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ORIGINAL ARTICLE

# Fresh and cumulative live birth rates in mild versus conventional stimulation for IVF cycles in poor ovarian responders: a systematic review and meta-analysis

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**STUDY QUESTION:** Are cumulative and live birth rates (LBRs) comparable in poor ovarian response women treated with different protocols of mild stimulation IVF (i.e. oral compounds, lower doses or shorter treatments) versus conventional IVF?

**SUMMARY ANSWER:** Mild ovarian stimulation (MOS) results in comparable outcomes to those of conventional stimulation in poor ovarian response patients with low ovarian reserve.

**WHAT IS KNOWN ALREADY:** Several randomized trials and meta-analyses have been published evaluating the role of mild (MOS) versus conventional ovarian stimulation in poor ovarian response patients. Most report a potentially higher safety profile, patient satisfaction and lower costs, suggesting that the higher cycle cancellation rate and fewer oocytes retrieved following MOS does not affect the final reproductive outcome. Additionally, over the last few years, new publications have added data regarding MOS, and shown the possible benefit of a higher oocyte yield which may also improve prognosis in patients with poor ovarian response.

**STUDY DESIGN, SIZE, DURATION:** We conducted a systematic search of relevant randomized controlled trials (RCTs). We searched electronic databases, including MEDLINE, EMBASE, LILACS-BIREME, CINAHL, The Cochrane Library, CENTRAL (Cochrane Register), Web of Science, Scopus, Trip Database and Open Grey, to identify all relevant studies published up to March 2020. We examined trial registries for ongoing trials. No publication-year or language restrictions were adopted. We explored the reference list of all included studies, reviews and abstracts of major scientific meetings. The primary outcomes were cumulative and fresh LBR (CLBR and FLBR) per woman randomized.

**PARTICIPANTS/MATERIALS, SETTING, METHODS:** We included subfertile women undergoing IVF/ICSI characterized as poor responders and compared primary and secondary outcomes between the different protocols of mild stimulation IVF (i.e. oral compounds, lower doses or shorter treatments) and conventional IVF. We used the PICO (Patients, Intervention, Comparison and Outcomes) model to select our study population.

**MAIN RESULTS AND THE ROLE OF CHANCE:** Overall, 15 RCTs were included in the meta-analysis. CLBR and FLBR were comparable between mild versus conventional stimulation (RR 1.15; 95% CI: 0.73 − 1.81; $I^2$ = 0%, n = 424, moderate certainty and RR 1.01; 95% CI: 0.97 − 1.04; $I^2$ = 0%, n = 1001, low certainty, respectively). No difference was observed either when utilizing oral compounds (i.e. letrozole and clomiphene) or lower doses. Similarly, ongoing pregnancy rate (OPR) and clinical pregnancy rate (CPR) were equivalent when comparing the two groups (RR 1.01; 95% CI: 0.98 − 1.05; $I^2$ = 0%, n = 1480, low certainty, and RR 1.00; 95% CI: 0.97 − 1.03; $I^2$ = 0%, n = 2355, low certainty, respectively). A significantly lower oocyte yield (mean differences (MD) −0.80; 95% CI: −1.28, -0.32; $I^2$

= 83%, n = 2516, very low certainty) and higher rate of cycle cancellation (RR 1.48; 95% CI: 1.08 – 2.02; $I^2$ = 62%, n = 2588, low certainty) was observed in the MOS group.

**LIMITATIONS, REASONS FOR CAUTION:** The overall quality of the included studies was low to moderate. Even though strict inclusion criteria were used, the selected studies were heterogeneous in population characteristics and treatment protocols. We found no differences in CLBR between MOS and COS (95% CI: 0.73 – 1.81.)

**WIDER IMPLICATIONS OF THE FINDINGS:** MOS could be considered as a treatment option in low prognosis poor responder patients, given that it results in similar fresh and CLBRs compared with COS. A milder approach is associated with a lower number of oocytes retrieved and a higher cancellation rate, although treatment cost is significantly reduced. Future research should focus on which type of ovarian stimulation may be of benefit in better prognosis women.

**STUDY FUNDING/COMPETING INTERESTS:** There were no sources of financial support. N.P.P. received research grants, honoraria for lectures from: Merck Serono, MSD, Ferring Pharmaceuticals, Besins International, Roche Diagnostics, IBSA, Theramex and Gedeon Richter. P.D. received unrestricted grants and honoraria from Merck Serono, MSD and Ferring Pharmaceuticals. I.G.F. received unrestricted grants and honoraria from Merck Serono, MSD, Ferring Pharmaceuticals, Gedeon-Richter and IBSA. P.M.B. reported no conflict of interest.

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**Key words:** systematic review / meta-analysis / mild stimulation / conventional stimulation / poor ovarian response

## WHAT DOES THIS MEAN FOR PATIENTS?

The objective of this study was to examine whether a lower (mild stimulation) or higher (conventional stimulation) dose used during ovarian stimulation makes a difference to the chances of a successful outcome (i.e. live birth, pregnancy) in women with a low ovarian reserve (also named 'poor responders') undergoing IVF.

For many years, there has been a debate on whether poor responders would benefit from a mild ovarian stimulation regimen (i.e. lower doses, the use of an oral medication (letrozole or clomiphene) or delaying the start of the treatment) compared with conventional stimulation (higher doses to obtain more oocytes and consequently more embryos), with studies yielding conflicting results.

We performed a systematic review (i.e. literature review that uses systematic methods to collect data) and a meta-analysis (i.e. a statistical analysis that combines the results of multiple scientific studies) to evaluate whether one strategy was superior to the other.

Based on our study, mild stimulation could be considered as an option for women with poor ovarian reserve, as we found similar results between the two strategies.

## Introduction

Ovarian stimulation has been undeniably one of the breakthroughs in ART, resulting in a significant increase in pregnancy outcomes when compared with unstimulated IVF cycles (Niederberger *et al.*, 2018). Nonetheless, despite the substantial contribution of conventional ovarian stimulation (COS) to the final reproductive outcome, the intensity of the ovarian stimulation in IVF/ICSI cycles has been a matter of debate over the last decade, especially in the subgroup of low prognosis patients.

Women with a poor ovarian response (POR) remain a challenge for clinical practice mainly due to the low live birth rates (LBR) described in this population, irrespective of the treatment modality used (Polyzos *et al.*, 2012; Polyzos and Drakopoulos, 2019). In this regard, given that previous studies have demonstrated a small benefit of COS in fresh LBR (FLBR) of poor responders (Polyzos *et al.*, 2014; Busnelli *et al.*, 2015; La Marca *et al.*, 2015), clinicians have started adopting mild ovarian stimulation (MOS) approaches (Revelli *et al.*, 2014; Youssef *et al.*, 2017). However, although several randomized controlled trials (RCTs) have been published comparing MOS with COS in this particular group of patients, most have been small underpowered trials not able to detect a difference in key reproductive outcomes (Kamath *et al.*, 2017; Youssef *et al.*, 2018).

According to the proposed definition by the International Society for Mild Approaches to Assisted Reproduction (ISMAAR), the term 'mild stimulation' may apply in three scenarios: (i) when oral compounds (anti-oestrogens or aromatase inhibitors) are used (alone or with gonadotropins) (Branigan and Estes, 2000); (ii) when stimulation is performed with low gonadotropin doses and (iii) in case of delay in the start of stimulation (shorter duration) in a GnRH antagonist co-treated cycle (Nargund *et al.*, 2007; Zegers-Hochschild *et al.*, 2017). However, despite the proposed definition, previous systematic reviews and meta-analyses have either separately analysed the comparison of COS versus only one of the MOS strategies (low gonadotropin dose, use of an oral compound with gonadotropins or delayed-start gonadotropins) or reported only the fresh cycle outcomes (Datta *et al.*, 2020). Nevertheless, nowadays, it is more than evident that the reporting of an IVF treatment should not only incorporate outcomes associated with fresh embryo transfer but also those resulting from the transfer of supplementary frozen-thawed embryos in order to provide a cumulative success rate which is comprehensive, relevant and meaningful for the infertile couple (Maheshwari *et al.*, 2015).

Thus, we set out to perform the first systematic review and meta-analysis to evaluate the effect of MOS (as defined by the ISMAAR organization) versus COS on the fresh and cumulative LBR (FLBR and CLBR) in poor ovarian response women.

# Materials and methods

## Protocol and registration

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study protocol is accessible at http://www.crd.york.ac.uk/PROSPERO/CRD42020167260. This study was exempted from the institutional review board approval as it was a meta-analysis.

## Eligibility criteria

We used the PICO (Patients, Intervention, Comparison and Outcomes) model to select our study population. We included only RCTs that compared the reproductive outcomes between the different protocols of mild (i.e. oral compounds, lower doses or shorter treatments) and conventional IVF stimulation in POR.

## Search strategy

We conducted a systematic search using the following electronic databases: MEDLINE (Ovid SP, 1956 to date), EMBASE (Ovid SP, 1982 to date) *Literatura Latinoamericana y del Caribe Ciencias de la Salud* (LILACS) (BIREME, 1982 to date), The Cumulative Index to Nursing and Allied Health Literature (CINAHL), The Cochrane Library (DARE and CDSR), The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SCOPUS, Trip Database, Open Grey (unpublished literature from Europe—www.opengrey.eu), the Central Register of Controlled Trials (http://clinicaltrials.gov/), Current Controlled Trials (www.controlled-trials.com), the World Health Organization International Clinical Trials Registry Platform search portal (http://apps.who.int/trialsearch/Default.aspx) and the Australian and New Zealand Clinical Trials Registry—ANZCTR (https://www.anzctr.org.au), to identify all relevant studies published covering the period up to March 2020.

Combinations of the following keywords, MeSH and DeCS (Spanish and Portuguese) search terms were used: 'COH', 'COS', 'controlled ovarian stimulation', GnRH antagonist, long GnRH agonist, oral compounds, clomiphene citrate, letrozole, aromatase inhibitors, low dose gonadotropins, mild ovarian stimulation, minimal ovarian stimulation, mini-FIV, friendly IVF, poor ovarian reserve, poor responders, poor respon*, GnRH analogues, GnRH agonist, gonadotropins, low dose, high dose, cumulative live birth rate, live birth rate, pregnancy rate, number of oocytes, cancellation rate 'AND' IVF/ICSI/ART 'AND' randomized controlled trial(s) 'OR' randomised controlled trial(s). No publication-year or language restrictions were adopted. We scrutinized the reference list of all identified primary studies, reviews, citation lists of all relevant publications, abstracts of major conference meetings (i.e. ESHRE and ASRM), and references from all included studies to identify further appropriate citations.

## Selection of studies and validity assessment

Duplicates were removed, and all citations were subsequently screened by the title and abstract by two of the authors (P.M.B. and I.G.F.). Any discrepancies were solved by discussion, and, if needed, a consensus was reached with senior authors (N.P.P. and P.D.). Trials published only as abstracts, quasi-randomized trials, case series, case reports, book chapters and studies retracted from the literature after publication were excluded upfront. Next, the full texts of eligible RCTs were obtained to evaluate the study eligibility by two authors. We documented the study selection process in a PRISMA flow diagram (Fig. 1).

## Data extraction

Three authors (P.M.B., I.G.F. and P.D.) extracted data on study characteristics to a study-specific format and included data on the assessment of quality and investigation of heterogeneity. We cross-tabulated the numerical information in a spreadsheet software and showed the results in RevMan tables. The outcome definitions adhered to The International Committee Monitoring Assisted Reproductive Technologies/World Health Organization glossary (Zegers-Hochschild *et al.*, 2017). The primary outcomes were FLBR and cumulative LBR (CLBR). Fresh LBR was defined as the ratio between the number of deliveries resulting in at least one live birth per woman randomized (i.e. intention-to-treat). CLBR was defined as the ratio between the number of deliveries resulting in at least one live birth per woman when using all the fresh and cryopreserved embryos in one IVF cycle. Secondary outcomes were clinical pregnancy rates (CPRs), ongoing pregnancy rates (OPRs), number of oocytes retrieved and cancellation rates (Zegers-Hochschild *et al.*, 2017).

## Quantitative analysis

All analyses were performed based on intention-to-treat and defined as the inclusion of all randomized participants in the denominator. Risk ratio (RR) and the 95% confidence intervals (CIs) were utilized and combined for meta-analysis. Data related to the dichotomous outcomes were pooled to determine the RR with corresponding 95% CIs. Data from the continuous outcomes (i.e. number of oocytes) were pooled using the inverse variance model, and the mean differences (MD) with 95% CI were calculated between the groups to determine the effect size. A meta-analysis was conducted only if at least two studies were available for the outcome, using, initially, the fixed-effect model. In contrast, when the authors detected significant heterogeneity ($I^2$) among studies, the random-effect model was used. We assessed $I^2$ by detecting study-to-study variation and a value >50% indicated significant heterogeneity. Statistical significance was set at $P < 0.05$. Statistical analysis was carried out using the Review Manager (RevMan, 2014: version 5.3).

To assess the strength of the conclusions drawn, a sensitivity analysis was carried out for the primary outcomes (CLBR and FLBR). It also allowed evaluation of whether the results would have been different in case of using the odds ratio (OR) instead of RR, the fixed-effects model instead of the random-effect model, or in case of restricted eligibility to studies without a high risk of bias (in all domains). Finally, sensitivity analyses of all outcomes containing only those studies that

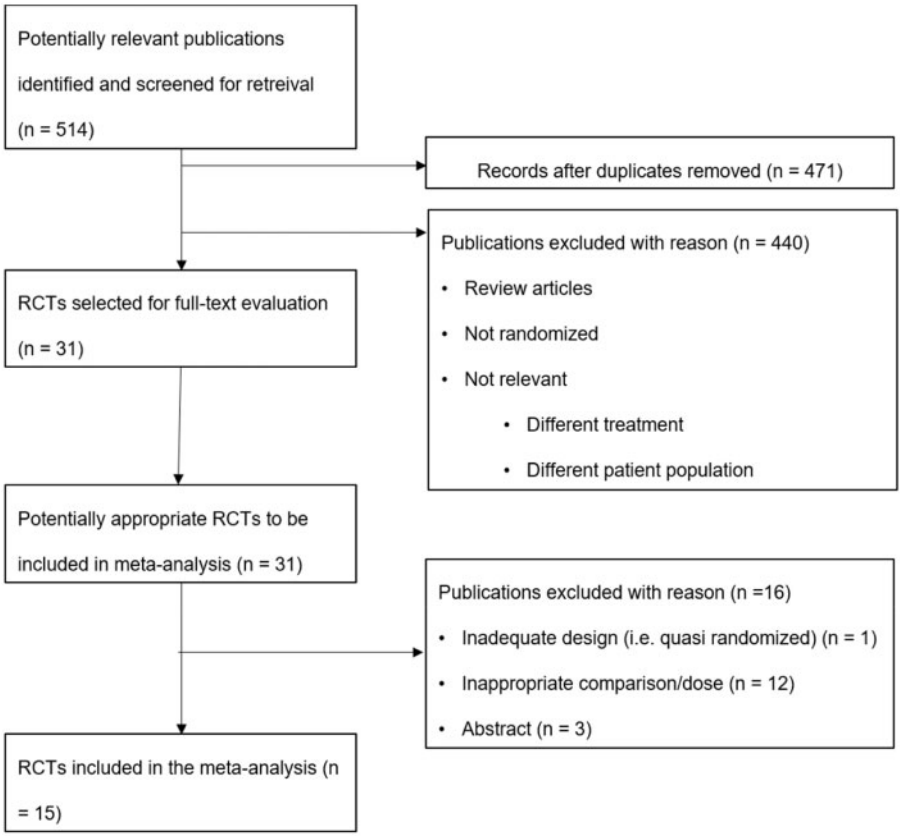


**Figure 1** PRISMA flow chart showing the selection of publications identified in the systematic review of the literature.

used the Bologna criteria (Ferraretti *et al.*, 2011) to include their patients was performed.

## Qualitative analysis

We evaluated the methodological quality and the risk of bias of the included studies in this meta-analysis. Two authors (P.M.B. and I.G.F.) assessed the risk bias of each study in an independent and duplicate fashion. The other authors (N.P.P. and P.D.) resolved conflicts. The Cochrane Collaboration's tool for assessing the risk of bias of RCTs was used to evaluate the included studies as recommended by Cochrane Handbook for Systematic Reviews of Interventions (Higgins *et al.*, 2019).

We assessed the quality of the evidence using the GRADE criteria: risk of bias, the inconsistency of the effect, indirectness, imprecision and publication bias. Using GRADEpro GDT (GRADEpro GDT, 2015), we created the tables for evaluating the overall quality of the body of evidence for the primary and secondary outcomes (CLBR, FLBR, CPR, OPR, oocytes retrieved and cancellation rates) Two review authors (P.M.B. and P.D.) independently made judgments about evidence quality (high, moderate, low or very low); in the case of disagreement between the review authors, a third and fourth review authors (N.P.P. and I.G.F.) were consulted to establish consensus.

# Results

## Study selection

In total, 514 studies were selected from the primary screening by checking titles and abstracts. After eliminating duplicates, evaluating for real randomization and relevance of the comparisons, 15 RCTs were finally included (Fig. 1). The selected studies are summarized in Supplementary Table SI and the excluded studies in Supplementary Table SII.

## Description of included studies

Overall, 15 studies comparing different forms of MOS versus COS were included in the meta-analysis. Studies were subdivided into three categories according to the type of intervention, following the ISMAAR definition of mild stimulation (Nargund *et al.*, 2007): (i) oral compounds (anti-oestrogens or aromatase inhibitors) used alone or with gonadotropins; (ii) gonadotropins in lower doses and (iii) delayed start of the stimulation with gonadotropins in a GnRH antagonist co-treated cycle.

Among the eligible studies, 12 compared an anti-oestrogen (clomiphene citrate (CC), n = 6) or an aromatase inhibitor (letrozole, n = 6) with COS. In the control arm, nine RCTs used the long GnRH agonist protocol and three used the antagonist protocol. Three studies were

included in the lower gonadotropin dose group and used a starting dose of gonadotropins of 150IU/day versus COS in a long agonist or GnRH antagonist protocol. Finally, no studies were included in the delayed-start group.

Although all RCTs clearly defined inclusion of women with POR, the definition was consistently different (14 different definitions) (Supplementary Table SIII), with only 3 out of 15 RCTs (18.8%) employing the Bologna criteria as an inclusion criterion (Ferraretti *et al.*, 2011).

## Risk of bias and overall quality of the body of evidence

Overall, from the 15 studies included, 13 reported the method of randomization and in 7, the allocation concealment method was clearly explained.

The risk of bias summary and graph containing the authors' judgments about each risk of bias item for each included study is included in Supplementary Fig. S1.

We prepared 'Summary of findings' tables using GRADEpro GDT and Cochrane methods. Global quality of the body of evidence table containing the judgments about each item for each included outcome is included in Supplementary Table SIV.

## Cumulative live birth, live birth and pregnancy outcomes

CLBRs were reported in two trials, including 424 patients with POR. Pooled results demonstrated no significant difference between MOS and COS (RR 1.15; 95% CI: 0.73 – 1.81; $I^2 = 0\%$, moderate certainty) (Fig. 2).

FLBRs were reported in five trials, including 1001 patients with POR. Pooled results demonstrated no significant difference between MOS and COS (RR 1.01; 95% CI: 0.97 – 1.04; $I^2 = 0\%$ , low certainty) (Fig. 3).

Similarly, no significant differences were observed either when pooling the results for the comparison of MOS versus COS for CPRs (12 trials included, 2355 women, RR 1.00; 95% CI: 0.97 – 1.03; $I^2 = 0\%$, low certainty) (Supplementary Fig. S2) or when examining OPR (6 trials, 1480 women, RR 1.01; 95% CI: 0.98 – 1.05; $I^2 = 0\%$, low certainty), respectively (Supplementary Fig. S3).

## Number of oocytes retrieved and cycle cancellation

The meta-analysis for the number of oocytes retrieved showed a significantly lower oocyte yield in the MOS group compared with the COS group (13 studies, 2516 women, MD −0.80; 95% CI: −1.28 to −0.32; $I^2 = 83\%$, $P = 0.001$, very low certainty) (Fig. 4).

Similarly, pooled results demonstrated significantly higher cancellation rates in women treated with MOS when compared with COS (14 studies, 2588 women, RR 1.48; 95% CI: 1.08 – 2.02; $I^2 = 62\%$, $P = 0.02$, low certainty) (Supplementary Fig. S4).

## Sensitivity analysis

To better explore the heterogeneity and, given the discrepancy in POR definitions, we prepared a sensitivity analysis, including the measures of association of all outcomes containing only those studies that used the Bologna criteria to include their patients. No significant differences were observed in any of the outcomes except for the oocytes retrieved (three studies, MD -0.72; 95% CI: −1.34 to −0.10; $I^2 = 47\%$). The only change of an outcome, when compared with the original analysis, was the cancellation rate (RR 1.04; 95% CI: 0.73 – 1.47; $I^2 = 0\%$) (Supplementary Table SV).

# Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis to provide pooled data on the effect MOS versus COS

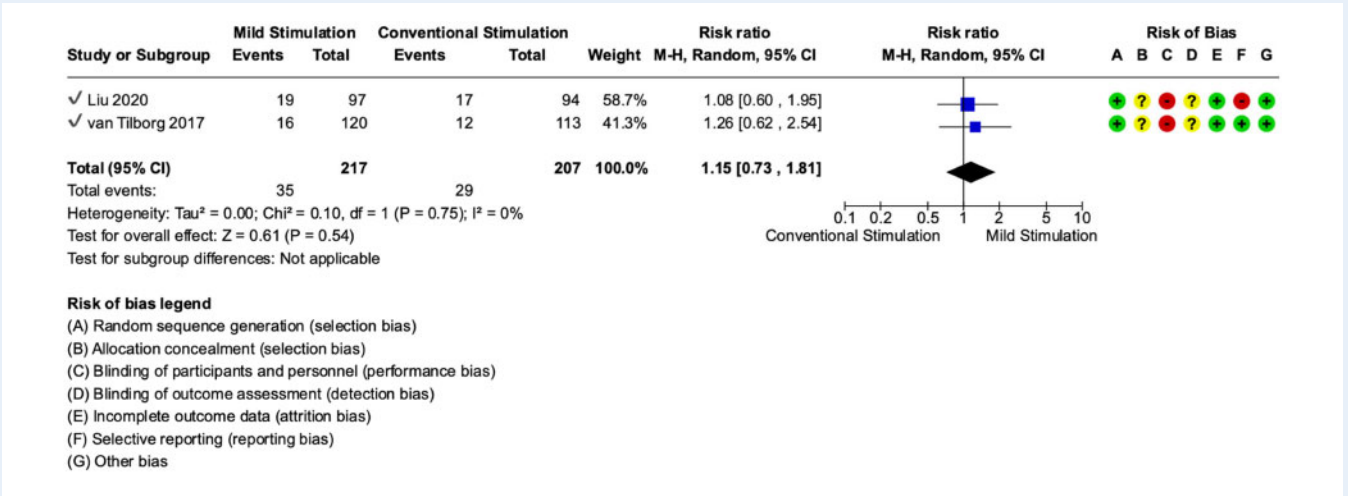


**Figure 2** Forest plot of comparison : Mild versus conventional stimulation in IVF and ICSI cycles (poor ovarian response), Outcome 1: cumulative live birth rate.

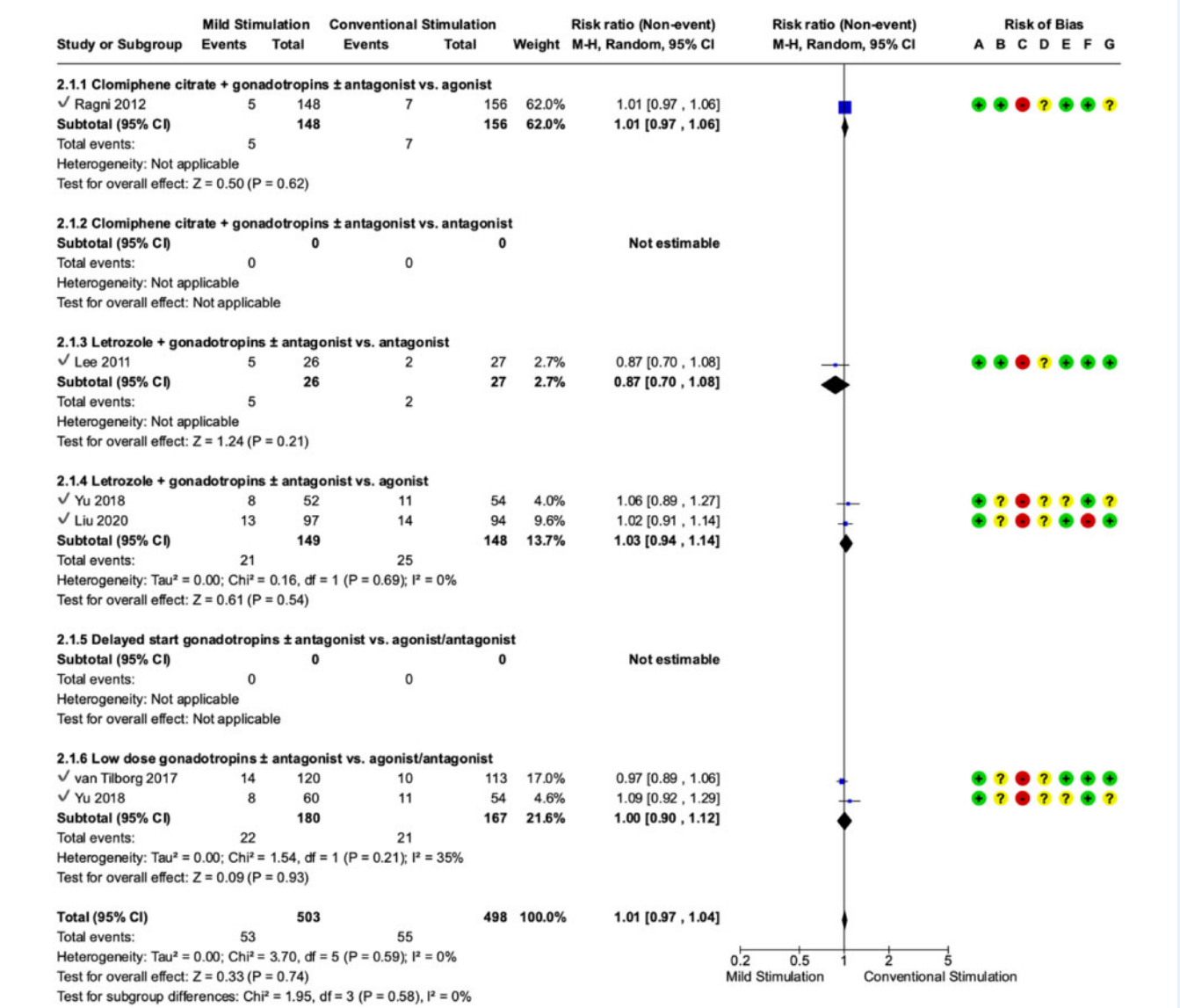


**Figure 3** Forest plot of comparison: Mild versus conventional stimulation in IVF and ICSI cycles (poor ovarian response), Outcome 2: live birth rates.

on women with a poor ovarian response, not only on pregnancy and FLBR but also on CLBR. According to our findings, while COS results in slightly higher oocyte yield and lower cancellation rates when compared with MOS, clinical and OPR and FLBR and CLBR do not significantly differ between the two treatment strategies.

Although several previous systematic reviews and meta-analyses have been published on the topic, none of them have reported on CLBR, and the vast majority have not evaluated all the different types of MOS as we did in the current article (Matsaseng *et al.*, 2013; Fan *et al.*, 2017; Youssef *et al.*, 2018). Some of the previous systematic reviews focussed only on oral compounds (i.e. CC or letrozole) (Figueiredo *et al.*, 2013; Song *et al.*, 2016; Kamath *et al.*, 2017), whereas others failed to include all eligible studies (Figueiredo *et al.*, 2013; Youssef *et al.*, 2018; Datta *et al.*, 2020) or included studies with interventions not considered as MOS (Figueiredo *et al.*, 2013; Fan *et al.*, 2017; Youssef *et al.*, 2018; Datta *et al.*, 2020). In particular, a pooled analysis of studies comparing a CC protocol versus a standard long GnRH protocol in POR (Song *et al.*, 2016) showing comparable CPRs between the two strategies (OR 0.71, 95% CI: 0.22 – 2.29 and OR 1.11, 95% CI: 0.80 – 1.55, respectively), erroneously included a quasi-randomized trial by D'Amato *et al.* (2004) (in which, in the 'mild' arm very high daily rFSH doses of 600 IU/day were used), while other relevant RCTs were not included (Lee *et al.*, 2011). Likewise, in a recent meta-analysis by Youssef *et al.* (2018) comparing low versus high doses of gonadotropins in POR, an RCT evaluating high doses of gonadotropins (i.e. 300 IU/day and FSH 450 IU/day) in the MOS arm was included (Berkkanoglu and Ozgur, 2010).

Finally, in the most recent meta-analysis, Datta *et al.* compared low-dose gonadotropins (≤150 IU daily) alone or in combination with oral medications versus a conventional dose (≥225 IU/daily) for POR.

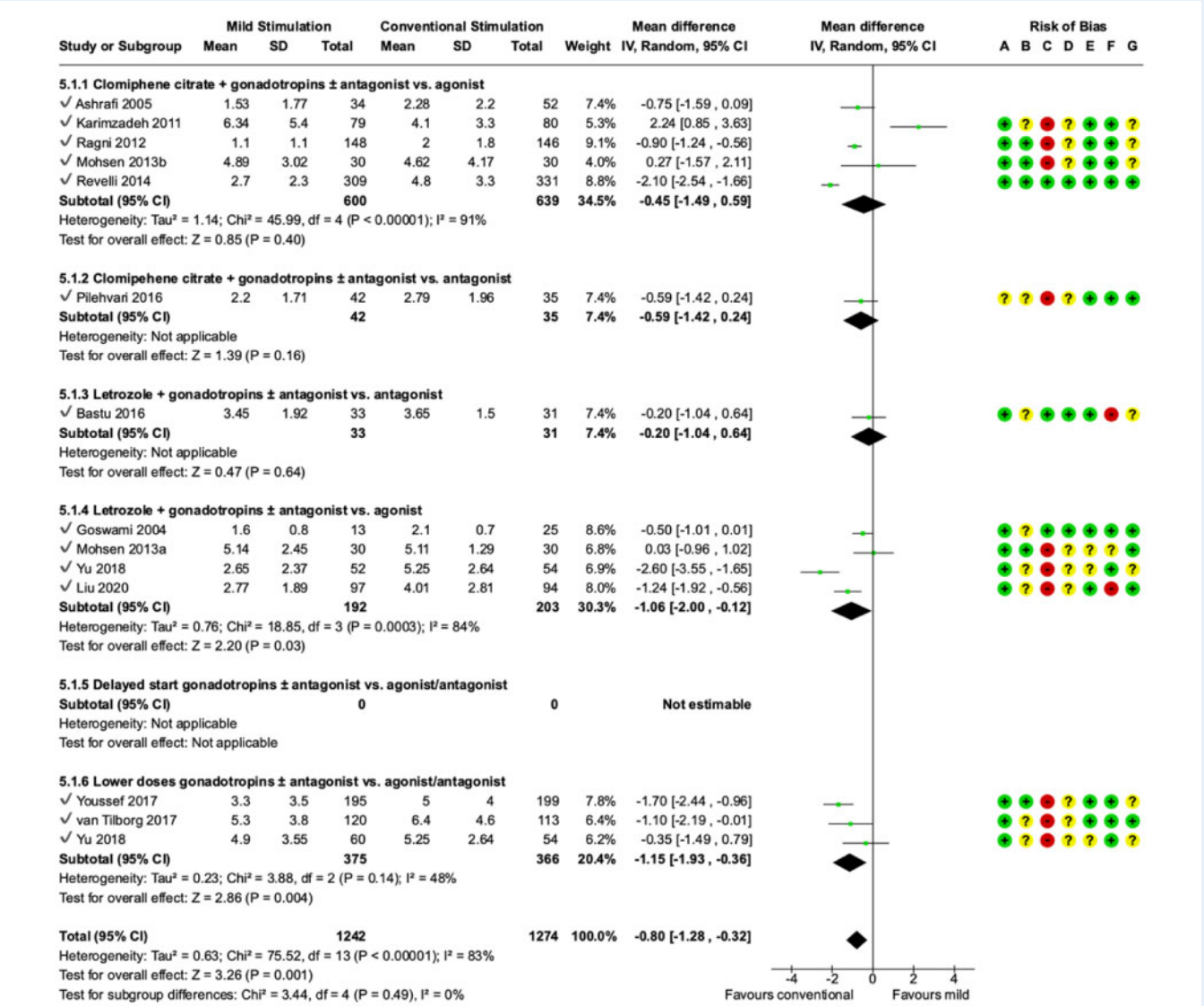


**Figure 4** Forest plot of comparison: Mild versus conventional stimulation in IVF and ICSI cycles (poor ovarian response), Outcome 5: oocytes.

They found equal efficacy in terms of FLBRs between the two treatment modalities (Datta *et al.*, 2020). However, the absence of data on CLBRs, the inclusion of studies not fulfilling the ISMAAR definition for MOS (Kim *et al.*, 2009), and the fact that suboptimal (and not poor) ovarian responders may have been included (van Tilborg *et al.*, 2017), represent important limitations.

Based on our meta-analysis, although MOS resulted in a significantly lower number of oocytes, the difference was small and, probably, clinically insignificant (thirteen studies, 2516 women, MD −0.80; 95% CI: −1.28, −0.32; $I^2 = 83\%$, $P = 0.001$.) Therefore, although lower cycle cancellation rates in the COS arm were found, we were not able to demonstrate any differences in pregnancy, fresh and cumulative LBRs. A potential explanation for this discrepancy may be the inferior clinical prognosis of patients included in the eligible RCTs, taking into account that even among poor responders, not all patients have a similar prognosis (Polyzos and Popovic-Todorovic, 2020). Overall, the mean number of oocytes retrieved in both arms was disappointingly low, with only five studies reporting a mean of more than five oocytes in any of the two groups (Karimzadeh *et al.*, 2011; Abdel Mohsen and Ezz El Din, 2013; Youssef *et al.*, 2017; van Tilborg *et al.*, 2017; Yu *et al.*, 2018). Consequently, it could be hypothesized that low prognosis poor responders are highly unlikely to have better outcomes, even when a more intense stimulation protocol is implemented. Another hypothesis is that high gonadotropin doses may have a negative impact on oocyte/embryo quality (Baart *et al.*, 2007; Heijnen *et al.*, 2007; Verberg *et al.*, 2009); albeit recent evidence suggests no association between stimulation dose and euploidy/LBR (Irani *et al.*, 2020). Future studies should focus on identifying alternative treatment strategies that may increase the recruitable cohort of antral follicles, given that ovarian stimulation in POR women (with very poor prognosis) is unlikely to increase FLBRs and CLBRs. Research has focussed on this direction, either with the use of pre-treatment strategies (i.e. androgens)

(Polyzos et al., 2018a; Montoya-Botero et al., 2019) or with the *in-vitro* activation of oocytes (Kawamura et al., 2013), yet, both strategies still appear to be at an experimental stage.

On the other hand, our research cannot exclude a potentially beneficial effect of COS over MOS in women with a better prognosis. Patients of intermediate prognosis (Polyzos and Sunkara, 2015; Alviggi et al., 2016) may experience better outcomes since previous reports have shown that not only age but also the number of oocytes plays a crucial role in CLBRs in this group (Li et al., 2019). Thus, it would be of great interest to evaluate whether COS could improve reproductive outcomes (especially CLBR) in better prognosis women (i.e. the general population), mainly if we take into account evidence supporting that the number of oocytes retrieved is associated with the number of euploid embryos (La Marca et al. 2017) and CLBRs (Sunkara et al. 2011; Drakopoulos et al. 2016; Devesa et al. 2018; Polyzos et al. 2018b).

A significant strength of the current meta-analysis relies upon its robust methodological approach for the trial selection. Thus, by applying strict selection criteria using the ISMAAR definition for MOS (Nargund et al. 2007), we excluded studies that were erroneously included in previous meta-analyses, and we further included recent RCTs, which were not part of the previous systematic reviews. Furthermore, we, for the first time, evaluated the outcome 'CLBR', which is the most comprehensive measure of success in ART; even though only 2 studies involving 424 participants were included and the results should be interpreted with caution. Also, to better explore the heterogeneity and, given the discrepancy in POR definitions, we performed a sensitivity analysis where we only evaluated studies that used the Bologna criteria for POR. The results were replicated for all outcomes, except for cancellation rates (Supplementary Table SV).

However, despite our robust approach, we need to consider methodological issues related to the included RCTs that should be taken into consideration when interpreting the results of our meta-analysis. Thirteen out of 15 studies reported the method of randomization and in 7, the allocation concealment method was clearly explained. Only three reported any blinding of the clinicians or embryologists to the studied intervention and outcomes (Goswami et al., 2004; Revelli et al., 2014; Bastu et al., 2016). Based on the above, the overall quality of evidence for CLBR, FLBR, OPR and CPR was assessed as moderate or low.

Lastly, an important limitation of the current meta-analysis, as in all similar studies, is the vast diversity in the definitions in the trials included. The striking variability in the definitions of POR among published RCTs has been highlighted before by our group (Polyzos and Devroey, 2011), and this has been shown to affect the validity of the outcomes (Polyzos and Tournaye, 2014). Although this variability also exists in the trials included in the current meta-analysis (we detected 14 different definitions), it appears that most of the trials included POR women with a poor prognosis (as shown in the mean number of oocytes retrieved in all of the eligible trials; Fig. 4). Thus, it is unlikely to affect the validity of our results significantly. Also, disparities in the stimulation protocols (GnRH agonist and antagonist cycles, gonadotropin doses and types, criteria for triggering ovulation, luteal phase support methods and cancellation policies) were detected.

Despite the limitations described above, our meta-analysis provides robust evidence to suggest that in POR women with very poor response prognosis, MOS should be considered as a treatment option given that it results in comparable FLBRs and CLBRs with COS. However, a milder approach is associated with a lower number of oocytes retrieved and a higher cancellation rate. Future research should focus on whether COS may be of benefit in better prognosis women.

## Supplementary data

Supplementary data are available at *Human Reproduction Open* online.

## Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

## Authors' roles

N.P.P. and P.M.B. conceptualized the review. P.M.B. searched databases and selected articles and performed data extraction and analysis. P.M.B. took the lead in writing the review. N.P.P. critically revised the first and final draft manuscript. P.D. and I.G.F. revised several draft versions of the manuscript. All authors read and approved the submission of the final version of the manuscript.

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## Conflict of interest

N.P.P. received research grants, honoraria for lectures from: Merck Serono, MSD, Ferring Pharmaceuticals, Besins International, Roche Diagnostics, IBSA, Theramex and Gedeon-Richter. P.D. received unrestricted grants and honoraria from Merck Serono, MSD, and Ferring Pharmaceuticals. I.G.F. received unrestricted grants and honoraria from Merck Serono, MSD, Ferring Pharmaceuticals, Gedeon-Richter and IBSA. P.M.B. reported no conflict of interest.

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