



# Effectiveness of hormone add-on strategies in ovarian stimulation for women with poor ovarian response: a systematic review and network meta-analysis of randomized controlled trials

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## Abstract

**Purpose** Despite various stimulation protocols and adjuvant treatments, optimizing the reproductive success of women with poor ovarian response (POR) undergoing assisted reproduction techniques (ART) remains a challenge. The aim was to evaluate and compare the ovarian stimulation and reproductive outcomes of hormonal add-ons in women with POR undergoing ART.

**Methods** MEDLINE, LILACS, SCOPUS, EMBASE, Scielo.br, PROSPERO, CINAHL, PsycINFO, AMED, Clinicaltrials.gov, ICTRP, Cochrane Library, and conference proceedings were searched for randomized controlled trials without temporal, geographic, and language restrictions. We included only RCTs that allocated women with POR, according to Bologna criteria, undergoing ART to at least two different ovarian stimulation protocols, with the treatment arm including at least one hormonal add-on. A random-effect network meta-analysis was performed for mixed multiple treatment comparisons to rank available add-ons by the surface under the cumulative ranking curve area (SUCRA). Primary outcome was the live birth rate.

**Results** Twenty-two studies (4131 women) were directly and indirectly compared. Concerning the live birth rate, no significant differences among add-ons were noted (very low evidence), with testosterone (SUCRA = 34.0%) showing the highest probability of the best treatment. For the clinical pregnancy rate, according to SUCRA ranking, human growth hormone (SUCRA = 46.3%) and testosterone (SUCRA = 44.6%) had increased chances of being ranked first, with growth hormone being significantly more efficacious than estrogens (OR 3.46 [95% CI 1.59 to 7.53]; low evidence) while recombinant luteinizing hormone was significantly less efficacious (OR 0.50 [95% CI 0.26 to 0.96]; very low evidence). Regarding the overall number of retrieved oocytes and the mean number of metaphase II oocytes, human growth hormone was confirmed best ranked (SUCRA = 53.2% and SUCRA = 67.9%). Letrozole had significantly less gonadotropins used than controls (SMD − 7.02 [95% CI − 12.82 to − 1.22]; low evidence) (SUCRA = 67.0%) and the smallest stimulation duration (SUCRA = 52.0%).

**Conclusion** Low to very-low evidence shows that women with POR undergoing controlled ovarian stimulation may benefit from adding human growth hormone or testosterone for improved reproductive outcomes. However, additional high-quality randomized controlled trials are needed to overcome the limitations of the current literature.

Trial registration: PROSPERO CRD42024618797, date: 25 November 2024.

**Keywords** Diminished ovarian reserve · Poor responders · Assisted reproductive technologies · IVF · Infertility

## Introduction

Ovarian reserve refers to the number of oocytes a woman has at a given stage of her life. Poor ovarian response (POR) is due to a decline in the number of oocytes

resulting in inadequate ovarian function and reduced fertility [1]. This condition is typically characterized by decreased levels of anti-Müllerian hormone (AMH), decreased antral follicle number (AFC), and sometimes also elevated follicle-stimulating hormone (FSH) at baseline [2]. Some pieces of evidence report that the decline in number is also often accompanied by a concomitant decline in oocyte quality [3]. In fact, it is debated whether

Extended author information available on the last page of the article

the natural decline in oocyte quantity is related to a decrease in oocyte quality and an increased risk of aneuploidies [4]. In support of this hypothesis, data suggest that women with POR are at higher risk of aneuploid pregnancies and miscarriages [5, 6]. Therefore, compromised reproductive potential characterizes women with POR undergoing ovarian stimulation (OS) and assisted reproductive technologies (ART) compared with comparably aged counterparts with normal ovarian reserve and OS responsiveness [7]. However, the ideal stimulation regimen for patients with POR is currently unknown. In fact, several therapeutic strategies have been proposed to manage women with POR, seeking to increase the number of good-quality oocytes collected following OS and to optimize ART outcomes [8–10]. Among these, several stimulation protocols, with or without pre-treatment, and involving the use of various hormonal [11–15], pharmacological [16, 17] and non-pharmacological [18–20] add-ons to gonadotropins have been described in numerous randomized controlled trials (RCTs). In fact, a recent meta-analysis of RCTs suggested that pretreatment with testosterone could improve the live birth rate (LBR) in women with (POR) [21]. However, this conclusion is derived from heterogeneous comparisons that include different treatment protocols, making the interpretation of the results difficult. To date, there is only one analysis that attempts such a multiple comparison to evaluate adjuvant treatments in OS for poor responder women in IVF cycles, but it has important methodological limitations and doubts about the quality and appropriateness of the included studies [22]. Therefore, given these assumptions, to date the superiority of one protocol with one add-on over another has not yet been demonstrated. This systematic review and network meta-analysis aims to explore the superiority of an OS protocol with hormonal add-ons over the same protocol without additions in terms of reproductive and ART outcomes in women with POR according to the Bologna criteria [23], analyzing currently available randomized controlled trials conducted for this purpose.

## Methods

This network meta-analysis was carried out using the procedures described in the Cochrane Handbook for Systematic Reviews of Interventions [24] and the Mbuagbaw et al. methodological specifications [25]. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analyses (PRISMA-NMA) was adhered to. The study protocol (CRD42024618797) was submitted to the PROSPERO

(International Prospective Register of Systematic Reviews) database on 25 November 2024.

## Data sources and search strategy

The following Medical Subject Heading (MeSH) terms and keywords were used to search the electronic databases MEDLINE (available through PubMed), SCOPUS, LILACS, EMBASE, Scielo.br, and PROSPERO: “ovarian stimulation”/“ovulation induction” (MeSH Unique ID: D010062), “assisted reproductive technologies” (MeSH Unique ID: D027724), “in vitro fertilization” (MeSH Unique ID: D005307), “reproductive techniques”, “POSEIDON criteria”, “Bologna criteria”, “low responders”, “poor responders”, “poor ovarian response”, “poor response”, “poor ovarian responsiveness”, “ovarian reserve” (MeSH Unique ID: D065851), “diminished ovarian reserve”, “poor ovarian response” and “poor ovarian reserve”. without any date restrictions. The search query was changed to fit the format of each database (Appendix 1). A filter for randomized controlled trials (RCTs) was used in each database. Additional searches were conducted to find more relevant papers on CINAHL, PsycINFO, and AMED in order to reduce publication bias. The Cochrane Central Register of Controlled Studies, Clinicaltrials.gov, and the World Health Organization’s International Clinical Trials Registry Platform (ICTRP) were also searched to locate additional randomized controlled trials. Additionally, the gray literature (NTIS, PsycEXTRA) was examined to find national and international conference abstracts. The included study’s references and pertinent reviews were also reviewed to locate more articles that eluded our first search. The analysis did not include any editorials, letters to the editor, comments, or second thoughts publications. A.E. and V.A. carried out the approach for the literature search.

## Data collection and study selection

The titles and abstracts of all the papers were separately screened by two reviewers (G.R. and J.C.C.F.) to identify which research should be evaluated further and to omit citations that were judged unnecessary by both observers. The authors, institutions, publication titles, and study findings were all concealed during this initial screening. Any ambiguity or disagreement was cleared up by talking with a third reviewer (A.F.R.). Two reviewers (A.B.G. and B.M.R.) retrieved and evaluated full texts of possibly relevant articles based on the pre-established inclusion criteria. In addition, methodological validity was evaluated before being included in the review. Every doubt or disagreement was cleared up by discussion among reviewers in order to reach an agreement. Add-ons have been defined as any additional

treatment used, in addition to gonadotropin releasing hormone (GnRH) analogs and gonadotropins, during the vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycle, with the goal of increasing pregnancy success in women with POR. As such, hormonal add-ons directly affect the endocrine system and influence ovarian response, oocyte quality, or endometrial receptivity. In this review, we include letrozole (LTZ) and clomiphene citrate (CC) as hormonal add-ons, although they are more commonly defined as ovulation-inducing agents. We included only RCTs that allocated women with POR, according to Bologna criteria [23], undergoing ART to at least two different OS protocols with the treatment arm including at least one hormonal add-on. We chose to use the Bologna criteria to strictly limit the inclusion criteria of patients with POR in the network meta-analysis. Considering the recent introduction but the paucity of studies adopting exclusively or predominantly the POISEDON criteria, we opted to exclusively use the Bologna criteria in the present analysis to ensure greater homogeneity of the population, significantly reducing clinical and methodological variability and thus increasing the reliability and generalizability of the results thanks to their validation and consolidation in a wider amount of RCTs.

Control arms consisted of women undergoing the same OS protocol without the hormonal add-ons.

The exclusion criteria were the following: studies including different OS protocols between treatment and control groups, studies with women not matching the Bologna criteria [23] and studies evaluating non-hormonal add-ons defined as additional treatments that improve metabolic, immunologic, and supportive factors without directly modifying hormonal balance.

## Data extraction

The extraction forms were made especially for this network meta-analysis.

The nation, study design, study type, inclusion and exclusion criteria, study period, location, were extracted from each study. For each group (OS + add-ons and OS without add-ons) the following study characteristics were gathered in order to characterize the included studies: factors such as the number of women, the women's age, body mass index (BMI), the type and duration of her infertility, the AFC, the AMH, day-3 FSH, the number of previous failed fertility treatments, the cause of infertility besides poor ovarian response, the method of diagnosis, the characteristics of IVF/ICSI, the protocol for OS, the duration of the stimulation, the total dosage of gonadotropins used during the OS, the cancellation rate, the number of retrieved and metaphase

II (MII) oocytes, the rates of fertilization, the clinical pregnancy rate (CPR) and the LBR.

Each abstract was examined and categorized independently by two authors (A.E. and V.A.). In order to agree on possible application, the same two writers carefully read the texts of the selected studies and independently gathered pertinent information about the research characteristics and the noteworthy findings.

After discussing each contradiction with the other three authors (J.C.C.F., A.F.R. and B.M.R.), the reviewers came to a consensus. Unpublished data were acquired by contacting the original study authors directly when the study methods specified that additional outcome data were collected.

## Assessment of risk of bias

The risk of bias for the included RCTs was assessed using the Cochrane Risk of Bias Tool version 2 (RoB 2.0) [26]. This tool categorizes the risk of bias in research into five areas: the randomization process, deviations from intended interventions, missing outcome data, outcome evaluation, and choice of reported result. Three risk levels are evaluated for every domain: “low risk”, “some concerns” or “high risk”.

Three authors (A.E., V.A. and G.R.) independently evaluated the risk of bias assessment. The dispute was settled after concealment with J.C.C.F., A.F.R. and A.B.G.

We examined the feasibility and comparability of baseline patient characteristics, the reported results, and the registration of trials before the recruitment of the first patient (for RCTs that began less than 15 years ago) to further assess the reliability of the studies. Additionally, we examined each study's compliance with the CONSORT declaration and any believable retractions or expressions of concern using the PubMed and RetractionWatch.org databases. Furthermore, the Confidence in Network Meta-Analysis framework (CINeMA) criteria were used to evaluate the certainty of the evidence [27]. Publication bias was assessed using funnel plots and Egger's test for each outcome reported in at least 10 trials.

## Outcomes

The primary outcome of the present network meta-analysis was the LBR, where a live birth was defined according to the International Glossary on Infertility and Fertility Care [28] as the complete expulsion or removal of a fetus from a woman after at least 22 weeks' gestation, which, when separated, manifests vital signs.

Secondary outcomes were the CPR, defined as pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy [28]; total dosage of gonadotropins used during the OS;

duration in days of the OS; the serum estrogen levels at the day of trigger with the human chorionic gonadotropin (hCG) or the agonist of the GnRH; the number of oocytes retrieved; the number of MII oocytes retrieved; the fertilization rate, defined as the number of fertilized oocytes on the total number of oocytes; the cancellation rate defined as the number of cycles cancelled due to ultrasonographic non-response to gonadotropin administration or absence of oocytes obtained out of the number of oocyte retrievals.

## Data synthesis

All data analysis and graphical representations were done using STATA version 14.1 (StataCorp, College Station, TX).

The network assumption of overall consistency was statistically confirmed for every meaningful result using the `<network meta consistency>` command. The local test on loop inconsistencies was then carried out using the Separating Indirect from Direct Evidence (SIDE) procedure with the command `<network sidesplit all>`. When no discrepancy between the global and local testing findings was found, the consistency assumption was accepted. The study's direct and indirect comparisons would undoubtedly yield pertinent results in this case, as the consistency model demonstrated that any differences in the results were only attributable to chance mistakes and the effect of the intervention. The summary measurements were presented as odds ratios (OR) for categorical variables and standardized mean differences (SMD) for continuous variables with 95% confidence intervals (CI) using the Der Simonian and Laird random effects model. A Higgins  $I^2$  score higher than 25% suggested the possibility of heterogeneity. To evaluate the efficacy of the different hormonal add-ons and rank the therapies to determine which was statistically better, a forest plot and an interval plot together with a Surface Under the Cumulative Ranking curve Area [SUCRA] ranking plot were made for each outcome under study.

## Results

A total of 7327 studies were initially identified using database searches. Of those, 1267 were removed as duplicates. After title and abstract screening, 5962 papers were subsequently removed (Fig. 1). Ninety-eight papers underwent Full-text assessment, of which 36 studies [10, 18–20, 29–59] were excluded for not having an appropriate hormonal add-on, 13 studies [14, 15, 60–70] for not respecting the POR definition according to Bologna criteria [23], 11 studies [9, 71–80] were excluded for inappropriate control group, 8 studies for not being registered in appropriate RCT repositories, 3 studies [81–83] for being registered after enrollment of the first patient, 2 studies [84, 85] for being

non-randomized, 1 study [86] for having an expression of concern, 1 study [87] for being retracted, and 1 study [88] for untrustworthiness for the criteria mentioned above (Supplementary Table 1) (Fig. 1).

Therefore, 22 studies [12, 13, 16, 17, 89–106] were included in the systematic review and network meta-analysis (Fig. 1).

The potential benefits of the following protocols with hormonal add-ons were analyzed: addition of LTZ [16, 95, 97], addition of CC [17, 98, 100], addition of recombinant luteinizing hormone (rLH) [94, 102, 104], pretreatment with estrogen [13], pretreatment with dehydroepiandrosterone (DHEA) [92, 103, 105, 106], pretreatment with testosterone [89, 91, 93, 99, 101], and addition of human growth hormone (GH) [12, 90, 96].

## Study characteristics

The main characteristics of the included studies are summarized in Table 1, and the baseline patients' characteristics are presented in Table 2.

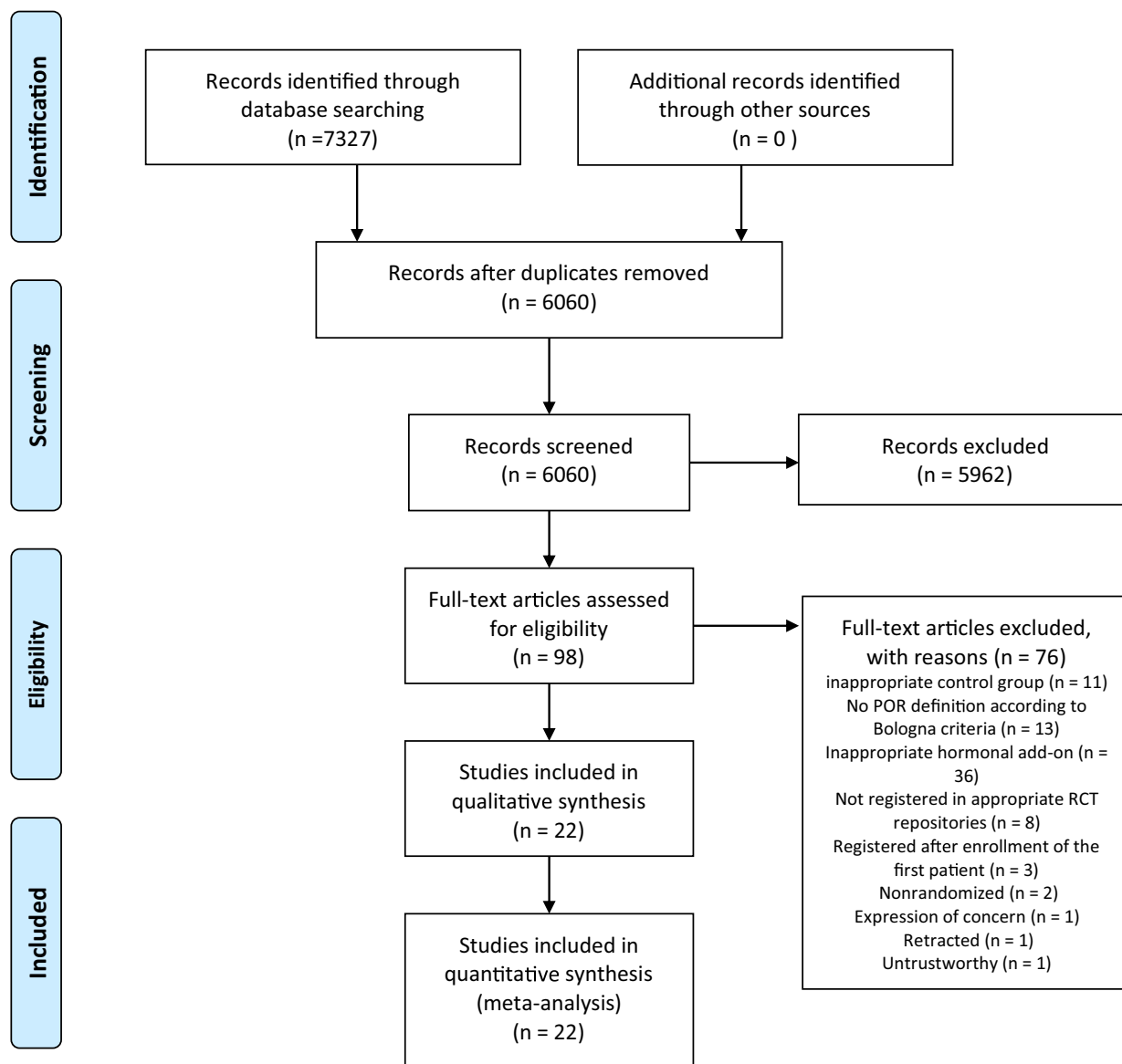
Among the 22 included studies, all were RCTs [12, 13, 16, 17, 89–106]. Of these, 5 studies [13, 92, 95, 103, 105] were from China, 3 studies [89, 97, 99] were from Iran, 2 studies [16, 102] were from Turkey, 2 studies were from Greece [91, 100], 2 studies were from Egypt [90, 96], 1 study was from Denmark [94], 1 study was from Italy [98], 1 study was from Spain [101], 1 study was from Switzerland [17], 1 study was from Australia [12], 1 study was from Hong Kong [106], 1 study was from Israel [104], and 1 study was from Vietnam [93]. A total of 4131 infertile patients with a diagnosis of POR according to Bologna criteria [23] were included in this analysis; of these, 2069 patients underwent OS without hormonal add-ons and 2062 patients received hormonal additions in the context of OS. Two hundred ten patients were given LTZ as a hormonal add-on during the OS [16, 95, 97], 214 patients were given CC during the OS [17, 98, 100], 509 patients were given rLH during the OS [94, 102, 104], 276 patients were pre-treated with estrogen before the OS [13], 493 patients were pre-treated with DHEA before the OS [92, 103, 105, 106], 167 patients were pre-treated with testosterone before the OS [89, 91, 93, 99, 101], and 200 patients were given GH during the OS [12, 90, 96].

## Risk of bias of included studies

Figure S1a shows the quality of the methodology used in the 22 included RCTs, and Figure S1b shows a percentage-based assessment of the methodological quality of these trials. Overall, one RCT [90] was deemed at high risk of bias, six RCTs [89, 93, 98–101] were judged as having



## PRISMA 2009 Flow Diagram



**Fig. 1** PRISMA flowchart of included studies in systematic review and network meta-analysis

“some concerns” and 15 RCTs [12, 13, 16, 17, 92, 94–97, 102–106] were considered at low risk, respectively.

In detail, nine trials [90–92, 95, 98–100, 105, 106] had some or severe concerns for biases arising from the randomization process (Figure S1a-b). No study was deemed at high risk for bias due to deviations from intended interventions or missing data. On the contrary, there was a high risk of bias in the measurement of the outcomes in three

studies [89, 93, 101]. Conversely, the vast majority of RCTs were at low risk for selection biases (Figure S1a-b).

All the included RCTs [12, 13, 16, 17, 70, 89–105] were registered in valid prospective repositories prior to the enrollment of the first woman.

Certainty of evidence according to CINeMA criteria ranged from very low to low, principally due to major concerns in the imprecision and incoherence domains, which

**Table 1** Main characteristics of studies included in network meta-analysis

| Study             | Primary outcome(s)                                      | Add-ons                        | Inclusion criteria                              | Exclusion criteria                                                                                                                                                                                                                         | Nationality | Trial ID             |
|-------------------|---------------------------------------------------------|--------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|----------------------|
| Aflatoonain, 2022 | Clinical and biochemical pregnancy rates                | Addition of testosterone       | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Endocrine disorders</li> <li>• Intrauterine disorders</li> <li>• Azoospermia</li> <li>• Severe endometriosis</li> </ul>                                                                           | Iran        | IRCT20180818040828N1 |
| Bastu, 2016       | Number of oocytes retrieved                             | Addition of letrozole          | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• History of chemotherapy/radiotherapy</li> <li>• ovarian surgery</li> <li>• DHEA/testosterone use</li> </ul>                                                                                       | Turkey      | NCT02293668          |
| Bayoumi, 2016     | Mean numbers of mature oocytes retrieved and fertilized | Addition of Growth Hormone     | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• FSH &gt; 20 IU/L, previous ovarian surgery</li> <li>• Non-POR infertility causes</li> <li>• PCOS</li> <li>• Endocrine disorders</li> <li>• Male factor infertility</li> </ul>                     | Egypt       | NCT02185326          |
| Bosdou, 2016      | Number of COCs retrieved                                | Addition of testosterone       | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• BMI <math>\geq 32</math> kg/m<sup>2</sup></li> <li>• Endometriosis stage III-IV</li> <li>• Ovarian surgery</li> <li>• Endocrine/metabolic disorders</li> <li>• Use of testicular sperm</li> </ul> | Greece      | NCT01961336          |
| Fu, 2017          | High-quality embryo yield                               | Addition of DHEA               | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Endometriosis</li> <li>• History of chemotherapy</li> <li>• Ovarian surgery</li> <li>• Prior DHEA use</li> </ul>                                                                                  | China       | NCT02866253          |
| Hoang, 2021       | Number of mature oocytes retrieved                      | Addition of testosterone       | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• POI</li> <li>• Male factor infertility</li> <li>• Severe endometriosis</li> <li>• Thyroid/liver/kidney disease</li> <li>• Abnormal genitalia</li> </ul>                                           | Vietnamese  | NCT04602143          |
| Humaidan, 2017    | Number of oocytes retrieved                             | Addition of rLH                | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Women aged <math>\geq 41</math> years</li> <li>• POI</li> <li>• Preimplantation genetic screening</li> </ul>                                                                                      | Denmark     | NCT02047227          |
| Liu, 2020         | Cumulative Live Birth Rate                              | Addition of Letrozole          | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Repeated IVF failure</li> <li>• Severe endometriosis</li> <li>• PCOS</li> </ul>                                                                                                                   | China       | ChiCTR-TRC-13003454  |
| Moffat, 2021      | Number of oocytes retrieved                             | Addition of Clomiphene Citrate | Poor ovarian response based on Bologna criteria | N/D                                                                                                                                                                                                                                        | Switzerland | NCT01577472          |

**Table 1** (continued)

| Study          | Primary outcome(s)                                        | Add-ons                        | Inclusion criteria                              | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Nationality | Trial ID            |
|----------------|-----------------------------------------------------------|--------------------------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|---------------------|
| Mohammad, 2020 | Clinical pregnancy rate                                   | Addition of Growth Hormone     | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Known medical disease (e.g. severe hypertension or hepatic disease)</li> <li>• History of altered karyotype in one or both partners</li> <li>• History of chronic autoimmune or metabolic diseases</li> <li>• Presence of endocrinopathies</li> <li>• Male factor infertility</li> </ul>                                                                                                                                                                                                      | Egypt       | NCT03759301         |
| Moini, 2019    | number of oocytes retrieved and the number of oocytes MII | Addition of Letrozole          | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• POI</li> <li>• Donor/recipient treatments</li> <li>• Metabolic or endocrine disorders including hyperprolactinemia and hypothyroidism</li> <li>• Endometriosis</li> <li>• Body mass index (BMI) &gt; 30 kg/m<sup>2</sup></li> <li>• Azospermic male partner</li> </ul>                                                                                                                                                                                                                        | Iran        | IRCT201701291952N8  |
| Norman, 2019   | Live birth rate                                           | Addition of Growth Hormone     | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Any clinically significant systemic disease,</li> <li>• History of radiotherapy or chemotherapy</li> <li>• Any current history of malignant disease</li> <li>• Pituitary or hypothalamic disease</li> <li>• Current ovarian cyst &gt; 3 cm</li> <li>• Any chronic infectious diseases</li> <li>• PCOS</li> <li>• Unexplained menstrual bleeding</li> <li>• Preimplantation genetic testing</li> <li>• Smokers</li> <li>• Using steroids, DHEA or prednisolone in the last 3 months</li> </ul> | Australia   | ACTRN12609001060235 |
| Ragni, 2012    | delivery rate per started cycle                           | Addition of Clomiphene Citrate | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Number of previous IVF cycles ≥ 3</li> <li>• Cycles requiring the use of spermatozoa from MESA-TESE procedures</li> </ul>                                                                                                                                                                                                                                                                                                                                                                     | Italy       | NCT01389713         |

**Table 1** (continued)

| Study              | Primary outcome(s)                                                                     | Add-ons                        | Inclusion criteria                              | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                        | Nationality | Trial ID                      |
|--------------------|----------------------------------------------------------------------------------------|--------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------------------------|
| Saharkhiz, 2018    | mean number of oocytes and embryo                                                      | Addition of Testosterone       | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Presence of endocrine disorders (thyroid, prolactin, etc.)</li> <li>• Presence of endometrioma and any history of surgery on the ovaries</li> <li>• Reluctance to participate in the project</li> <li>• New clinical conditions or a change in a treatment procedure</li> <li>• Sensitivity to testosterone gel</li> </ul>                       | Iran        | IR.SBMU.RETECH. REC.1395.1007 |
| Siristatidis, 2017 | Number of Cumulus- oocyte complexes retrieved                                          | Addition of Clomiphene Citrate | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Basal level of FSH at day 3 of menstrual cycle &gt; 20 IU/l)</li> <li>• Increased BMI &gt; 35 kg/m2</li> <li>• History of endocrine or metabolic disorders</li> <li>• History of ovarian cystectomy or oophorectomy</li> <li>• Severe endometriosis</li> <li>• Severe azoospermia</li> </ul>                                                     | Greece      | NCT01319708                   |
| Subirà, 2021       | Number of MII oocytes                                                                  | Addition of Testosterone       | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Non-corrected uterine malformations, endometrial pathology</li> <li>• Severe male factor (motile sperm count &lt; 1)</li> <li>• Hydrosalpinx</li> <li>• Premature ovarian insufficiency, body mass index (BMI) &gt; 35 kg/m2</li> <li>• Androgen treatment within the last 3 months</li> <li>• Known allergy to the experimental drug</li> </ul> | Spain       | NCT03378713                   |
| Tosun, 2021        | GCs apoptosis rate in terms of viability, early apoptosis, late apoptosis and necrosis | Addition of rLH                | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Male factor</li> <li>• POI</li> <li>• Need of preimplantation genetic testing</li> </ul>                                                                                                                                                                                                                                                         | Turkey      | NCT03527823                   |

**Table 1** (continued)

| Study        | Primary outcome(s)                                                | Add-ons          | Inclusion criteria                              | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Nationality | Trial ID            |
|--------------|-------------------------------------------------------------------|------------------|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|---------------------|
| Wang, 2022   | Live birth rate                                                   | Addition of DHEA | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Women that failed to obtain clinical pregnancy after three or more IVF/ICSI cycles</li> <li>• History of two or more recurrent pregnancy losses</li> <li>• Diagnosis of uterine abnormalities using hysteroscopy</li> <li>• Diagnosed with hydrosalpinx using hystero salpingography</li> <li>• History of chemotherapy with cytotoxic agents</li> <li>• History of pelvic radiotherapy</li> <li>• Epilepsy;</li> <li>• Treatment with DHEA before study enrolment</li> <li>• Allergy to DHEA</li> </ul> | China       | ChiCTR-IPR-15006909 |
| Yeung, 2014  | AFC after 12 weeks of treatment                                   | Addition of DHEA | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• History of ovarian cystectomy or oophorectomy</li> <li>• History of cytotoxic chemotherapy</li> <li>• History of pelvic irradiation</li> <li>• History of taking testosterone or DHEA supplementation</li> </ul>                                                                                                                                                                                                                                                                                         | Hong Kong   | NCT01915186         |
| Younis, 2016 | maximal serum E2 level on the day of hCG administration           | Addition of rLH  | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Severe endometriosis</li> <li>• Uncontrolled thyroid disease</li> <li>• Diabetes mellitus</li> <li>• Significant hyperprolactinaemia</li> <li>• Hypogonadotropic hypogonadism</li> <li>• More than four previous unsuccessful ART attempts</li> </ul>                                                                                                                                                                                                                                                    | Israel      | NCT01016210         |
| Zhang, 2014  | follicular fluid BMP-15, GDF-9 and serum AMH, FSH, E <sub>2</sub> | Addition of DHEA | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• History of ovarian cystectomy or oophorectomy</li> <li>• Diagnosis of endometriosis</li> <li>• History of DHEA supplementation or hormonal replacement therapy</li> </ul>                                                                                                                                                                                                                                                                                                                                | China       | ChiCTR-TRC-14005002 |

**Table 1** (continued)

| Study       | Primary outcome(s)                | Add-ons              | Inclusion criteria                              | Exclusion criteria                                                                                                                                                                                                                                                                                                                                                                                                | Nationality | Trial ID    |
|-------------|-----------------------------------|----------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|-------------|
| Zhang, 2022 | total number of retrieved oocytes | Addition of Estrogen | Poor ovarian response based on Bologna criteria | <ul style="list-style-type: none"> <li>• Preimplantation genetic testing cycle</li> <li>• Donor cycle</li> <li>• Family history of thrombosis or a high risk of thrombosis</li> <li>• Previous history of hypertension or hypertension</li> <li>• Hyperlipidemia</li> <li>• Estrogen-dependent breast disease</li> <li>• Cervical biopsy showing cervical intraepithelial neoplasia grade III or above</li> </ul> | China       | NCT03300518 |

*PCOS* polycystic ovary syndrome, *POI* premature ovarian insufficiency, *BMI* body mass index, *FSH* follicle-stimulating hormone, *rLH* recombinant luteinizing hormone, *DHEA* Dehydroepiandrosterone, *MII* metaphase II, *MESA* microsurgical epididymal sperm aspiration, *TESE* testicular epididymal sperm extraction, *AMH* anti-Müllerian hormone, *BMP*–15 bone morphogenetic protein-15, *GDF*-9 growth differentiation factor-9, *E2* estradiol

were related to the low number of direct comparisons available (Supplementary Table 2). Potential publication bias was visually displayed in Figure S2a–g.

## Synthesis of results

### Live birth rate

Eight studies [12, 17, 91, 94, 95, 98, 103, 106] reported on the LBR. The following add-ons were directly compared with controls and indirectly compared among them: LTZ, CC, rLH, DHEA, testosterone, and GH. The network map for the outcome is shown in Fig. 2a. The general analysis for inconsistency revealed no degrees of inconsistency. As outlined in the forest and interval plots (Fig. 2b, c), there were no significant differences among all the evaluated add-ons (very low evidence) (Supplementary Table 2).

According to SUCRA ranking of available choices, testosterone (SUCRA = 34.0%) and GH (SUCRA = 23.9%) had the highest probability of being ranked treatment of choice (Fig. 2d). Publication bias for the LBR was not assessed since less than 10 studies reported the outcome.

### Clinical pregnancy rate

Nineteen RCTs [13, 16, 17, 89–99, 101–105] estimated the CPR. All the included interventions (LTZ, CC, rLH, estrogen, DHEA, testosterone and GH) were directly and indirectly compared. The network of direct comparisons is shown in Fig. 3a. No source of inconsistency was notable. The forest and interval plots displayed in Fig. 3b and c show the results of direct and indirect comparisons for CPR. GH was more efficacious than adding estrogens (OR 3.46 [95% CI 1.59 to 7.53]; low evidence) while adding estrogens was less efficacious than controls (OR 0.49 [95% CI 0.29 to 0.84]; low evidence) and DHEA (OR 0.46 [95% CI 0.24 to 0.89]; very low evidence). Similarly, adding rLH was significantly less efficacious than GH (OR 0.50 [95% CI 0.26 to 0.96]; very low evidence). No significant differences were retrieved among the protocol comparisons (low to very low evidence) (Supplementary Table 2) (Fig. 3c). According to the SUCRA ranking, GH (SUCRA = 46.3%) and testosterone (SUCRA = 44.6%) had increased chances of being ranked first among the hormonal add-ons (Fig. 3d). Publication bias was not apparent in both Egger’s test ( $p = 0.329$ ) and funnel plot analysis (Figure S2a).

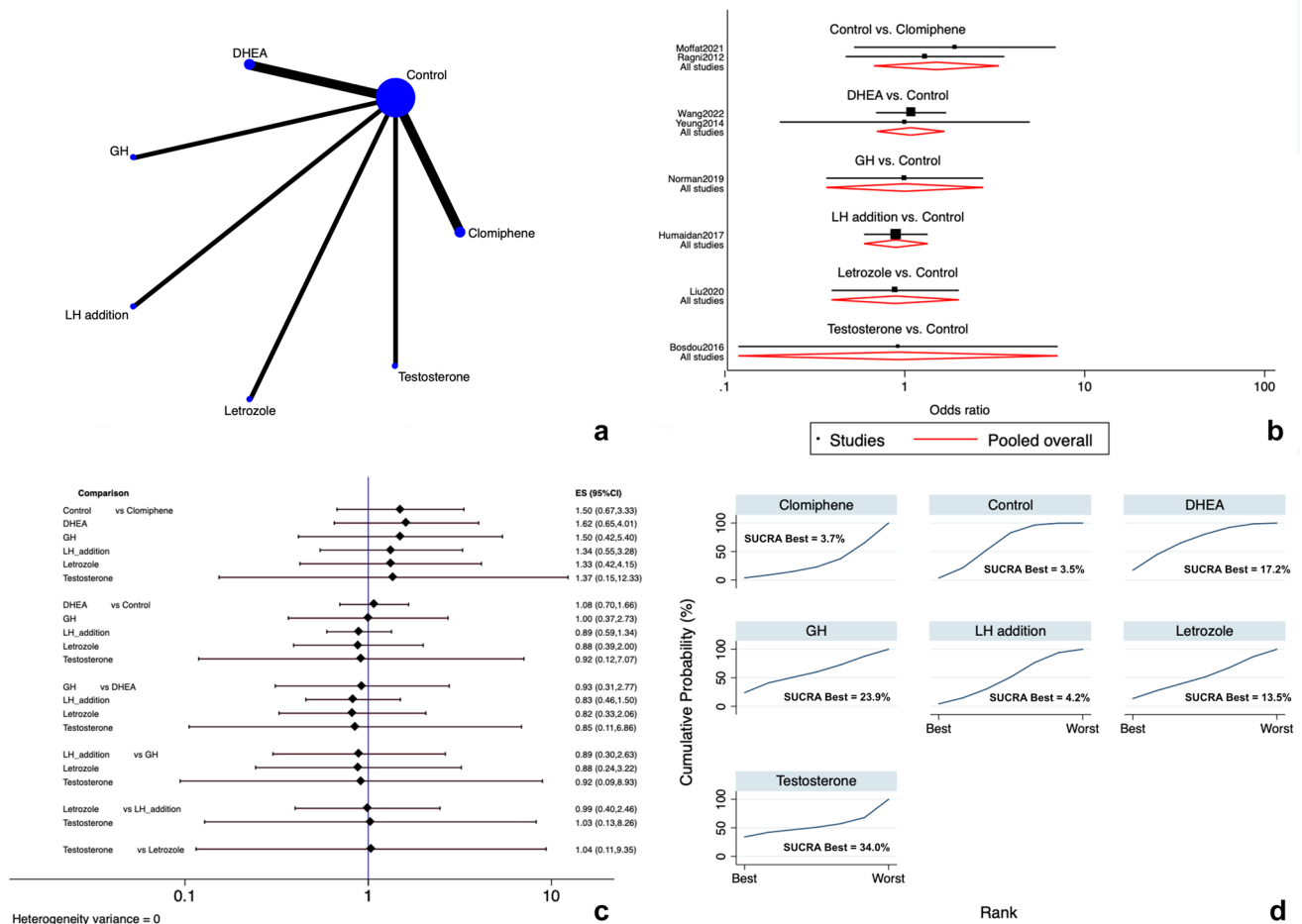
### Number of overall oocytes and MII oocytes retrieved

Regarding the overall mean number of retrieved oocytes, reported in all the 22 studies [12, 13, 16, 17, 89–106], all the seven hormonal add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone, and GH) were directly and indirectly

**Table 2** Baseline patient characteristics

| Study              | Group                                   | Age<br>(mean $\pm$ SD), years | AMH<br>(mean $\pm$ SD), ng/ml | AFC<br>(mean $\pm$ SD), <i>n</i> | Previously cycles<br>with POR |
|--------------------|-----------------------------------------|-------------------------------|-------------------------------|----------------------------------|-------------------------------|
| Aflatoonain, 2022  | Control                                 | 36.21 $\pm$ 3.01              | 0.82 $\pm$ 0.08               | 5.54 $\pm$ 2.13                  | N/D                           |
|                    | Addition of Testosterone                | 35.38 $\pm$ 5.23              | 0.88 $\pm$ 0.08               | 5.34 $\pm$ 1.69                  | N/D                           |
| Bastu, 2016        | Control (450 IU)                        | 36.94 $\pm$ 3.33              | 0.55 $\pm$ 0.35               | 4                                | N/D                           |
|                    | Control (300 IU)                        | 35.00 $\pm$ 3.10              | 0.71 $\pm$ 0.28               | 3                                | N/D                           |
|                    | Addition of Letrozole                   | 37.52 $\pm$ 4.06              | 0.64 $\pm$ 0.41               | 4                                | N/D                           |
| Bayoumi, 2016      | Control                                 | 34.8 $\pm$ 5.6                | 0.5 $\pm$ 0.2                 | 5.9 $\pm$ 1.7                    | 2.7 $\pm$ 1.5                 |
|                    | Addition of Growth Hormone              | 34.9 $\pm$ 4.8                | 0.4 $\pm$ 0.2                 | 5.9 $\pm$ 1.6                    | 2.4 $\pm$ 1.5                 |
| Bosdou, 2016       | Control                                 | 42.5 $\pm$ 4.0                | 0.65 $\pm$ 0.78               | 5.0 $\pm$ 3.0                    | N/D                           |
|                    | Addition of Growth Hormone              | 41.5 $\pm$ 3.0                | 0.97 $\pm$ 0.65               | 6.0 $\pm$ 4.0                    | N/D                           |
| Fu, 2017           | Control                                 | 36.8 $\pm$ 4.3                | 1.00 $\pm$ 0.77               | 3.57 $\pm$ 1.16                  | N/D                           |
|                    | Addition of DHEA                        | 37.4 $\pm$ 3.6                | 1.01 $\pm$ 0.61               | 3.74 $\pm$ 1.43                  | N/D                           |
| Hoang, 2021        | Control                                 | 36.4 $\pm$ 5.2                | 1.0 $\pm$ 0.3                 | 5.9 $\pm$ 3.6                    | N/D                           |
|                    | Addition of Testosterone<br>(4 weeks)   | 35.9 $\pm$ 5.4                | 1.0 $\pm$ 0.4                 | 5.4 $\pm$ 2.6                    | N/D                           |
|                    | Addition of Testosterone<br>(6 weeks)   | 36.2 $\pm$ 4.7                | 0.9 $\pm$ 0.4                 | 4.9 $\pm$ 1.9                    | N/D                           |
| Humaidan, 2017     | Control                                 | 38.3 $\pm$ 3.0                | 0.60 $\pm$ 0.48               | 4.8 $\pm$ 2.2                    | 84.3%                         |
|                    | Addition of rLH                         | 38.3 $\pm$ 2.9                | 0.58 $\pm$ 0.50               | 4.9 $\pm$ 2.3                    | 82.0%                         |
| Liu, 2020          | Control                                 | 39 $\pm$ 1.5                  | 0.8 $\pm$ 0.1                 | 5 $\pm$ 0.33                     | N/D                           |
|                    | Addition of Letrozole                   | 37 $\pm$ 1.17                 | 0.6 $\pm$ 0.1                 | 4 $\pm$ 0.33                     | N/D                           |
| Moffat, 2021       | Control (450 IU)                        | 38.8 $\pm$ 1.3                | 0.78 $\pm$ 0.15               | 5.5 $\pm$ 1.2                    | N/D                           |
|                    | Control (150 IU)                        | 39.9 $\pm$ 0.6                | 0.66 $\pm$ 0.09               | 6.0 $\pm$ 1.0                    | N/D                           |
|                    | Addition of Clomiphene Citrate (450 IU) | 38.4 $\pm$ 1.0                | 0.64 $\pm$ 0.12               | 6.0 $\pm$ 0.5                    | N/D                           |
|                    | Addition of Clomiphene Citrate (150 IU) | 39.9 $\pm$ 1.2                | 0.84 $\pm$ 0.14               | 6.5 $\pm$ 0.8                    | N/D                           |
| Mohammad, 2020     | Control                                 | 34.7 $\pm$ 2.0                | 0.69 $\pm$ 0.16               | 5.8 $\pm$ 1.8                    | 2.6 $\pm$ 0.3                 |
|                    | Addition of Growth Hormone              | 34.3 $\pm$ 2.4                | 0.72 $\pm$ 0.09               | 5.7 $\pm$ 1.8                    | 2.5 $\pm$ 0.2                 |
| Moini, 2019        | Control                                 | 36.5 $\pm$ 3.7                | 0.73 $\pm$ 0.31               | 4.8 $\pm$ 1.5                    | 1.1 $\pm$ 0.6                 |
|                    | Addition of Letrozole                   | 37.2 $\pm$ 3.3                | 0.75 $\pm$ 0.35               | 5.1 $\pm$ 2.0                    | 1.0 $\pm$ 0.9                 |
| Norman, 2019       | Control                                 | N/D                           | N/D                           | N/D                              | N/D                           |
|                    | Addition of Growth Hormone              | N/D                           | N/D                           | N/D                              | N/D                           |
| Ragni, 2012        | Control                                 | 38.5 $\pm$ 3.1                | 0.76 $\pm$ 1.0                | 3.9 $\pm$ 2.6                    | N/D                           |
|                    | Addition of Clomiphene Citrate          | 38.6 $\pm$ 2.9                | 0.71 $\pm$ 1.0                | 3.4 $\pm$ 2.5                    | N/D                           |
| Saharkhiz, 2018    | Control                                 | 39.7 $\pm$ 3.3                | 0.6 $\pm$ 0.5                 | 3.1 $\pm$ 2.6                    | N/D                           |
|                    | Addition of Testosterone                | 41.0 $\pm$ 3.8                | 0.5 $\pm$ 0.6                 | 2.2 $\pm$ 0.6                    | N/D                           |
| Siristatidis, 2017 | Control                                 | 40.0 $\pm$ 3.0                | N/D                           | 4.0 $\pm$ 2.2                    | N/D                           |
|                    | Addition of Clomiphene Citrate          | 39.0 $\pm$ 2.7                | N/D                           | 3.0 $\pm$ 1.3                    | N/D                           |
| Subirà, 2021       | Control                                 | 35.2 $\pm$ 3.0                | 0.5 $\pm$ 0.3                 | N/D                              | 0.8 $\pm$ 0.4                 |
|                    | Addition of Testosterone (short)        | 37.1 $\pm$ 3.3                | 0.74 $\pm$ 0.41               | N/D                              | 0.9 $\pm$ 0.7                 |
|                    | Addition of Testosterone (long)         | 36.9 $\pm$ 2.5                | 0.60 $\pm$ 0.32               | N/D                              | 0.9 $\pm$ 0.6                 |
| Tosun, 2021        | Control                                 | 34.4 $\pm$ 2.6                | 0.3 $\pm$ 0.2                 | 5.5 $\pm$ 1.4                    | N/D                           |
|                    | Addition of rLH                         | 35.6 $\pm$ 4.6                | 0.4 $\pm$ 0.3                 | 4.6 $\pm$ 1.5                    | N/D                           |
| Wang, 2022         | Control                                 | 39.5 $\pm$ 4.4                | 0.49 $\pm$ 0.11               | 4.9 $\pm$ 2.8                    | N/D                           |
|                    | Addition of DHEA                        | 39.0 $\pm$ 4.6                | 0.55 $\pm$ 0.10               | 5.1 $\pm$ 2.2                    | N/D                           |
| Yeung, 2015        | Control                                 | 37.0 $\pm$ 0.8                | 0.64 $\pm$ 0.17               | 3.0 $\pm$ 0.3                    | N/D                           |
|                    | Addition of DHEA                        | 36.0 $\pm$ 0.8                | 0.75 $\pm$ 0.19               | 4.0 $\pm$ 0.3                    | N/D                           |
| Younis, 2016       | Control                                 | 38.6 $\pm$ 3.7                | N/D                           | 6.6 $\pm$ 2.5                    | N/D                           |
|                    | Addition of rLH                         | 38.9 $\pm$ 2.8                | N/D                           | 6.0 $\pm$ 3.2                    | N/D                           |
| Zhang, 2014        | Control                                 | 37.4 $\pm$ 4.3                | 1.12 $\pm$ 0.84               | 3.0 $\pm$ 1.4                    | N/D                           |
|                    | Addition of DHEA                        | 37.2 $\pm$ 5.2                | 1.01 $\pm$ 0.77               | 2.9 $\pm$ 1.4                    | N/D                           |
| Zhang, 2022        | Control                                 | 40.2 $\pm$ 3.7                | 1.00 $\pm$ 0.80               | 5.7 $\pm$ 3.0                    | N/D                           |
|                    | Addition of Estrogen                    | 40.4 $\pm$ 4.1                | 1.00 $\pm$ 0.80               | 5.4 $\pm$ 2.9                    | N/D                           |

*POR* poor ovarian response, *BMI* body mass index, *POR* poor ovarian response, *rLH* recombinant luteinizing hormone, *DHEA* Dehydroepiandrosterone, *AMH* anti-Müllerian hormone, *IU* international unit



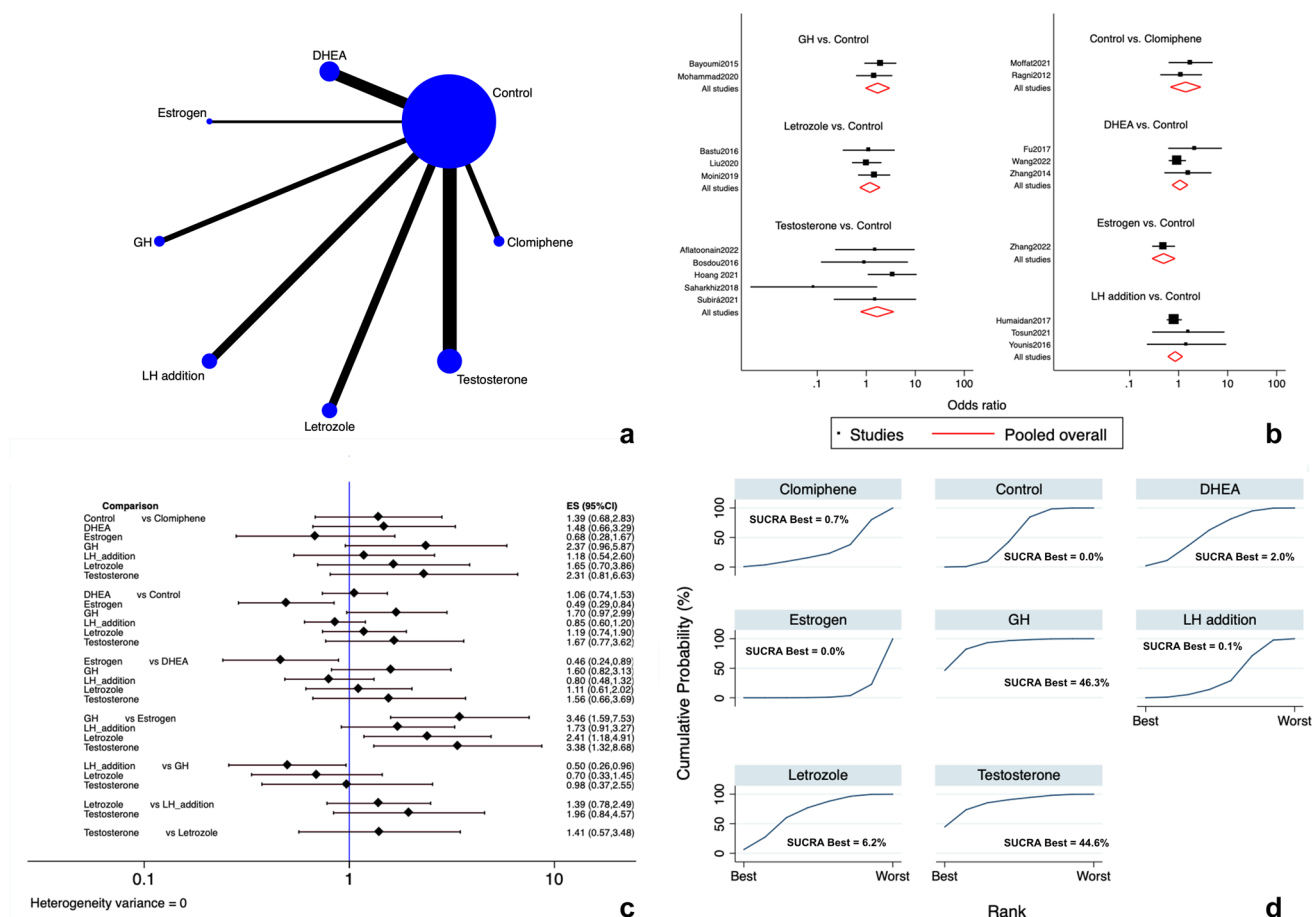
**Fig. 2** Live birth rate. **a** Network of comparisons of interventions analyzed in included studies. **b** Forest plot for the outcome. **c** Interval plot. **d** Ranking plot according to SUCRA analysis

compared (Fig. 4a) without the presence of inconsistency in the general analysis. Forest and interval plots showed that GH was significantly more efficacious than CC (SMD 1.33 [95% CI 0.04 to 2.62]; very low evidence) and controls (SMD 0.93 [95% CI 0.02 to 1.84]; very low evidence) (Fig. 4b, c) with no other significant differences noted (very low evidence) (Supplementary Table 2). SUCRA analysis revealed that GH was likely the treatment of choice for gaining a higher number of retrieved oocytes (SUCRA = 53.2%) (Fig. 4d). Egger's test ( $p = 0.010$ ) and funnel plot analysis (Figure S2e) reported the plausible presence of publication bias, warranting caution in the interpretation of the outcome. The mean number of MII oocytes was available in 17 trials [13, 16, 89–94, 96–98, 100–105] in which all the available hormonal add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone and GH) were compared (Fig. 5a). There were no degrees of inconsistency to report. Among all the add-on strategies, adding GH was more efficacious than CC (SMD 2.28 [95% CI 0.58 to 3.98]; very low evidence) and controls (SMD 1.46

[95% CI 0.26 to 2.66]; very low evidence). No other relevant differences were notable (very low evidence) (Supplementary Table 2) (Fig. 5b, c). According to the SUCRA ranking plot, GH was the add-on with the highest degree of best treatment (SUCRA = 67.9%) (Fig. 5d). Both Egger's test ( $p = 0.110$ ) and funnel plot analysis (Figure S2f) reported no apparent publication bias.

### Fertilization rate

The fertilization rate was reported in 14 studies [13, 16, 70, 89–94, 96–98, 100–105] comparing all the hormonal add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone, and GH) eligible for this network meta-analysis (Figure S3a). No degrees of inconsistency were retrieved in the general analysis. As shown in forest and interval plots (Figure S3b–c), adding estrogens was significantly less efficacious than the control group (OR 0.49 [95% CI 0.29 to 0.84]; low evidence) while GH was significantly more efficacious than estrogen too (OR 3.14 [95% CI 1.50 to 6.57]; low evidence).



**Fig. 3** Clinical pregnancy rate. **a** Network of comparisons of interventions analyzed in included studies. **b** Forest plot for the outcome. **c** Interval plot. **d** Ranking plot according to SUCRA analysis

There were no other significant differences between treatments and controls (very low evidence) (Supplementary Table 2) (Fig. S3c). SUCRA analysis revealed that rLH addition (SUCRA = 37.3%), DHEA (SUCRA = 18.8%) and testosterone (SUCRA = 14.8%) had the highest likelihood of being treatments of choice for raising the fertilization rate (Figure S3d). According to Egger's test ( $p = 0.376$ ) and funnel plot analysis (Figure S2g), there were no apparent issues of publication bias.

### Duration of OS

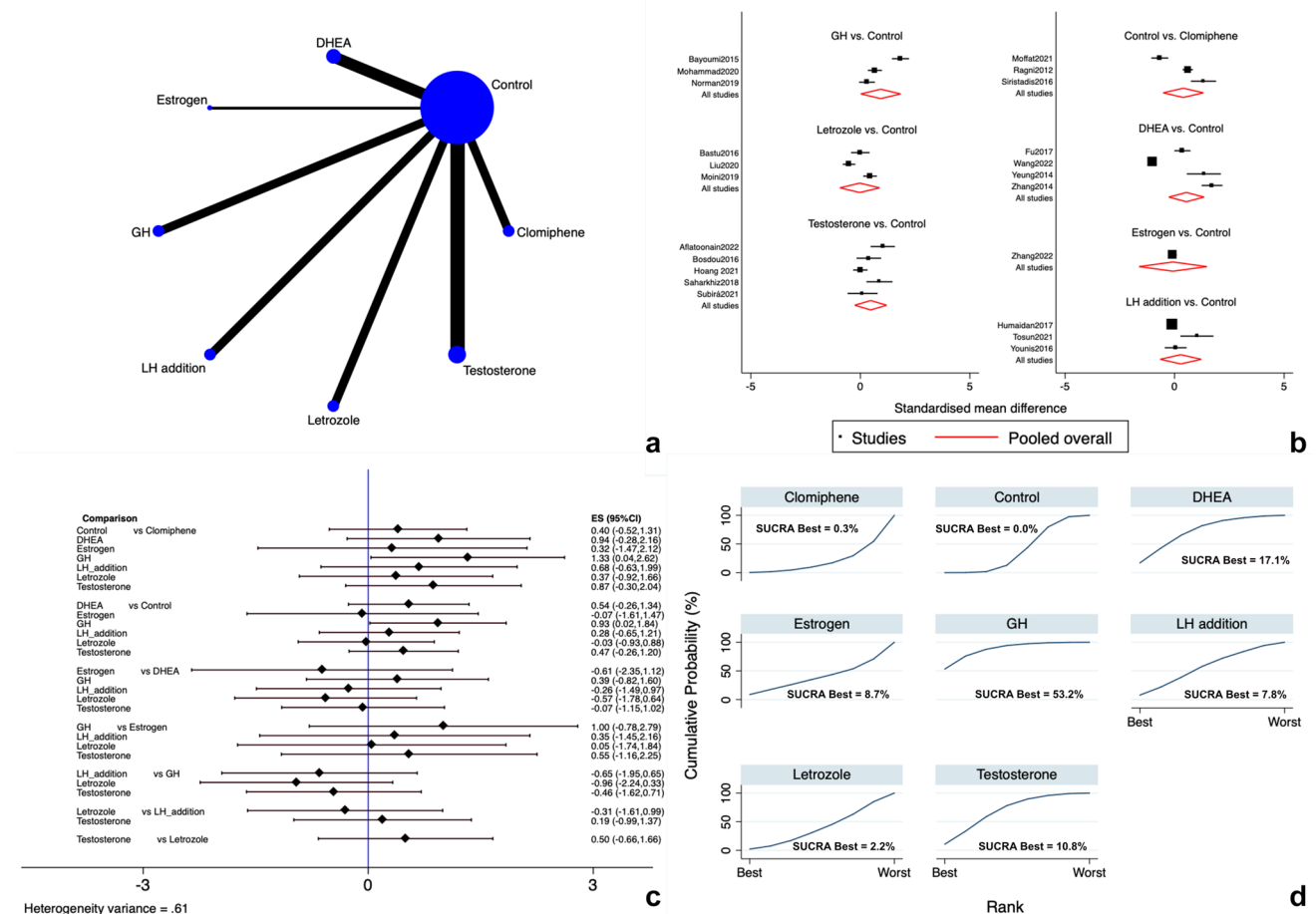
Fifteen studies [12, 13, 16, 17, 90, 91, 93, 95–97, 100–103, 106], directly and indirectly comparing all the add-ons, reported the outcome (Figure S4a). According to forest and interval plots (Figure S4b–c), there were no significant differences among the approaches (very low evidence) (Supplementary Table 2). SUCRA analysis reported that LTZ had increased chances of being the add-on with the shortest OS duration (SUCRA = 52.0%) (Figure S4d). No publication

bias was reported in Egger's test ( $p = 0.423$ ) and funnel plot analysis (Figure S2b).

### Total dose of gonadotropins

Out of 15 studies [12, 13, 16, 17, 70, 90, 91, 93–95, 97, 100, 102, 103, 106] reporting the mean total dose of gonadotropins used during COS for all the hormonal add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone and GH) (Figure S5a), no significant differences were notable (low to very low evidence) (Supplementary Table 2) among treatments except for a significantly smaller number of used gonadotropins with LTZ relative to controls (SMD  $-7.02$  [95% CI  $-12.82$  to  $-1.22$ ]; low evidence) (Figures S5b–c). According to the SUCRA ranking plot, LTZ (SUCRA = 67.0%) had the greatest degree of best treatment for the outcome (Figure S5d).

Publication bias was not apparent in both Egger's test ( $p = 0.339$ ) and funnel plot analysis (Figure S2c).



**Fig. 4** Mean number of retrieved oocytes. **a** Network of comparisons of interventions analyzed in included studies. **b** Forest plot for the outcome. **c** Interval plot. **d** Ranking plot according to SUCRA analysis

### Estrogen levels at trigger day

The outcome was reported in 14 studies [13, 17, 89–93, 95–97, 102–104, 106] in which all the hormone add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone, and GH) were compared (Figure S6a). The consistency analysis showed no source of inconsistency. Figures S6b and S6c show the forest and interval plots, in which estrogen levels were significantly less with the use of LTZ relative to CC (SMD  $-3.47$  [95% CI  $-6.85$  to  $-0.01$ ]; very low evidence), controls (SMD  $-2.42$  [95% CI  $-4.38$  to  $-0.47$ ]; very low evidence) and GH (SMD  $-4.04$  [95% CI  $-6.80$  to  $-1.28$ ]; very low evidence). Similarly, testosterone was more efficacious than LTZ (SMD  $2.83$  [95% CI  $0.31$  to  $5.36$ ]; very low evidence). No other differences were notable (very low evidence) (Supplementary Table 2) (Figure S6c). According to SUCRA analysis, GH (SUCRA = 46.3%) was the add-on with the highest likelihood of best treatment (Figure S6d).

According to Egger's test ( $p = 0.913$ ) and funnel plot analysis (Figure S2d), no publication bias was apparent.

### Cancellation rate

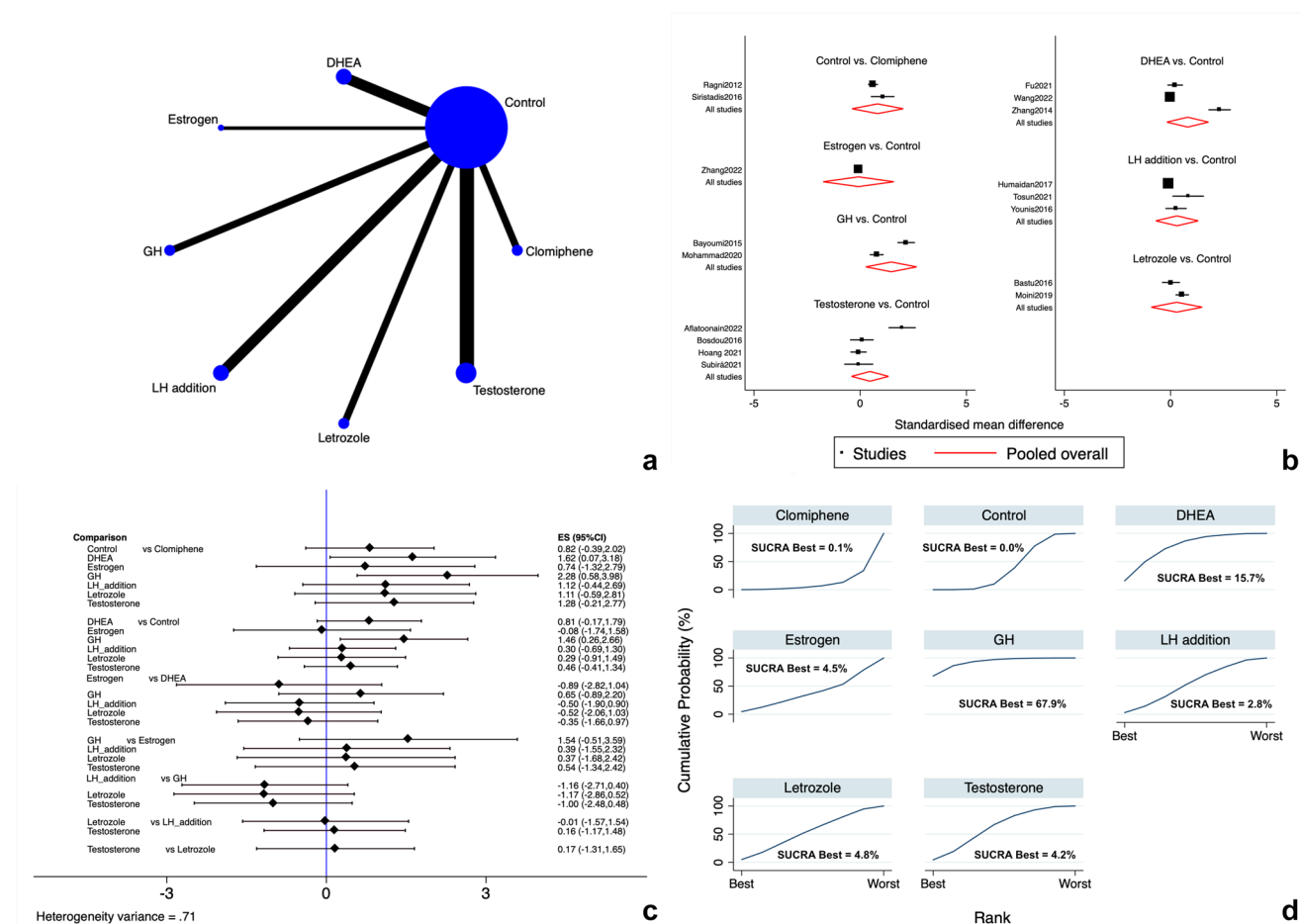
With all the evaluated hormonal add-ons (LTZ, CC, rLH, estrogen, DHEA, testosterone, and GH), eight RCTs [13, 16, 91, 94–96, 98, 101] reported the cancellation rate (Figure S7a). There were zero degrees of inconsistency to report.

According to forest and interval plots (Figure S7b–c), no significant differences among all the add-ons were notable (very low evidence) (Supplementary Table 2). SUCRA analysis revealed that GH (SUCRA = 45.1%) was the most likely best-ranked treatment (Figure S7d). Publication bias was not evaluated since less than 10 studies reported the outcome.

## Discussion

### Principal findings

The aim of this systematic review and network meta-analysis of RCTs was to evaluate the reproductive outcomes of



**Fig. 5** Mean number of M2 oocytes. **a** Network of comparisons of interventions analyzed in included studies. **b** Forest plot for the outcome. **c** Interval plot. **d** Ranking plot according to SUCRA analysis

hormonal add-ons in women with POR undergoing ART. For the LBR, which was our primary outcome, no significant differences were observed between the evaluated interventions; however, testosterone showed the highest probability of improving LBR according to SUCRA analysis. Meanwhile, GH showed the highest SUCRA score for CPR. Moreover, GH also demonstrated better results in terms of total number of retrieved oocytes and mean number of MII oocytes. Finally, LTZ demonstrated benefits in reducing gonadotropin usage and stimulation duration.

### Comparison with existing literature

Several add-ons to OS have been explored in POR women. However, available studies did not ensure their effectiveness. A recent meta-analysis of RCTs concluded that pretreatment with testosterone appears to be related to a better LBR in women with POR [21]. The authors of the study, however, compared not only hormonal add-ons with controls, but also variations in OS protocols including GnRH agonists or

antagonists, different types of gonadotropins, and dual-stimulation regimen. This heterogeneity, combined with the limitations derived from a classic meta-analysis approach, makes it difficult to interpret how their conclusions were derived. In fact, a conventional pairwise meta-analysis, which only compares treatments directly from primary studies, does not allow treatments to be ranked according to their efficacy or safety, offering a more limited basis for clinical decision-making. Because the ideal goal should be to compare available hormonal add-on therapies within each other to achieve a broader and more quantitative view of their comparative effectiveness of, a network meta-analytic approach should be preferred, as performed by Zhang et al. in 2020 [22]. However, this study is not without strong limitations. First, the reliability of the included studies has not been evaluated and is not adequate to the actual trustworthiness standards [107]. In addition, although the authors claimed to include only patients defined as POR according to the March 2010 Bologna criteria of the European Society of Human Reproduction and Embryology (ESHRE) [23], multiple studies

published before this date were included, some of which enrolled patients who could not be defined as POR according to them [23]. This lower homogeneity of the included population consequently significantly reduces the clinical and methodological variability and thus also the reliability and generalizability of the results. Moreover, a crucial strength of our analysis compared to that of Zhang et al. [22] concerns the primary outcome analyzed. The choice of LBR as the primary outcome, compared to the CPR used by the authors of the previous network meta-analysis, represents a substantial advantage. In fact, the ESHRE explicitly recommends the use of LBR as the primary outcome in clinical trials and systematic reviews conducted with the aim to evaluate the clinical effectiveness of using add-ons in ART treatments, as LBR is considered the most clinically relevant parameter, being directly related to the final success of treatment and reflecting the ultimate goal of couples undertaking reproductive medicine treatment [108]. Therefore, the use of LBR as the primary endpoint in this network meta-analysis significantly increases its clinical relevance and relevance to the information needs of physicians and patients, clearly distinguishing it from the previous meta-analysis by Zhang et al. [22].

It is crucial to underline that SUCRA rankings reflect the probability that an intervention is among the best options based on the entire network of evidence. However, a higher SUCRA score does not imply that the intervention is statistically superior to others in direct or indirect comparisons. In our analysis, no statistically significant differences were observed among most pairwise comparisons, which suggests limited certainty in the relative superiority of the treatments. Nevertheless, the consistency of higher SUCRA values for GH and testosterone across multiple outcomes suggests a favorable trend that warrants further investigation. Therefore, SUCRA rankings should be interpreted as hypothesis-generating tools rather than definitive clinical guidance, particularly in this scenario where statistical significance is lacking. Our findings highlight GH and testosterone as the agents with the highest probability of improving reproductive outcomes in women with POR undergoing ART.

The exact mechanism by which GH might improve the outcomes of OS remains unclear. However, it is known that GH enhances insulin-like growth factor 1 (IGF-1) activity in the follicle, which plays a critical role in granulosa cell function and follicular maturation [109]. The studies included in our meta-analysis [12, 18, 90] reported a higher number of oocytes retrieved after the administration of GH in POR women. Nevertheless, the benefit for the LBR could not be clearly demonstrated. A review by Kolibianakis et al. in 2009 [110] had already suggested a significant increase in the number of retrieved oocytes and an improvement in LBR when GH was added to OS in poor responders. However, with the implementation of Bologna criteria, recent reviews concluded that the effect

of GH administration on ovarian response or pregnancy rate is still contradictory and remains unclear [21, 111]. A recent Cochrane on this topic also reported similar results [112]. Conversely, the use of adjuvant GH in OS protocols has an uncertain effect on LBR and the average number of oocytes retrieved in patients expected to be good responders. Therefore, although promising, the use of GH as an add-on in women with POR requires further high-quality studies to confirm its efficacy, given the paucity of trials and their inherent biases and imprecisions.

Androgens play a crucial role in folliculogenesis. Specifically, they influence the proliferation of granulosa cells, the number of growing follicles as well as the expression of FSH receptors in the ovary [113]. Different agents have been explored to increase intraovarian androgen concentration: transdermal testosterone, DHEA, and androgen modulators such as LTZ. Our findings suggest that transdermal testosterone could have a positive impact on the LBR and CPR. However, the available evidence regarding the clinical utility of transdermal testosterone in poor responders shows contradictory results. Some authors reported an increase in pregnancy rates [93, 99] and ovarian response [89, 99] after testosterone administration. In contrast, well-designed clinical trials did not show differences in their primary outcomes (number of oocytes and pregnancy rate) using testosterone [91, 101]. Recently, a conference abstract of a multicenter multinational RCT concluded that testosterone pre-treatment prior to IVF/ICSI does not increase clinical pregnancy rates in poor ovarian responders [114]. Nevertheless, a recent meta-analysis [115] concluded that the probability of obtaining more oocytes and clinical pregnancies was significantly increased in women pretreated with transdermal testosterone compared with those who were not, with a lower cancellation rate in the testosterone group. However, available studies lack homogeneity regarding type, dose, and duration of testosterone supplementation. Thus, although it is suggested that the use of testosterone in POR women may improve reproductive outcomes, a consensus on the supplementation protocol needs to be reached.

In the current meta-analysis, the use of DHEA has shown no benefit in improving reproductive outcomes, except for a decrease in the cancellation rate. This contrasts with other reviews and meta-analyses suggesting that DHEA could improve oocyte response and pregnancy rates in patients with poor response [21, 22].

Another add-on that showed some results in our network meta-analysis was LTZ. LTZ is an aromatase inhibitor that increases intraovarian androgens by inhibiting the conversion of androgens into estrogens. In concordance with other authors [21], we did not observe a benefit with LTZ in the number of oocytes retrieved or pregnancy rate although we observed a reduction of gonadotropin consumption and duration of stimulation with the use of LTZ. Only a few studies have evaluated the use of this add-on in patients with

POR [8, 16, 97]. Authors who have evaluated the use of LTZ in mild stimulation compared to conventional stimulation without LTZ have observed no differences in reproductive outcomes [8, 16]. However, Moini et al. [97] showed that patients treated with conventional doses of gonadotrophins plus LTZ had an increase in the number of oocytes retrieved along with a decrease in gonadotropin consumption and duration of stimulation compared to the women without LTZ addition. LTZ is therefore a promising treatment that requires further exploration. According to our results, neither the use of CC, estrogen priming nor the addition of rLH would gain an additional benefit in patients with POR.

While this network meta-analysis was limited to hormonal add-ons, other interventions such as coenzyme Q10, low-dose hCG, and corifollitropin alfa showed promising potential in improving ovarian response. Coenzyme Q10, through its antioxidant and mitochondrial-supportive properties, may enhance oocyte quality in women with POR [19]. Low-dose hCG, when added during OS, may mimic LH activity and support follicular maturation, although high-quality RCTs in Bologna-defined POR are lacking [116]. Corifollitropin alfa offers the advantage of simplified stimulation protocols with a single injection replacing daily FSH, and may be useful in selected POR [117]. However, the current body of evidence is either methodologically limited or inconsistent with our inclusion criteria. Future high-quality RCTs are needed to assess the role of such agents and determine their integration into individualized OS strategies.

## Strengths and limitations

Several limitations should be considered while interpreting our findings. The certainty of evidence was primarily low due to imprecision and incoherence, mainly stemming from the limited number of direct comparisons available and variations in study methodologies.

The dosages, the beginning time, the length of ovulation stimulation, and the GnRH analog protocols employed in the suggested interventions and OS protocols also showed notable differences. Therefore, some small heterogeneity among included trials may have influenced the findings. Due to the small sample sizes of the eligible trials, it was typically impossible to properly investigate this clinical heterogeneity. Consequently, the current systematic review and network meta-analysis permitted only broad comparisons between various hormonal adjuvant treatments and no treatment, lowering the certainty of evidence for imprecision due to the lack of significant differences in several comparisons. Future research will allow for the assessment of a possible moderating influence of these parameters on the effectiveness of the interventions under investigation.

Conversely, to ensure the robustness and validity of such findings, we included only studies in which the POR

followed the Bologna criteria [23], excluding many trials that might increase inherent heterogeneity and thus be a strength of this network meta-analysis.

Moreover, all the most critical ART outcomes, including also the LBR, were analyzed, emphasizing the importance of our findings in clinical practice. Additionally, the consistency of the reported findings, showing agreement in the top-ranked add-ons (GH and testosterone) for most study outcomes, provides useful indications for routine practice in practitioners dealing with women with POR undergoing ART.

In conclusion, the results of the present systematic review and network meta-analysis of RCTs suggest that the addition of testosterone and GH may offer benefits to POR patients undergoing OS. The addition of LTZ also showed some sort of benefit, showing the improvement of some OS parameters. In contrast, the addition of DHEA, CC, estrogen, or rLH did not show significant benefit. However, the current certainty of evidence is still limited to low and very low; therefore, it is crucial to further investigate the real clinical value of these additional hormone treatments with further rigorous studies.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s10815-025-03633-z>.

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**Data availability** Raw data for this network meta-analysis are available at the corresponding author upon reasonable request.

## Declarations

**Competing interests** The authors declare no competing interests.

**Declaration of generative AI and AI-assisted technologies in the writing process** No AI or AI-assisted technology was involved in the writing process of the manuscript.

**Attestation statement** • All the data analyzed in this systematic review and meta-analysis has been published in the evaluated trials.

• Data will be made available to the editors of the journal for review or query upon request.

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## References

- Cedars MI. Managing poor ovarian response in the patient with diminished ovarian reserve. *Fertil Steril*. 2022;117:655–6.
- Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril*. 2015;103:e9–17.
- Jaswa EG, McCulloch CE, Simbulan R, Cedars MI, Rosen MP. Diminished ovarian reserve is associated with reduced euploid rates via preimplantation genetic testing for aneuploidy independently from age: evidence for concomitant reduction in oocyte quality with quantity. *Fertil Steril*. 2021;115:966–73.
- Hazout A, Bouchard P, Seifer DB, Aussage P, Junca AM, Cohen-Bacrie P. Serum antimüllerian hormone/müllerian-inhibiting substance appears to be a more discriminatory marker of assisted reproductive technology outcome than follicle-stimulating hormone, inhibin B, or estradiol. *Fertil Steril*. 2004;82:1323–9.
- Honorato TC, Henningsen AA, Haadsma ML, Land JA, Pinborg A, Lidegaard Ø, et al. Follicle pool, ovarian surgery and the risk for a subsequent trisomic pregnancy. *Hum Reprod*. 2015;30:717–22.
- Tarasconi B, Tadros T, Ayoubi J-M, Belloc S, de Ziegler D, Fanchin R. Serum antimüllerian hormone levels are independently related to miscarriage rates after in vitro fertilization-embryo transfer. *Fertil Steril*. 2017;108:518–24.
- Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. *Hum Reprod*. 2008;23:699–708.
- Liu X, Wen W, Wang T, Tian L, Li N, Sun T, et al. Increased versus standard gonadotrophin dosing in predicted poor responders of IVF: an open-label randomized controlled trial. *Hum Reprod*. 2022;37:1806–15.
- Revelli A, Gennarelli G, Sestero M, Canosa S, Carosso A, Salvagno F, et al. A prospective randomized trial comparing corifollitropin- $\alpha$  late-start (day 4) versus standard administration (day 2) in expected poor, normal, and high responders undergoing controlled ovarian stimulation for IVF. *J Assist Reprod Genet*. 2020;37:1163–70.
- Massin N, Abdennebi I, Porcu-Buisson G, Chevalier N, Descat E, Piétin-Vialle C, et al. The BISTIM study: a randomized controlled trial comparing dual ovarian stimulation (duostim) with two conventional ovarian stimulations in poor ovarian responders undergoing IVF. *Hum Reprod*. 2023;38:927–37.
- Wiser A, Gonen O, Ghetler Y, Shavit T, Berkovitz A, Shulman A. Addition of dehydroepiandrosterone (DHEA) for poor-responder patients before and during IVF treatment improves the pregnancy rate: a randomized prospective study. *Hum Reprod*. 2010;25:2496–500.
- Norman RJ, Alvino H, Hull LM, Mol BW, Hart RJ, Kelly T-L, et al. Human growth hormone for poor responders: a randomized placebo-controlled trial provides no evidence for improved live birth rate. *Reprod Biomed Online*. 2019;38:908–15.
- Zhang S, Tang Y, Wang X, Zong Y, Li X, Cai S, et al. Estrogen valerate pretreatment with the antagonist protocol does not increase oocyte retrieval in patients with low ovarian response: a randomized controlled trial. *Hum Reprod*. 2022;37:1431–9.
- Barrenetxea G, Agirregoikoa JA, Jiménez MR, de Larruzea AL, Ganzabal T, Carbonero K. Ovarian response and pregnancy outcome in poor-responder women: a randomized controlled trial on the effect of luteinizing hormone supplementation on in vitro fertilization cycles. *Fertil Steril*. 2008;89:546–53.
- Kucuk T, Sozen E. Luteal start of exogenous FSH in poor responder women. *J Assist Reprod Genet*. 2007;24:635–8.
- Bastu E, Buyru F, Ozsurmeli M, Demiral I, Dogan M, Yeh J. A randomized, single-blind, prospective trial comparing three different gonadotropin doses with or without addition of letrozole during ovulation stimulation in patients with poor ovarian response. *Eur J Obstet Gynecol Reprod Biol*. 2016;203:30–4.
- Moffat R, Hansali C, Schoetzau A, Ahler A, Gobrecht U, Beutler S, et al. Randomised controlled trial on the effect of clomiphene citrate and gonadotropin dose on ovarian response markers and IVF outcomes in poor responders. *Hum Reprod*. 2021;36:987–97.
- Mohammadi S, Eini F, Bazarganipour F, Taghavi SA, Kutenae MA. The effect of Myo-inositol on fertility rates in poor ovarian responder in women undergoing assisted reproductive technique: a randomized clinical trial. *Reprod Biol Endocrinol*. 2021;19:61.
- Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol*. 2018;16:29.
- Lok IH, Yip S-K, Cheung LP, Yin Leung PH, Haines CJ. Adjuvant low-dose aspirin therapy in poor responders undergoing in vitro fertilization: a prospective, randomized, double-blind, placebo-controlled trial. *Fertil Steril*. 2004;81:556–61.
- Conforti A, Carbone L, Di Girolamo R, Iorio GG, Guida M, Campitiello MR, et al. Therapeutic management in women with a diminished ovarian reserve: a systematic review and meta-analysis of randomized controlled trials. *Fertil Steril*. 2025;123:457–76.
- Zhang Y, Zhang C, Shu J, Guo J, Chang H-M, Leung PCK, et al. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. *Hum Reprod Update*. 2020;26:247–63.
- Ferraretti AP, La Marca A, Fauser BCJM, Tarlatzis B, Nargund G, Gianaroli L, et al. ESHRE consensus on the definition of “poor response” to ovarian stimulation for in vitro fertilization: the Bologna criteria. *Hum Reprod*. 2011;26:1616–24.
- Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10:ED000142.
- Mbuagbaw L, Rochweg B, Jaeschke R, Heels-Andsell D, Alhazani W, Thabane L, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Syst Rev*. 2017;6:79.
- Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:14898.
- Nikolakopoulou A, Higgins JPT, Papakonstantinou T, Chaimani A, Del Giovane C, Egger M, et al. CINeMA: An approach for assessing confidence in the results of a network meta-analysis. *PLoS Med*. 2020;17: e1003082.
- Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. *Fertil Steril*. 2017;108:393–406.
- Song J-Y, Gao D-D, Cao X-L, Xiang S, Chen Y-H, Teng Y-L, et al. The role of traditional chinese formula Ding-Kun Pill (DKP) in expected poor ovarian response women (POSEIDON Group 4) undergoing in vitro fertilization-embryo transfer: a multicenter, randomized, double-blind, placebo-controlled trial. *Front Endocrinol (Lausanne)*. 2021;12: 675997.

30. Davar R, Oskouian H, Ahmadi S, Firouzabadi RD. GnRH antagonist/letrozole versus microdose GnRH agonist flare protocol in poor responders undergoing in vitro fertilization. *Taiwan J Obstet Gynecol*. 2010;49:297–301.
31. Karimzadeh MA, Mashayekhy M, Mohammadian F, Moghaddam FM. Comparison of mild and microdose GnRH agonist flare protocols on IVF outcome in poor responders. *Arch Gynecol Obstet*. 2011;283:1159–64.
32. Demirel A, Gurgan T. Comparison of microdose flare-up and antagonist multiple-dose protocols for poor-responder patients: a randomized study. *Fertil Steril*. 2009;92:481–5.
33. Jinno M, Tamaoka Y, Teruya K, Watanabe A, Hatakeyama N, Goda T, et al. Granulocyte colony-stimulating factor priming improves embryos and pregnancy rate in patients with poor ovarian reserve: a randomized controlled trial. *Reprod Biol Endocrinol*. 2023;21:29.
34. Klinkert ER, Broekmans FJM, Looman CWN, Habbema JDF, te Velde ER. Expected poor responders on the basis of an antral follicle count do not benefit from a higher starting dose of gonadotrophins in IVF treatment: a randomized controlled trial. *Hum Reprod*. 2005;20:611–5.
35. Prapas Y, Petousis S, Dagklis T, Panagiotidis Y, Papatheodorou A, Assunta I, et al. GnRH antagonist versus long GnRH agonist protocol in poor IVF responders: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol*. 2013;166:43–6.
36. Llácer J, Moliner B, Luque L, Bernabéu A, Lledó B, Castillo JC, et al. Luteal phase stimulation versus follicular phase stimulation in poor ovarian responders: results of a randomized controlled trial. *Reprod Biol Endocrinol*. 2020;18:9.
37. Maged AM, Nada AM, Abohamila F, Hashem AT, Mostafa WA, Elzayat AR. Delayed start versus conventional GnRH antagonist protocol in poor responders pretreated with estradiol in luteal phase: a randomized controlled trial. *Reprod Sci*. 2015;22:1627–31.
38. Kahraman K, Berker B, Atabekoglu CS, Sonmezer M, Cetinkaya E, Aytac R, et al. Microdose gonadotropin-releasing hormone agonist flare-up protocol versus multiple dose gonadotropin-releasing hormone antagonist protocol in poor responders undergoing intracytoplasmic sperm injection-embryo transfer cycle. *Fertil Steril*. 2009;91:2437–44.
39. Liu X, Li W, Mol BW, Wen W, Wang T, Tian L, et al. Who may benefit from an increased gonadotropin dosing in predicted poor responders undergoing IVF/ICSI? A secondary analysis assessing treatment selection markers of a randomized trial. *Eur J Obstet Gynecol Reprod Biol*. 2023;291:76–81.
40. van Tilborg TC, Oudshoorn SC, Eijkemans MJC, Mochtar MH, van Golde RJT, Hoek A, et al. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis. *Hum Reprod*. 2017;32:2485–95.
41. Drakopoulos P, Vuong TNL, Ho NAV, Vaiarelli A, Ho MT, Blockeel C, et al. Corifollitropin alfa followed by highly purified HMG versus recombinant FSH in young poor ovarian responders: a multicentre randomized controlled clinical trial. *Hum Reprod*. 2017;32:2225–33.
42. Kolibianakis EM, Venetis CA, Bosdou JK, Zepiridis L, Chatzimeletiou K, Makedos A, et al. Corifollitropin alfa compared with follitropin beta in poor responders undergoing ICSI: a randomized controlled trial. *Hum Reprod*. 2015;30:432–40.
43. Cerrillo M, Cecchino GN, Toribio M, García-Rubio MJ, García-Velasco JA. A randomized, non-inferiority trial on the DuoStim strategy in PGT-A cycles. *Reprod Biomed Online*. 2023;46:536–42.
44. Weissman A, Horowitz E, Ravhon A, Golan A, Levran D. Dehydroepiandrosterone supplementation increases baseline follicular phase progesterone levels. *Gynecol Endocrinol*. 2011;27:1014–7.
45. Tazegül A, Gökemli H, Ozdemir S, Aktan TM. Comparison of multiple dose GnRH antagonist and minidose long agonist protocols in poor responders undergoing in vitro fertilization: a randomized controlled trial. *Arch Gynecol Obstet*. 2008;278:467–72.
46. Marci R, Caserta D, Dolo V, Tatone C, Pavan A, Moscarini M. GnRH antagonist in IVF poor-responder patients: results of a randomized trial. *Reprod Biomed Online*. 2005;11:189–93.
47. Youssef MA, van Wely M, Al-Inany H, Madani T, Jahangiri N, Khodabakhshi S, et al. A mild ovarian stimulation strategy in women with poor ovarian reserve undergoing IVF: a multicenter randomized non-inferiority trial. *Hum Reprod*. 2017;32:112–8.
48. Esfidani T, Moini A, Arabipour A, Mojtahedi MF, Mohiti S, Salehi E, et al. Early administration of gonadotropin-releasing hormone antagonist versus flexible antagonist ovarian stimulation protocol in poor responders: a randomized clinical trial. *Middle East Fertility Society Journal*. 2021;26:35.
49. Cheung L-P, Lam P-M, Lok IH, Chiu TT-Y, Yeung S-Y, Tjer C-C, et al. GnRH antagonist versus long GnRH agonist protocol in poor responders undergoing IVF: a randomized controlled trial. *Hum Reprod*. 2005;20:616–21.
50. Aflatoonian A, Hosseiniadat A, Baradaran R, Farid MM. Pregnancy outcome of “delayed start” GnRH antagonist protocol versus GnRH antagonist protocol in poor responders: a clinical trial study. *Int J Reprod Biomed*. 2017;15:231–8.
51. Ashrafi M, Arabipour A, Yahyaei A, Zolfaghari Z, Ghaffari F. Does the “delayed start” protocol with gonadotropin-releasing hormone antagonist improve the pregnancy outcome in Bologna poor responders? a randomized clinical trial. *Reprod Biol Endocrinol*. 2018;16:124.
52. Zarei A, Parsanezhad ME, Kutenaei MA, Jahromi BN, Esfahani PS, Bakhshaei P. Delayed start protocol with gonadotropin-releasing hormone antagonist in poor responders undergoing in vitro fertilization: a randomized, double-blinded, clinical trial. *Oman Med J*. 2018;33:506–11.
53. DiLuigi AJ, Engmann L, Schmidt DW, Benadiva CA, Nulsen JC. A randomized trial of microdose leuprolide acetate protocol versus luteal phase ganirelix protocol in predicted poor responders. *Fertil Steril*. 2011;95:2531–3.
54. Yu R, Jin H, Huang X, Lin J, Wang P. Comparison of modified agonist, mild-stimulation and antagonist protocols for in vitro fertilization in patients with diminished ovarian reserve. *J Int Med Res*. 2018;46:2327–37.
55. Lainas TG, Sfountouris IA, Papanikolaou EG, Zorzovilis JZ, Petas GK, Lainas GT, et al. Flexible GnRH antagonist versus flare-up GnRH agonist protocol in poor responders treated by IVF: a randomized controlled trial. *Hum Reprod*. 2008;23:1355–8.
56. Merviel P, Cabry-Goubet R, Lourdel E, Devaux A, Belhadri-Mansouri N, Copin H, et al. Comparative prospective study of 2 ovarian stimulation protocols in poor responders: effect on implantation rate and ongoing pregnancy. *Reprod Health*. 2015;12:52.
57. Malmusi S, La Marca A, Giulini S, Xella S, Tagliasacchi D, Marsella T, et al. Comparison of a gonadotropin-releasing hormone (GnRH) antagonist and GnRH agonist flare-up regimen in poor responders undergoing ovarian stimulation. *Fertil Steril*. 2005;84:402–6.
58. Ghaffari F, Jahangiri N, Madani T, Khodabakhshi S, Chehrizi M. Randomized controlled trial of gonadotropin-releasing hormone agonist microdose flare-up versus flare-up among poor responders undergoing intracytoplasmic sperm injection. *Int J Gynaecol Obstet*. 2020;148:59–64.
59. Sunkara SK, Coomarasamy A, Faris R, Braude P, Khalaf Y. Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. *Fertil Steril*. 2014;101:147–53.

60. Bülow NS, Skouby SO, Warzecha AK, Udengaard H, Andersen CY, Holt MD, et al. Impact of letrozole co-treatment during ovarian stimulation with gonadotrophins for IVF: a multicentre, randomized, double-blinded placebo-controlled trial. *Hum Reprod.* 2022;37:309–21.
61. Yang X, Lin G, Lu G, Gong F. Letrozole supplementation during controlled ovarian stimulation in expected high responders: a pilot randomized controlled study. *Reprod Biol Endocrinol.* 2019;17:43.
62. Bülow NS, Warzecha AK, Nielsen MV, Andersen CY, Holt MD, Petersen MR, et al. Impact of letrozole co-treatment during ovarian stimulation on oocyte yield, embryo development, and live birth rate in women with normal ovarian reserve: secondary outcomes from the RIOT trial. *Hum Reprod.* 2023;38:2154–65.
63. Kara M, Aydin T, Aran T, Turktekin N, Ozdemir B. Does dehydroepiandrosterone supplementation really affect IVF-ICSI outcome in women with poor ovarian reserve? *Eur J Obstet Gynecol Reprod Biol.* 2014;173:63–5.
64. Kim C-H, Howles CM, Lee H-A. The effect of transdermal testosterone gel pretreatment on controlled ovarian stimulation and IVF outcome in low responders. *Fertil Steril.* 2011;95:679–83.
65. Kansal Kalra S, Ratcliffe S, Gracia CR, Martino L, Coutifaris C, Barnhart KT. Randomized controlled pilot trial of luteal phase recombinant FSH stimulation in poor responders. *Reprod Biomed Online.* 2008;17:745–50.
66. Kucuk T, Göktolga U, Sozen E. Efficiency of follicle-stimulating hormone, commenced in the luteal phase, for overcoming a poor response in assisted reproduction. *J Obstet Gynaecol Res.* 2008;34:574–7.
67. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Addition of GnRH antagonist in cycles of poor responders undergoing IVF. *Hum Reprod.* 2000;15:2145–7.
68. Akman MA, Erden HF, Tosun SB, Bayazit N, Aksoy E, Bahceci M. Comparison of agonistic flare-up-protocol and antagonistic multiple dose protocol in ovarian stimulation of poor responders: results of a prospective randomized trial. *Hum Reprod.* 2001;16:868–70.
69. Kucuk T, Kozinoglu H, Kaba A. Growth hormone co-treatment within a GnRH agonist long protocol in patients with poor ovarian response: a prospective, randomized, clinical trial. *J Assist Reprod Genet.* 2008;25:123–7.
70. Yeung T, Chai J, Li R, Lee V, Ho PC, Ng E. A double-blind randomised controlled trial on the effect of dehydroepiandrosterone on ovarian reserve markers, ovarian response and number of oocytes in anticipated normal ovarian responders. *BJOG.* 2016;123:1097–105.
71. Raga F, Bonilla-Musoles F, Casañ EM, Bonilla F. Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome. *Hum Reprod.* 1999;14:1431–4.
72. Berkkanoglu M, Ozgur K. What is the optimum maximal gonadotropin dosage used in microdose flare-up cycles in poor responders? *Fertil Steril.* 2010;94:662–5.
73. Cedrin-Durnerin I, Bständig B, Hervé F, Wolf J, Uzan M, Hugues J. A comparative study of high fixed-dose and decremental-dose regimens of gonadotropins in a minidose gonadotropin-releasing hormone agonist flare protocol for poor responders. *Fertil Steril.* 2000;73:1055–6.
74. Lefebvre J, Antaki R, Kadoch I-J, Dean NL, Sylvestre C, Bissonnette F, et al. 450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial. *Fertil Steril.* 2015;104:1419–25.
75. Fouda UM, Sayed AM. Extended high dose letrozole regimen versus short low dose letrozole regimen as an adjuvant to gonadotropin releasing hormone antagonist protocol in poor responders undergoing IVF-ET. *Gynecol Endocrinol.* 2011;27:1018–22.
76. Berkkanoglu M, Isikoglu M, Aydin D, Ozgur K. Clinical effects of ovulation induction with recombinant follicle-stimulating hormone supplemented with recombinant luteinizing hormone or low-dose recombinant human chorionic gonadotropin in the midfollicular phase in microdose cycles in poor responders. *Fertil Steril.* 2007;88:665–9.
77. Parinaud J, Oustry P, Perineau M, Rème JM, Monroziès X, Pontonnier G. Randomized trial of three luteinizing hormone-releasing hormone analogues used for ovarian stimulation in an in vitro fertilization program. *Fertil Steril.* 1992;57:1265–8.
78. Mak SMJ, Wong WY, Chung HS, Chung PW, Kong GWS, Li TC, et al. Effect of mid-follicular phase recombinant LH versus urinary HCG supplementation in poor ovarian responders undergoing IVF - a prospective double-blinded randomized study. *Reprod Biomed Online.* 2017;34:258–66.
79. Revelli A, Chiado' A, Guidetti D, Bongioanni F, Rovei V, Genarelli G. Outcome of in vitro fertilization in patients with proven poor ovarian responsiveness after early vs. mid-follicular LH exposure: a prospective, randomized, controlled study. *J Assist Reprod Genet.* 2012;29:869–75.
80. De Placido G, Mollo A, Clarizia R, Strina I, Conforti S, Alviggi C. Gonadotropin-releasing hormone (GnRH) antagonist plus recombinant luteinizing hormone vs. a standard GnRH agonist short protocol in patients at risk for poor ovarian response. *Fertil Steril.* 2006;85:247–50.
81. Nabati A, Peivandi S, Khalilian A, Mirzaeirad S, Hashemi SA. Comparison of GnRh agonist microdose flare up and GnRh antagonist/letrozole in treatment of poor responder patients in intra cytoplasmic sperm injection: randomized clinical trial. *Glob J Health Sci.* 2015;8:166–71.
82. Ebrahimi M, Akbari-Asbagh F, Ghalandar-Attar M. Letrozole+GnRH antagonist stimulation protocol in poor ovarian responders undergoing intracytoplasmic sperm injection cycles: an RCT. *Int J Reprod Biomed.* 2017;15:101–8.
83. Pilehvari S, ShahrokhTehranejad E, Hosseinrashedi B, Keikhah F, Haghollahi F, Azimineko E. Comparison pregnancy outcomes between minimal stimulation protocol and conventional GnRH antagonist protocols in poor ovarian responders. *J Family Reprod Health.* 2016;10:35–42.
84. Schoolcraft WB, Surrey ES, Minjarez DA, Stevens JM, Gardner DK. Management of poor responders: can outcomes be improved with a novel gonadotropin-releasing hormone antagonist/letrozole protocol? *Fertil Steril.* 2008;89:151–6.
85. Lee Y-X, Shen M-S, Tzeng C-R. Low dose growth hormone adjuvant treatment with ultra-long ovarian stimulation protocol in poor responders showed non-inferior pregnancy outcome compared with normal responders. *Front Endocrinol (Lausanne).* 2019;10:892.
86. Dakhly DMR, Bassiouny YA, Bayoumi YA, Hassan MA, Gouda HM, Hassan AA. The addition of growth hormone adjuvant therapy to the long down regulation protocol in poor responders undergoing in vitro fertilization: randomized control trial. *Eur J Obstet Gynecol Reprod Biol.* 2018;228:161–5.
87. Elprince M, Kishk EA, Metawie OM, Albiely MM. Ovarian stimulation after dehydroepiandrosterone supplementation in poor ovarian reserve: a randomized clinical trial. *Arch Gynecol Obstet.* 2020;302:529–34.
88. Kotb MMM, Hassan AMA, AwadAllah AMA. Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria? A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 2016;200:11–5.
89. Aflatoonain A, Saeed L, Hosseiniasadat R. The effect of androgen administration on in vitro fertilization outcome in poor responders undergoing ovarian stimulation with microdose protocol: a randomized clinical trial. *Eur J Obstet Gynecol Reprod Biol.* 2022;279:72–6.

90. Bayoumi YA, Dakhly DMR, Bassiouny YA, Hashish NM. Addition of growth hormone to the microflare stimulation protocol among women with poor ovarian response. *Int J Gynaecol Obstet.* 2015;131:305–8.
91. Bosdou JK, Venetis CA, Dafopoulos K, Zepiridis L, Chatzimeletiou K, Anifandis G, et al. Transdermal testosterone pretreatment in poor responders undergoing ICSI: a randomized clinical trial. *Hum Reprod.* 2016;31:977–85.
92. Fu J, Jiang H-F, Li L, Xin A-J, Sun Y-J, Sun X-X. Effects of Dehydroepiandrosterone on embryo quality and follicular fluid markers in patients with diminished ovarian reserves. *Reproductive and Developmental Medicine.* 2017;01:1–8.
93. Hoang QH, Ho HS, Do HT, Nguyen TV, Nguyen HP, Le MT. Therapeutic effect of prolonged testosterone pretreatment in women with poor ovarian response: a randomized control trial. *Reprod Med Biol.* 2021;20:305–12.
94. Humaidan P, Chin W, Rogoff D, D'Hooghe T, Longobardi S, Hubbard J, et al. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. *Hum Reprod.* 2017;32:544–55.
95. Liu X, Li T, Wang B, Xiao X, Liang X, Huang R. Mild stimulation protocol vs conventional controlled ovarian stimulation protocol in poor ovarian response patients: a prospective randomized controlled trial. *Arch Gynecol Obstet.* 2020;301:1331–9.
96. Mohammad EH, Abou El Serour AG, Mohamed EAH, Abbasy AH, Zaatar M, Rageh KA, et al. Efficacy of growth hormone supplementation with ultrashort GnRH antagonist in IVF/ICSI for poor responders; randomized controlled trial. *Taiwan J Obstet Gynecol.* 2021;60:51–5.
97. Moini A, Lavasani Z, Kashani L, Mojtahedi MF, Yamini N. Letrozole as co-treatment agent in ovarian stimulation antagonist protocol in poor responders: A double-blind randomized clinical trial. *Int J Reprod Biomed.* 2019;17:653–60.
98. Ragni G, Levi-Setti PE, Fadini R, Brigante C, Scarduelli C, Alagna F, et al. Clomiphene citrate versus high doses of gonadotropins for in vitro fertilisation in women with compromised ovarian reserve: a randomised controlled non-inferiority trial. *Reprod Biol Endocrinol.* 2012;10: 114.
99. Saharkhiz N, Zademoares S, Salehpour S, Hosseini S, Nazari L, Tehrani HG. The effect of testosterone gel on fertility outcomes in women with a poor response in in vitro fertilization cycles: A pilot randomized clinical trial. *J Res Med Sci.* 2018;23:3.
100. Siristatidis C, Salamalekis G, Dafopoulos K, Basios G, Vogiatzi P, Papantoniou N. Mild versus conventional ovarian stimulation for poor responders undergoing IVF/ICSI. *In Vivo.* 2017;31:231–7.
101. Subirá J, Algaba A, Vázquez S, Taroncher Dasí R, Mollá Robles G, Monzó Fabuel S, et al. Testosterone does not improve ovarian response in Bologna poor responders: a randomized controlled trial (TESTOPRIM). *Reprod Biomed Online.* 2021;43:466–74.
102. Tosun SA, Ozkaya E, Aru B, Yanikkaya Demirel G, Cogendez E, Sipahi M. Does LH supplementation in poor responders affect granulosa cells apoptosis rate in ART? A prospective randomised controlled trial. *J Obstet Gynaecol.* 2022;42:133–8.
103. Wang Z, Yang A, Bao H, Wang A, Deng X, Xue D, et al. Effect of dehydroepiandrosterone administration before in vitro fertilization on the live birth rate in poor ovarian responders according to the Bologna criteria: a randomised controlled trial. *BJOG.* 2022;129:1030–8.
104. Younis JS, Izhaki I, Ben-Ami M. The effect of LH supplementation to the GnRH antagonist protocol in advanced reproductive ageing women: a prospective randomized controlled study. *Clin Endocrinol (Oxf).* 2016;84:99–106.
105. Zhang HH, Xu PY, Wu J, Zou WW, Xu XM, Cao XY, et al. Dehydroepiandrosterone improves follicular fluid bone morphogenetic protein-15 and accumulated embryo score of infertility patients with diminished ovarian reserve undergoing in vitro fertilization: a randomized controlled trial. *J Ovarian Res.* 2014;7:93.
106. Yeung TWY, Chai J, Li RHW, Lee VCY, Ho PC, Ng EHY. A randomized, controlled, pilot trial on the effect of dehydroepiandrosterone on ovarian response markers, ovarian response, and in vitro fertilization outcomes in poor responders. *Fertil Steril.* 2014;102:108–115.e1.
107. The OBGYN Editors' Integrity Group (OGEIG). Trustworthiness criteria for meta-analyses of randomized controlled studies: OBGYN journal guidelines. *Ultrasound Obstet Gyne.* 2025;65:9–12.
108. Lundin K, Bentzen JG, Bozdag G, Ebner T, Harper J, ESHRE Add-ons working group, et al. Good practice recommendations on add-ons in reproductive medicine†. *Hum Reprod.* 2023;38:2062–104.
109. Adashi EY, Resnick CE, D'Ercole AJ, Svoboda ME, Van Wyk JJ. Insulin-like growth factors as intraovarian regulators of granulosa cell growth and function. *Endocr Rev.* 1985;6:400–20.
110. Kolibianakis EM, Venetis CA, Diedrich K, Tarlatzis BC, Griesinger G. Addition of growth hormone to gonadotrophins in ovarian stimulation of poor responders treated by in-vitro fertilization: a systematic review and meta-analysis. *Hum Reprod Update.* 2009;15:613–22.
111. Orvieto R. Pretreatment: does it improve quantity or quality? *Fertil Steril.* 2022;117:657–63.
112. Sood A, Mohiyiddeen G, Ahmad G, Fitzgerald C, Watson A, Mohiyiddeen L. Growth hormone for in vitro fertilisation (IVF). *Cochrane Database Syst Rev.* 2021;11:CD000099.
113. Vendola KA, Zhou J, Adesanya OO, Weil SJ, Bondy CA. Androgens stimulate early stages of follicular growth in the primate ovary. *J Clin Invest.* 1998;101:2622–9.
114. Polyzos NP, Martinez F, Blockeel C, Gosalvez A, De la Fuente L, Pinborg A, et al. O-066 Transdermal testosterone prior to ovarian stimulation for in vitro fertilization in women with poor ovarian response. A multicenter multinational double-blind placebo-controlled randomized trial (The T-TRANSPORT). *Human Reproduction.* 2023;38:dead093 .080.
115. Katsika ET, Bosdou JK, Goulis DG, Grimbizis GF, Kolibianakis EM. Higher live birth rate following transdermal testosterone pretreatment in poor responders: a systematic review and meta-analysis. *Reprod Biomed Online.* 2023;46:81–91.
116. Madani T, Mohammadi Yeganeh L, Khodabakhshi S, Akhoond MR, Hasani F. Efficacy of low dose hCG on oocyte maturity for ovarian stimulation in poor responder women undergoing intracytoplasmic sperm injection cycle: a randomized controlled trial. *J Assist Reprod Genet.* 2012;29:1213–20.
117. Fusi FM, Zanga L, Arnoldi M, Melis S, Cappato M, Candeloro I, et al. Corifollitropin alfa for poor responders patients, a prospective randomized study. *Reprod Biol Endocrinol.* 2020;18:67.

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