo Transfer" OR "ovarian stimulation" OR "controlled ovarian stimulation" OR "ovulation induction" OR "ovulation stimulation" OR "superovulation" OR "superovulation induction" OR "ovarian hyperstimulation" OR "controlled ovarian hyperstimulation" OR "controlled ovarian stimulation" OR "COH" OR "long agonist protocol" OR "long-long protocol" OR "long protocol" OR "long v short 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 "microdose flare cycle" OR "microdose flare-up protocol" OR "microdose GnRH agonist flare" OR "flexible protocol" OR "multidose antagonist protocol" OR "GnRH agonist short protocol" OR "GnRH agonist vs antagonist" 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 "Gonadorelin" OR "gonadotropin releasing hormone agonist" OR "Gonadotrophin releasing agonist" OR "natural cycle" OR "natural cycles" OR "modified natural cycle" OR "artificial cycle"
Study design	("randomized controlled trial" OR "controlled clinical trial" OR "randomized" OR "placebo" OR "clinical trials as topic" OR "randomly") NOT ("animals" NOT "humans")

outcome data; randomisation method; allocation concealment; power calculation and financial support. The literature will be arranged in accordance with the code of intervening measures. The extracted data will be entered into a standardised spreadsheet file (Excel). If details of the included studies are inadequate to enable accurate grouping, the authors of the studies will be contacted for more detail.

Evaluation of risk of bias

Risk of bias will be assessed as 'low risk', 'some concerns risk' or 'high risk', in accordance with V.2 of the Cochrane Risk-of-Bias Tool for Randomized Trials (RoB 2) in the Cochrane Handbook for Systematic Reviews of Interventions (V.6, 2019).[42] This tool includes domains of bias: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome selection of the reported result and overall risk. Two authors (HX and QZ) will independently assess the risk of bias in the selected studies, and inconsistencies in evaluation will be resolved by another author (YF).

Data synthesis

For dichotomous data, results will be expressed as a summary risk ratio (RR) with corresponding 95% CIs. Continuous data will be expressed as standardised mean difference with corresponding 95% CI.

Pairwise meta-analysis for direct treatment comparisons

Traditional pairwise meta-analyses will be performed for all available direct evidence comparing two treatments using the bayesmeta package (V.2.5-0) in R (V.4.0.1). Bayesian random-effects meta-analysis will be used for data analysis.

NMA for indirect and mixed comparisons

The NMA will be conducted in a Bayesian hierarchical framework using the Markov Chain Monte Carlo (MCMC) framework and fitted the gemtc package (V.0.8-2) and the BUGSnet package (V.1.0.3) in R (V.4.0.1).[43] Deviance information criterion (DIC) statistics and leverage plots will be used to assess random effect model fit and to ensure that the overall fit is adequate.[44] Three chains with different initial values will be run simultaneously. For each analysis, the inference will be based on 150 000 iterations of MCMC after a 50 000 iteration burn-in period. Trace plots and Brooks-Gelman-Rubin diagnostic plots will be used to assess convergence.[45]

Clinical and methodological heterogeneity will be assessed by examining the characteristics and design of the studies included. The transitivity assumption underlying the NMA will be evaluated by comparing the distribution of clinical and methodological variables which could act as effect modifiers across treatment comparisons. The common COH protocol that is used to compare different protocols indirectly is similar when it appears in different comparisons (eg, long GnRH agonist protocol vs short GnRH agonist protocol is similar to long GnRH agonist protocol vs 'flare up' GnRH agonist protocol). Plots displaying clinical characteristics within each COH protocol arm will be generated. The statistical heterogeneity of entire NMA will be investigated using the magnitude of heterogeneity variance (τ^2) estimated from the NMA model. The estimate of the heterogeneity variance in the NMA will be compared with the estimates in the pairwise meta-analyses. Statistical evaluation of inconsistency will be conducted by separating direct evidence from indirect evidence on a specific comparison.

For each outcome, the treatment ranking will be summarised and reported as the surface under the cumulative ranking curve. Each iteration of the Markov chain produces a ranking of the treatments, from most effective to least effective. The percentages obtained by accumulating that information provide estimates of the probability of each treatment being in each position in the ranking, equal to 100% when the treatment is certain to be the best and 0 when it is certain to be the worst.[40] Comparison-adjusted funnel plots will be performed to investigate whether the integrated results have a difference between imprecise and precise trials.

Subgroup analysis and network meta-regression

If important heterogeneity and/or inconsistency is found, possible sources will be explored. If sufficient studies are available, network meta-regression or subgroup analyses will be performed using the following effect modifiers as possible sources of inconsistency and or heterogeneity: age; BMI; POR diagnosis (Bologna's criteria vs no Bologna's criteria); country (Asia or not Asia); baseline FSH level; baseline AMH level; baseline AFC level; the dosage of Gn; regimen; route of drug administration and mixed rFSH or hMG/rLH versus standard protocols (rFSH or hMG).

Sensitivity analysis

To assess the robustness of the results obtained by the primary model, sensitivity analyses for the following will be performed: overall quality of the studies (low vs high risk of overall bias); use of fixed-effect versus random-effects model and different effect measures (RR vs OR); different definition and calculation of pregnancy-related outcomes.

The list of detailed data analysis reports, we will submit to a peer-reviewed journal is provided in online supplemental file 1.

Dealing with the missing data

In cases of missing data, the authors will be contacted for the original data. If the original data cannot be obtained, missing data will be calculated using the outcome indicators provided in the article, such as using CPR and OPR to calculate MR. If there is high-level missing data (>15% of missing data), the authors will use multiple imputation to estimate missing data. Furthermore, sensitivity analysis will be used to explore the impact of high-level missing data on the results of the overall estimation of treatment effect.

Assessment of confidence in network estimates

A 'summary of findings table' will be produced using CINeMA (Confidence in Network Meta-Analysis), which is a web application (see https://cinema.ispm.unibe.ch/) that simplifies the evaluation of confidence in the findings from NMA.[46] This table will evaluate the overall quality of the body of evidence for the primary outcomes (LBR and OR) on the basis of within-study bias, indirectness, imprecision, heterogeneity and inconsistency, and reporting bias. The quality of evidence will be classified according to the Grading of Recommendations, Assessment, Development and Evaluations group into four levels: high, moderate, low and very low quality.

Ethics and dissemination

This review does not require ethics approval because it does not require the collection of primary data. Findings of the NMA will be published in a peer-reviewed journal for dissemination.

Patient and public involvement

There was no patient or public involvement in the design of this study, or the development and drafting of this manuscript.

DISCUSSION

This systematic review and Bayesian NMA will compare current COH protocols in women who are POR undergoing IVF/ICSI, and generate a clinically useful ranking of these regimens. The results of this NMA will make it easier for POR patients undergoing IVF/ICSI and their physicians to choose the appropriate COH strategy. However, the interpretation based on evidence from the NMA for ranking results is limited. As such, it needs to be combined with clinical experience and the specific situations of patients with POR. Previous published systematic reviews and meta-analyses only included RCTs before 2018. Importantly, some published RCTs and trials have provided additional data regarding COH for IVF/ICSI.[47–49] Additionally, the natural cycle and progestin-primed ovarian stimulation were not considered in previous studies. To our knowledge, this will be the first NMA aimed at determining the optimal COH protocol for POR women during IVF/ICSI treatment. Our findings will contribute to the development of clinical practice guidelines for COH protocols to improve the pregnancy and the NOR of IVF/ICSI. Nevertheless, our NMA may have limitations. First, the different diagnostic criteria and the various Gn preparations (ie, rFSH, HMG, rLH, uMG and rFSH/rLH) may cause potential heterogeneity. Second, differences in the definition and calculation of pregnancy-related outcomes may affect the quality of evidence.

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Acknowledgements We thank the support of the National Key Research and Development Programme of TCM Modernization Research Project and the National Natural Science Foundation of China.

Contributors HY and YF conceived the network meta-analysis. XL, MH and HX participated in the literature quality assessment, data extraction and analysis. CZ and QZ explained the results. HY and YF drafted the agreement. CZ revised this manuscript. All authors reviewed the protocol and approved the submission of the final manuscript.

Funding This work is supported by the National Key Research and Development Programme of TCM Modernization Research Project (grant no. 2017YFC1703603), and the National Natural Science Foundation of China (grant no. 81674087).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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