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Evidence-based recommendations for managing poor ovarian response

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Introduction: Ovarian response is crucial in assisted reproductive technology, and mature oocyte retrieval is directly linked to higher live birth rates. Poor ovarian responders (POR) experience limited stimulation outcomes that contribute to significant cycle cancellations. Managing POR involves tailored protocols, yet no single approach has been universally validated as the most effective.

Methods: Addressing this challenge, the Indian Fertility Society (IFS) developed comprehensive evidence-based guidelines for the diagnosis and management of POR. Using the PICO framework, a Guideline Development Group (GDG) conducted a comprehensive literature review across major databases up to October 31, 2023. Key outcomes included efficacy, safety, and patient-related measures. The GDG employed the GRADE approach to assess the quality of evidence and risk of bias. Recommendations were formulated based on the strength of evidence, benefit-harm balance, feasibility, stakeholder acceptability, and resource implications. The resulting evidence-based recommendations (EBRs) reflect the certainty of evidence and consensus among GDG members.

Results: The guidelines offered 44 EBRs (33 strong and 11 conditional) addressing 37 key questions to guide the management of POR. Among the EBRs, 1 was based on high-quality evidence, 6 on moderate-quality evidence, 25 on low-quality evidence, and 8 on very low-quality evidence and lack of evidence with recommendation for further research in 4. Most of the EBRs were based on low or very low-quality evidence, underscoring the need for further research.

Conclusion: These guidelines prioritize patient safety and improve clinical outcomes, offering actionable insights into POR diagnosis and treatment protocols. Anti-Müllerian hormone and antral follicle count are reliable predictors for identifying patients at high risk of POR. The Corifollitropin alfa offers a comparable alternative to traditional gonadotropins. These guidelines serve as a valuable resource for assisted reproductive technology professionals by promoting a structured approach to managing POR and highlighting areas for future research.

Keywords: poor ovarian response, ovarian stimulation, assisted reproductive technology, in vitro fertilization, GRADE, live birth rate, clinical pregnancy rate, cycle cancellation

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Introduction

Ovarian response, defined as the quality and quantity of follicles and oocytes obtained during stimulation, is a critical metric in assisted reproductive technology (ART) procedures. The number of mature oocytes retrieved strongly correlates with live birth rates (LBRs)[1]. However, a subset of women, known as poor ovarian responders, exhibit a limited response to ovarian stimulation, leading to lower in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) success rates[2]. This condition affects an estimated 9%–24% of patients undergoing ART[3], with data from the American Society for Reproductive Medicine (ASRM) and Society for Assisted Reproductive Technology (SART) indicating that poor ovarian response (POR) is a significant factor in over half of cycle cancellations[4,5].

In practice, managing POR includes a variety of strategies such as tailored pituitary suppression regimens, customized gonadotropin dosing, and alternative interventions like mild stimulation or dual stimulation. Adjuvant therapies, including androgens, growth hormones, and antioxidants, may enhance ovarian response by increasing the number of oocytes retrieved[6]. Moreover, preimplantation genetic testing for aneuploidy (PGT-A) is increasingly utilized to improve clinical outcomes, though it involves a complex procedure requiring careful embryo handling[7].

A primary challenge in managing POR lies in the considerable variability among patients, making it difficult to apply standardized diagnostic criteria like the Bologna criteria[8]. To address this, the POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) classification, introduced in 2016, provides a more refined framework for stratifying and categorizing POR patients. This approach helps clinicians craft personalized treatment plans and set realistic patient expectations[9–12]. Further, the absence of a universally accepted definition or diagnostic criteria for POR leads to inconsistencies in treatment practices. While various stimulation protocols and adjuvant therapies are available, no single approach has been universally validated as the most effective, leaving clinicians to choose from a range of treatment options. These challenges emphasize the complexity of POR management and the need for ongoing research and consensus-building in the field of ART[13,14].

Currently, there are no international guidelines for managing POR and existing recommendations remain insufficient because of heterogeneous patient populations, lack of uniform diagnostic criteria, and offer inconsistent treatment protocols, making it difficult for clinicians, especially in resource-constrained settings, to apply them confidently. The Indian Fertility Society (IFS) recognized the need for standardized, evidence-based guidelines to optimize the diagnosis and management of POR. These guidelines aim to provide clear, actionable evidence-based recommendations (EBRs) for infertility specialists to enhance clinical outcomes, focusing on key aspects of POR diagnosis, treatment protocols, and outcome improvement while prioritizing patient safety. This guideline serves as a resource for ART professionals, promoting a structured, evidence-based approach to the management of POR.

Methodology

The IFS developed clinical guidelines for the management of POR. The process was initiated by an expert committee from the IFS, which defined the scope, key questions, outcomes, and objectives. A Guideline Development Group (GDG) was formed to address population, intervention, comparator, and outcomes (PICO) against the key questions. Key outcomes included efficacy measures (eg, cumulative LBR, miscarriage rate), safety outcomes [eg, ovarian hyperstimulation syndrome (OHSS), adverse outcomes like multiple pregnancy], and patient-related outcomes (eg, cycle cancellation rates, patient preference).

A structured literature search was conducted using databases such as PUBMED/MEDLINE, Cochrane Library, EMBASE, and Scopus, covering studies up to 31 October 2023. The search strategy was developed using keywords based on the PICO framework, ensuring consistency through independent searches by 2 experts. A total of 21935 records were identified through database search, and 116 articles were included in the final review. The details are illustrated in the PRISMA flowchart (**Fig. 1**). Studies were classified as meta-analyses, randomized controlled trials (RCTs), and observational studies. Nonrelevant study designs (eg, case reports, case series, review articles, etc) and non-English articles were excluded. Initial relevance checks were performed on titles and abstracts, followed by full-text reviews of relevant articles to assess the quality of the evidence.

The quality of evidence was assessed using AMSTAR-2 for systematic reviews and meta-analyses[15], and structured checklists were employed to evaluate biases (selection, performance, detection, and attrition) in RCTs and observational studies by GDG. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework[16] was used to classify evidence quality as high (⊛⊛⊛⊛), moderate (⊛⊛⊛⊘), low (⊛⊛⊘⊘), or very low (⊛⊘⊘⊘), depending on study design, biases, effect size, and confounding factors. The GDG summarized evidence for each key question in evidence tables, which included the study design, population, interventions, comparators, outcomes, conclusions, and quality assessment.

The EBRs were developed by GDG using the GRADE approach, which evaluated the strength of evidence, balance of benefits versus harms, feasibility, stakeholder acceptability, and resource implications. In addition, EBRs were classified as strong or conditional based on the strength and certainty of the evidence and consensus among GDG experts and stakeholders. Strongly recommended interventions were supported by high-certainty evidence, where the benefits clearly outweighed potential harms, implementation was feasible, and there was broad stakeholder support. Conditionally recommended options were based on moderate-certainty evidence, but uncertainties existed regarding the benefit–harm balance, resource use, or stakeholder acceptability. Conditionally not recommended interventions were supported by low-certainty evidence or posed more harm than benefit, involved significant resource implications, and had limited stakeholder endorsement. Lastly, strongly not recommended interventions were backed by no evidence or very low-certainty evidence or clear evidence of harm, substantial resource requirements, and strong stakeholder opposition. Each EBR was supported by a rationale considering the balance of desirable and undesirable effects, health equity, and resource utilization. Good practice points (GPPs) are provided when the GDG offers a recommendation primarily based on clinical expertise and consensus, in the absence of adequate direct evidence from systematic research.

The draft guidelines were presented to the IFS executive committee and then circulated for stakeholder review between

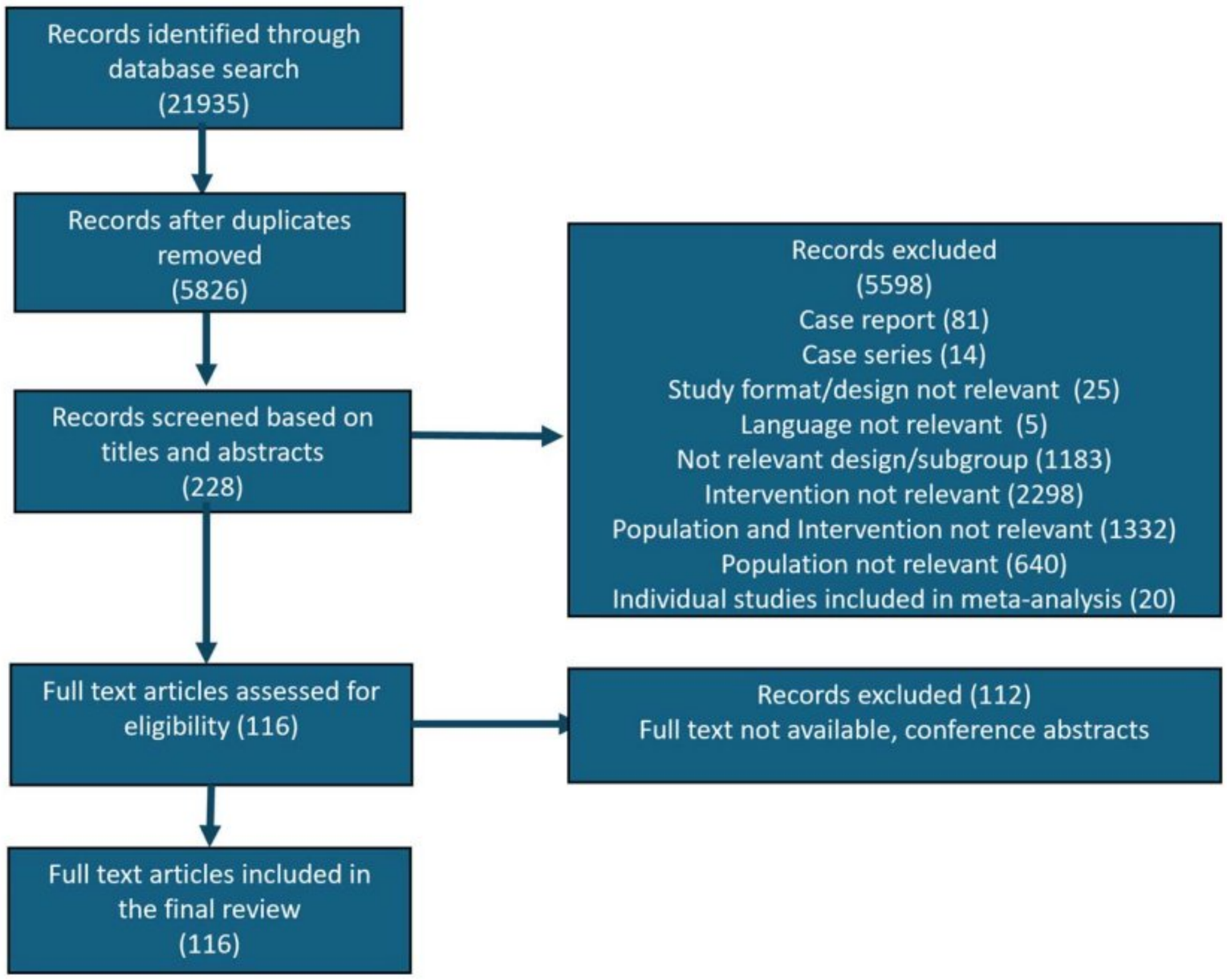

Figure 1. PRISMA flowchart.

February 2024 and May 2024 through online platforms and direct invitations. Feedback was collected through the IFS website and email. The GDG reviewed and incorporated relevant feedback into the final draft, with a detailed summary documented in the Stakeholder Review Report. The summary of stakeholders' inputs is provided in the Supplemental Digital Content 1 (http://links.lww.com/GRH/A9, stakeholders' summary report).

Results

The guideline on POR addresses key aspects such as optimizing ovarian response and enhancing clinical pregnancy rates (CPRs) and LBRs while prioritizing patient safety, compliance, and individualized care. The guideline offers 44 EBRs categorized into 33 strong recommendations and 11 conditional ones, alongside one GPP, from 37 key questions to help clinicians provide the best care for patients with POR. Of the 44 EBRs, 1 was derived from high-quality evidence, 6 were supported by moderate-quality evidence, 25 were based on low-quality evidence, 8 relied on very low-quality evidence, and lack of evidence with recommendation for further research in 4.

All the recommendations from the guideline are included in this document as EBR (**Table 1**). The supporting documents, background information, and full version of the IFS guidelines are available (at https://indianfertilitysociety.org/wp-content/uploads/2024/07/POR-guideline-print-version-2july24.pdf). The list of key questions is available in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/GRH/A10).

Discussion

The evidence for the EBRs was mostly from meta-analyses, systematic literature reviews, RCTs, and cohort studies.

Among hormonal biomarkers, anti-Müllerian hormone (AMH) has emerged as the most reliable predictor of POR. AMH levels can be assessed at any time during the menstrual cycle and have shown high accuracy in predicting both low (<4 oocytes) and high (>15 oocytes) ovarian responses[17–19]. Similarly, antral follicle count (AFC) offers a strong predictive ability for both poor and high ovarian responses in IVF treatment[20]. AMH and AFC exhibit similar accuracy and clinical value in predicting POR, with AFC being a more effective measure of ovarian reserve than the other ultrasound markers, such as ovarian volume[21–23].

Multiple meta-analyses have shown no significant difference between agonist and antagonist protocols regarding CPRs, ongoing pregnancy rates (OPRs), and the number of oocytes retrieved in POR[24,25]. Some studies suggest that long and short gonadotropin-releasing hormone (GnRH) agonist protocols may yield comparable or superior outcomes to antagonist protocols; however, further research is needed to confirm these findings[26,27].

The guideline on POR strongly recommends mild stimulation with low-dose gonadotropins as equally effective as conventional stimulation for poor responders. This reflects the understanding that higher gonadotropin doses may not improve outcomes and that milder protocols can reduce treatment burden and cost. Similarly, the ASRM practice committee guidelines reported no significant difference in clinical pregnancy rates between mild (≤ 150 IU/d) and conventional protocols in poor responders. However, ASRM highlighted the absence of definitive data on live birth rates with mild stimulation in this group[28]. Studies

Table 1

Evidence-based recommendations: Summary.

Sl No.	Evidence-based recommendations	Strength of recommendation	Level of evidence
Prestimulation management in poor responders			
Evidence-based recommendations for clinical practice			
1	The use of anti-Müllerian hormone levels as a biomarker for predicting poor ovarian response is recommended	Strong	Low ⊛⊛⊘⊘
2	Assessment of basal antral follicle count through transvaginal ultrasonography is recommended for predicting POR	Strong	Low ⊛⊛⊘⊘
Interventions not recommended for POR in clinical practice			
3	Routine genetic polymorphism testing is not recommended to predict POR	Strong	Low ⊛⊛⊘⊘
4	Routine pretreatment with estrogen in the luteal phase (estrogen priming) is not recommended for poor responders	Conditional	Low ⊛⊛⊘⊘
5	Oral contraceptive pills pretreatment is not recommended for improving live births in poor responders	Strong	Low ⊛⊛⊘⊘
6	Routine use of the gonadotropin-releasing hormone (GnRH) antagonist delayed start protocol is not recommended for poor responders	Conditional	Low ⊛⊛⊘⊘
7	Pretreatment with antioxidants is not recommended for poor responders due to lack of evidence	Conditional	Low ⊛⊛⊘⊘
8	There is lack of evidence to recommend specific lifestyle-related interventions to improve outcomes in poor ovarian responders	Strong	Low ⊛⊛⊘⊘
Insufficient evidence to make a recommendation and further research recommended			
9	There is insufficient data to make a recommendation for routine immunologic testing at baseline to predict POR and recommend further research	Strong	No evidence
10	There is insufficient data to make a recommendation for alternative medicine-based therapy for poor responders and recommend further research	Strong	No evidence
Ovarian stimulation protocols			
Evidence-based recommendations for clinical practice			
11	The GnRH antagonist protocol and long GnRH agonist protocol are equally recommended for poor responders	Strong	Low ⊛⊛⊘⊘
12	Mild stimulation with low-dose gonadotropin and conventional stimulation are equally recommended for poor responders	Strong	Low ⊛⊛⊘⊘
13	Mild stimulation with oral letrozole in combination with low-dose gonadotropin or conventional stimulation is equally recommended for poor responders	Strong	Moderate ⊛⊛⊛⊘
14	Mild stimulation with oral clomiphene citrate in combination with low-dose gonadotropin or conventional stimulation is equally recommended in poor responders	Strong	Moderate ⊛⊛⊛⊘
15	The decision to use clomiphene citrate alone as a mild stimulation strategy in poor responders is based on patient characteristics and previous treatment response	GPP	No evidence
Interventions not recommended for POR in clinical practice			
16	The GnRH agonist flare protocol is not recommended over the long GnRH agonist protocol for ovarian stimulation in poor responders	Strong	Low ⊛⊛⊘⊘
17	The DuoStim protocol is not recommended over the GnRH antagonist protocol in poor responders	Strong	Low ⊛⊛⊘⊘
18	Luteal phase stimulation is not recommended over follicular phase stimulation in poor responders	Strong	Low ⊛⊛⊘⊘
19	The modified natural cycle protocol is not recommended over the GnRH antagonist protocol for poor responders	Strong	Low ⊛⊛⊘⊘
20	The progesterone primed ovarian stimulation protocol is not recommended over the GnRH antagonist protocol for poor responders	Strong	Low ⊛⊛⊘⊘
21	The short GnRH agonist protocol is not recommended over the GnRH antagonist protocol for poor responders	Conditional	Low ⊛⊛⊘⊘
Types of stimulation drugs			
Evidence-based recommendations for clinical practice			
22	The use of either human menopausal gonadotropin (hMG) or recombinant FSH (rFSH) is equally recommended in poor responders	Strong	Low ⊛⊛⊘⊘
23	Mid-follicular addition of hMG in long agonist cycles is recommended for patients hyporesponsive to rFSH	Conditional	Low ⊛⊛⊘⊘
24	Early or mid-follicular initiation of r-hLH is equally recommended in poor responders	Conditional	Low ⊛⊛⊘⊘
25	Corifollitropin alfa (CFA) and rFSH are equally recommended in poor responders	Strong	Moderate ⊛⊛⊛⊘
26	CFA and hMG are equally recommended in poor responders	Strong	Low ⊛⊛⊘⊘

Table 1

(*Continued*)

Sl No.	Evidence-based recommendations	Strength of recommendation	Level of evidence
Interventions not recommended for POR in clinical practice			
27	The use of urinary FSH over rFSH is not recommended in poor responders	Conditional	Low ⊛⊛⊘⊘
28	Increasing the dose of gonadotropins beyond standard dose to improve live birth rates among expected poor ovarian responders is not recommended	Strong	High ⊛⊛⊛⊛
29	Recombinant follicle-stimulating hormone (rFSH) monotherapy is not recommended over Recombinant human luteinizing hormone (r-hLH) in poor responders	Conditional	Low ⊛⊛⊘⊘
Adjuvant therapies			
Interventions not recommended for POR in clinical practice			
30	Adjuvant use of growth hormone in ovarian stimulation is not recommended for poor responders	Strong	Low ⊛⊛⊘⊘
31	Adjuvant use of testosterone in ovarian stimulation is not recommended for poor responders	Conditional	Low ⊛⊛⊘⊘
32	Adjuvant use of dehydroepiandrosterone in ovarian stimulation is not recommended for poor responders	Strong	Moderate ⊛⊛⊛⊘
33	Adjuvant use of co-enzyme Q10 in ovarian stimulation is not recommended for poor responders	Strong	Moderate ⊛⊛⊛⊘
Insufficient evidence to make a recommendation and further research recommended			
34	There is insufficient data to make a recommendation for the use of glucocorticoids as an adjuvant to ovarian stimulation in poor responders and recommend further research	Strong	No evidence
Monitoring stimulation protocols			
Insufficient evidence to make a recommendation and further research recommended			
35	There is insufficient data to make a recommendation for the addition of routine hormonal assessment (oestradiol/progesterone/luteinizing hormone) to ultrasound monitoring for poor responders and recommend further research	Conditional	No evidence
Criteria for conversion to intrauterine insemination or cycle cancellation			
Interventions not recommended for POR in clinical practice			
36	Routine transition to intrauterine insemination is not recommended for poor responders	Conditional	Very low ⊛⊘⊘⊘
Criteria for triggering of final oocyte maturation			
Interventions not recommended for POR in clinical practice			
37	Dual trigger [combining GnRH agonist and human chorionic gonadotropin (hCG)] is not recommended over the conventional hCG trigger for poor responders in GnRH antagonist cycles	Conditional	Low ⊛⊛⊘⊘
38	Routine elective freeze-all embryo transfer is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
Oocyte retrieval and embryology			
Interventions not recommended for POR in clinical practice			
39	Routine use of the follicular flushing technique during oocyte retrieval is not recommended in poor responders	Strong	Moderate ⊛⊛⊛⊘
40	Routine use of intracytoplasmic sperm injection over in vitro fertilization for non-male factor infertility is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
41	Routine preimplantation genetic testing- aneuploidy testing is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
42	Routine in vitro maturation of oocytes is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
Ovarian rejuvenation			
Interventions not recommended for POR in clinical practice			
43	Intraovarian platelet-rich plasma therapy is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
44	Intraovarian stem-cell therapy is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘
45	In vitro activation of ovarian tissue is not recommended in poor responders	Strong	Very low ⊛⊘⊘⊘

have reported no significant difference in fresh LBRs between patients with POR undergoing low-dose gonadotropin treatment with or without an antagonist and conventional stimulation protocols (using GnRH agonist or antagonist)[29]. Moderate-quality evidence from several meta-analyses and RCTs suggests that oral ovarian stimulation drugs (such as clomiphene or letrozole) combined with low-dose gonadotropins offer comparable CPRs, OPRs, cumulative LBRs, and fresh LBRs to conventional stimulation protocols, making this combination a feasible option. However, some studies indicate a lower number

of oocytes retrieved and higher cancellation rates[29,30]. Currently, there are insufficient data to recommend letrozole alone over conventional stimulation for poor responders, due to the limited number of studies. Increasing the dose of gonadotropins beyond the standard dose to improve LBR among expected poor ovarian responders did not improve results, as shown by a number of RCTs[31–35].

An RCT in women aged 35 years and older undergoing IVF found that human menopausal gonadotropin (hMG) and recombinant FSH (rFSH) achieved comparable LBRs per initiated cycle, despite the rFSH group retrieving more oocytes[36]. This similarity in effectiveness was further supported by a large retrospective cohort study of poor responders, which demonstrated similar oocyte recovery rates, CPRs, LBRs, and cycle cancellation rates for the 2 treatments[37]. Moreover, no cases of OHSS were reported, underscoring the safety of both treatment regimens. Therefore, either treatment can be recommended, enabling personalized approaches without compromising safety and efficacy.

An RCT involving women with suboptimal ovarian response to rFSH in agonist cycles suggests that adding hMG may better prevent low oocyte recovery and improve LBR compared with increasing the FSH dose or maintaining the current rFSH dose[38]. However, findings from 2 other RCTs are inconclusive[39,40]. In addition, low-quality evidence from 3 cohort studies of antagonist cycles indicates that the impact of hMG supplementation on LBRs, compared with continuing the existing rFSH dose, is inconsistent[41–43]. Hence, mid-follicular addition of hMG in long agonist cycles is recommended for those hyporesponsive to rFSH.

A systematic review and meta-analysis of multiple studies revealed that combined rLH and rFSH therapy significantly improved CPRs compared with rFSH monotherapy. In addition, implantation rates and number of oocytes retrieved were higher with rLH and rFSH combination therapy[44]. The recommendation of r-hLH + rFSH combination therapy over rFSH monotherapy in poor responders is reinforced by systematic reviews and individual studies, which revealed the benefits of rLH supplementation in improving CPR, especially in poor responders[45–47]. Notably, an RCT found a lower incidence of total pregnancy outcome failure with the r-hFSH/r-hLH combination compared with r-hFSH alone, further highlighting the superiority of combined therapy in improving reproductive outcomes for poor responders[48].

RCTs support the recommendation that early or mid-follicular initiation of rLH in poor responders is equally effective. A study on patients (n = 202) starting rLH in either the early or mid-follicular phase alongside rFSH found no significant difference in the number of oocytes retrieved between the groups[49]. Similarly, another RCT found no disparity in oocyte retrieval when comparing early and late rLH initiation in women with POR during IVF. These results suggest that the timing of rLH initiation does not significantly affect oocyte retrieval, making both strategies viable for optimizing IVF outcomes[50].

Corifollitropin alfa (CFA) is a recombinant glycoprotein that has the follicle-stimulating properties of FSH with the extended half-life characteristic of human chorionic gonadotropin (hCG). Structurally, it consists of the FSH alpha-subunit and a modified beta-subunit, which integrates the FSH beta-subunit with the C-terminal peptide sequence of the beta-subunit of hCG[51]. Research suggests that clinical outcomes, such as LBRs, CPRs, and the total number of oocytes retrieved, are comparable between CFA and daily rFSH or hMG in poor responders or women aged 35–45 undergoing IVF[52–58]. Although overall live birth and pregnancy rates with CFA are not significantly different from those seen with conventional stimulation protocols. CFA offers a viable alternative due to the reduced number of injections required[52,59].

Studies have shown that dual triggering can lead to higher numbers of total and mature oocytes, fertilization, implantation, and clinical pregnancy rates[60–64]. However, similar outcomes have also been observed with the conventional hCG trigger[60,63,65,66]. Therefore, despite variability across studies, both dual trigger (GnRH agonist combined with hCG) and traditional hCG trigger are conditionally recommended for poor responders in GnRH antagonist cycles.

Moreover, the GDG advised against implementing certain EBRs in clinical practice due to lack of evidence, particularly routine genetic polymorphism testing, pretreatment with estrogen in the luteal phase, luteal phase stimulation, modified natural cycle, adjuvant therapy with growth hormone, dehydroepiandrosterone (DHEA), testosterone, follicular flushing, PGT-A, elective freeze-all embryo transfer, intraovarian platelet-rich plasma, intraovarian stem-cell therapy, and in vitro activation of ovarian tissue. Our guideline advises against the routine use of preimplantation genetic testing for aneuploidy in poor responders due to insufficient evidence of benefit and limited embryo availability, which reduces its feasibility. This aligns with the ASRM practice committee guidelines, which do not support routine preimplantation genetic testing for aneuploidy for all IVF patients, citing a lack of proven improvement in pregnancy outcomes and miscarriage reduction. Unlike ASRM's broader, population-level guidance, our recommendation is more specific, addressing the unique clinical challenges and risk–benefit considerations in poor responders, thus offering a targeted, evidence-based approach to this subgroup of patients[67]. In addition, due to insufficient data, no recommendation could be made regarding routine immunologic testing, alternative medicine therapies, glucocorticoids as adjuvants, and routine hormonal monitoring alongside ultrasound in poor responders. Further research is warranted in these areas. While no definitive or relevant evidence was available to address those key questions, the absence of evidence should not be interpreted as a lack of effect or a conclusive answer. Further prospective RCTs with larger sample sizes, along with continuous literature reviews, will be essential for future guideline development in this domain.

Conclusion

Managing POR in ART remains complex due to patient variability and a lack of standardized protocols. Evidence supports AMH and AFC as reliable predictors for identifying patients at high risk of POR. Although various stimulation protocols exist, no single approach has emerged as superior for all patients with POR, highlighting the need for personalized treatment plans. Dual trigger protocols, combined rLH/rFSH therapies, and flexible rLH timing offer promising options. The CFA, requiring fewer injections, provides a comparable alternative to traditional gonadotropins. Overall, these findings underscore the importance of tailored strategies and ongoing research to optimize outcomes for this patient population.

In low and middle-income countries (LMICs), where resource constraints and access challenges prevail, these evidence-based

guidelines offer a practical framework to enhance consistency and quality in clinical decision-making. By promoting individualized care and identifying effective yet feasible interventions, they can help optimize the use of limited resources and improve patient outcomes. To ensure continued relevance, periodic validation through local data and real-world implementation studies in LMIC settings is essential. Regular updates of the guidelines, based on emerging evidence and stakeholder feedback, will further strengthen their impact and support their integration into everyday clinical practice.

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Author contributions

All members of the expert panel contributed equally to writing the paper and critical reading. All authors approved the final version.

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References

[1] Sunkara SK, Rittenberg V, Raine-Fenning N, *et al*. Association between the number of eggs and live birth in IVF treatment: an analysis of 400,135 treatment cycles. Hum Reprod 2011;26:1768–74.
[2] Gonda KJ, Domar AD, Gleicher N, *et al*. Insights from clinical experience in treating IVF poor responders. Reprod Biomed Online 2018;36:12–9.
[3] Venetis CA, Kolibianakis EM, Tarlatzi TB, *et al*. Evidence-based management of poor ovarian response. Ann N Y Acad Sci 2010;1205: 199–206.
[4] Devine K, Mumford SL, Wu M, *et al*. Diminished ovarian reserve in the United States assisted reproductive technology population: diagnostic trends among 181,536 cycles from the Society for Assisted Reproductive Technology Clinic Outcomes Reporting System. Fertil Steril 2015;104:612–9.e3.
[5] Society for Assisted Reproductive TechnologyAmerican Society for Reproductive Medicine. Assisted reproductive technology in the United States: 2001 results generated from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology registry. Fertil Steril 2007;87:1253–66.
[6] Drakopoulos P, Bardhi E, Boudry L, *et al*. Update on the management of poor ovarian response in IVF: the shift from Bologna criteria to the Poseidon concept. Ther Adv Reprod Health 2020;14: 2633494120941480.
[7] Yang H, DeWan AT, Desai MM, *et al*. Preimplantation genetic testing for aneuploidy: challenges in clinical practice. Hum Genomics 2022;16:69.
[8] Papathanasiou A. Implementing the ESHRE "poor responder" criteria in research studies: methodological implications. Hum Reprod 2014;29: 1835–8.
[9] Blumenfeld Z. What is the best regimen for ovarian stimulation of poor responders in ART/IVF? Front Endocrinol (Lausanne) 2020;11:192.
[10] Humaidan P, Alviggi C, Fischer R, *et al*. The novel POSEIDON stratification of "Low prognosis patients in Assisted Reproductive Technology" and its proposed marker of successful outcome. F1000Res 2016;5:2911.
[11] Poseidon GroupAlviggi C, Andersen CY, *et al*. A new more detailed stratification of low responders to ovarian stimulation: from a poor ovarian response to a low prognosis concept. Fertil Steril 2016;105: 1452–3.
[12] Vaiarelli A, Cimadomo D, Ubaldi N, *et al*. What is new in the management of poor ovarian response in IVF? Curr Opin Obstet Gynecol 2018; 30:155–62.
[13] Giannelou P, Simopoulou M, Grigoriadis S, *et al*. The conundrum of poor ovarian response: from diagnosis to treatment. Diagnostics (Basel) 2020; 10:687.
[14] Zhang Y, Zhang C, Shu J, *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.
[15] Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Brit Med J 2017; 358:j4008.
[16] Guyatt GH, Oxman AD, Vist GE, *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Brit Med J 2008;336:924–6.
[17] Baker VL, Glassner MJ, Doody K, *et al*. Validation study of the Access antimüllerian hormone assay for the prediction of poor ovarian response to controlled ovarian stimulation. Fertil Steril 2021;116:575–82.
[18] Huang J, Lin J, Gao H, *et al*. Anti-Müllerian hormone for the prediction of ovarian response in progestin-primed ovarian stimulation protocol for IVF. Front Endocrinol 2019;10:325.
[19] Wang X, Jin L, Mao YD, *et al*. Evaluation of ovarian reserve tests and age in the prediction of poor ovarian response to controlled ovarian stimulation—a real-world data analysis of 89,002 patients. Front Endocrinol 2021;12:702061.
[20] Liu Y, Pan Z, Wu Y, *et al*. Comparison of anti-Müllerian hormone and antral follicle count in the prediction of ovarian response: a systematic review and meta-analysis. J Ovarian Res 2023;16:117.
[21] Broer SL, Mol BWJ, Hendriks D, *et al*. The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. Fertil Steril 2009;91:705–14.
[22] Esteves SC, Yarali H, Vuong LN, *et al*. Antral follicle count and anti-Müllerian hormone to classify low-prognosis women under the POSEIDON criteria: a classification agreement study of over 9000 patients. Hum Reprod 2021;36:1530–41.
[23] Kwee J, Elting ME, Schats R, *et al*. Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization. Reprod Biol Endocrinol 2007;5:9.
[24] Lambalk CB, Banga FR, Huirne JA, *et al*. GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update 2017;23:560–79.
[25] Sunkara SK, Coomarasamy A, Faris R, *et al*. 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.
[26] Papamentzelopoulou M, Stavros S, Mavrogianni D, *et al*. Meta-analysis of GnRH-antagonists versus GnRH-agonists in poor responder protocols. Arch Gynecol Obstet 2021;304:547–7.
[27] Prapas Y, Petousis S, Dagklis T, *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.
[28] American Society for Reproductive Medicine. Comparison of pregnancy rates for poor responders using IVF with mild ovarian stimulation versus conventional IVF: a guideline. Fertil Steril 2018;109:993–9.
[29] Montoya-Botero P, Drakopoulos P, González-Foruria I, *et al*. Fresh and cumulative live birth rates in mild versus conventional stimulation for IVF cycles in poor ovarian responders: a systematic review and meta-analysis. Hum Reprod Open 2021;2021:hoaa066.
[30] Bechtejew TN, Nadai MN, Nastri CO, *et al*. Clomiphene citrate and letrozole to reduce follicle-stimulating hormone consumption during ovarian stimulation: systematic review and meta-analysis. Ultrasound in Obstet Gyne 2017;50:315–23.
[31] Leijdekkers JA, Van Tilborg TC, Torrance HL, *et al*. Do female age and body weight modify the effect of individualized FSH dosing in IVF/ICSI

treatment? a secondary analysis of the OPTIMIST trial. Acta Obstet Gynecol Scand 2019;98:1332–40.
[32] Lensen SF, Wilkinson J, Leijdekkers JA, *et al*. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). Cochrane Database Syst Rev 2018;2:CD012693.
[33] Liu X, Wen W, Wang T, *et al*. Increased versus standard gonadotrophin dosing in predicted poor responders of IVF: an open-label randomized controlled trial. Hum Reprod 2022;37:1806–5.
[34] Liu X, Wang D, Wen W, *et al*. Effect of increased gonadotropin dosing on maternal and neonatal outcomes in predicted poor responders undergoing IVF: follow-up of a randomized trial. Eur J Obstet Gynecol Reprod Biol 2023;285:123–9.
[35] van Tilborg TC, Torrance HL, Oudshoorn SC, *et al*. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: the predicted poor responder. Hum Reprod 2017;32:2496–505.
[36] Drakopoulos P, Di Guardo F, Boudry L, *et al*. Does the dose or type of gonadotropins affect the reproductive outcomes of poor responders undergoing modified natural cycle IVF (MNC-IVF)? Eur J Obstet Gynecol Reprod Biol 2022;278:95–9.
[37] Ye H, Huang G, Pei L, *et al*. Outcome of in vitro fertilization following stimulation with highly purified hMG or recombinant FSH in down-regulated women of advanced reproductive age: a prospective, randomized and controlled trial. Gynecol Endocrinol 2012;28:540–4.
[38] De Placido G, Mollo A, Alviggi C, *et al*. Rescue of IVF cycles by HMG in pituitary down-regulated normogonadotrophic young women characterized by a poor initial response to recombinant FSH. Hum Reprod 2001;16:1875–9.
[39] Ferraretti AP, Gianaroli L, Magli MC, *et al*. Exogenous luteinizing hormone in controlled ovarian hyperstimulation for assisted reproduction techniques. Fertil Steril 2004;82:1521–6.
[40] Toporcerová S, Hredzák R, Ostró A, *et al*. Influence of exogenous supplementation with luteinizing hormone during controlled ovarian hyperstimulation on the results of IVF cycle. Ceska Gynekol 2005;70: 187–91.
[41] Berker B, Şükür YE, Özdemir EÜ, *et al*. Human menopausal gonadotropin commenced on early follicular period increases live birth rates in POSEIDON Group 3 and 4 poor responders. Reprod Sci 2021;28: 488–94.
[42] Wu X, Chen Y, Zhou X, *et al*. Timing of HMG supplementation and clinical outcomes of advanced-age patients with diminished ovarian reserve receiving gonadotropin-releasing hormone antagonist protocol. Nan Fang Yi Ke Da Xue Xue Bao 2021;41:412–7.
[43] Yenigul NN, Ozelçi R, Baser E, *et al*. The value of LH supplementation in young women with diminished ovarian reserve treated with GnRH antagonist protocol for ovarian hyperstimulation in ICSI-cycles. Ginekol Pol. 2021.
[44] Conforti A, Esteves SC, Di Rella F, *et al*. The role of recombinant LH in women with hypo-response to controlled ovarian stimulation: a systematic review and meta-analysis. Reprod Biol Endocrinol 2019;17:18.
[45] Alviggi C, Conforti A, Esteves SC, *et al*. Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review. Fertil Steril 2018;109:644–64.
[46] Lehert P, Kolibianakis EM, Venetis CA, *et al*. Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis. Reprod Biol Endocrinol 2014;12:17.
[47] Mochtar MH, Danhof NA, Ayeleke RO, *et al*. Recombinant luteinizing hormone (rLH) and recombinant follicle stimulating hormone (rFSH) for ovarian stimulation in IVF/ICSI cycles. Cochrane Gynaecology and Fertility Group, ed Cochrane Database Syst Rev 2017;2017:CD005070.
[48] Humaidan P, Chin W, Rogoff D, *et al*. Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Hum Reprod 2017;32:544–5.
[49] Behre HM, Howles CM, Longobardi S. Randomized trial comparing luteinizing hormone supplementation timing strategies in older women undergoing ovarian stimulation. Reprod Biomed Online 2015;31: 339–46.
[50] Revelli A, Chiado' A, Guidetti D, *et al*. 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.
[51] Rombauts L, Talmor A. Corifollitropin alfa for female infertility. Expert Opin Biol Ther 2012;12:107–2.
[52] Boostanfar R, Shapiro B, Levy M, *et al*. Large, comparative, randomized double-blind trial confirming noninferiority of pregnancy rates for corifollitropin alfa compared with recombinant follicle-stimulating hormone in a gonadotropin-releasing hormone antagonist controlled ovarian stimulation protocol in older patients undergoing in vitro fertilization. Fertil Steril 2015;104:94–103.e1.
[53] Cozzolino M, Vitagliano A, Cecchino GN, *et al*. Corifollitropin alfa for ovarian stimulation in in vitro fertilization: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril 2019;111:722–33.
[54] Drakopoulos P, Vuong TNL, Ho NAV, *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.
[55] Kolibianakis EM, Venetis CA, Bosdou JK, *et al*. Corifollitropin alfa compared with follitropin beta in poor responders undergoing ICSI: a randomized controlled trial. Hum Reprod 2015;30:432–0.
[56] Ob'edkova KV, Kogan IY, Muller VC, *et al*. IVF protocol efficacy in women with expected suboptimal response depending on ovary stimulation mode. Gynecol Endocrinol 2021;37(suppl 1):44–8.
[57] Selman H, Rinaldi L. Effectiveness of corifollitropin alfa used for ovarian stimulation of poor responder patients. Int J Womens Health 2016;8: 609–15.
[58] Vuong NL, Pham DT, Phung HT, *et al*. Corifollitropin alfa vs recombinant FSH for controlled ovarian stimulation in women aged 35-42 years with a body weight $\geq$ 50 kg: a randomized controlled trial. Hum Reprod Open 2017;2017:hox023.
[59] Taronger R, Martínez-Cuenca S, Ferreros I, *et al*. Ovarian stimulation with corifollitropin alfa followed by hp-hMG compared to hp-hMG in patients at risk of poor ovarian response undergoing ICSI: a randomized controlled trial. Eur J Obstet Gynecol Reprod Biol 2018;231:192–7.
[60] Haas J, Zilberberg E, Nahum R, *et al*. Does double trigger (GnRH-agonist + hCG) improve outcome in poor responders undergoing IVF-ET cycle? a pilot study. Gynecol Endocrinol 2019;35:628–30.
[61] Mutlu I, Demirdag E, Cevher F, *et al*. Dual trigger with the combination of gonadotropin-releasing hormone agonist and standard dose of human chorionic gonadotropin improves in vitro fertilisation outcomes in poor ovarian responders. J Obstet Gynaecol 2022;42:1239–44.
[62] Ren YM, Wang YB, Fu M, *et al*. Effect of dual trigger in vitro fertilization and intracytoplasmic sperm injection during the gonadotropin-releasing hormone-antagonist cycle on final oocyte maturation and cumulative live birth rate in women with diminished ovarian reserve. Curr Med Sci 2022; 42:1066–70.
[63] Sloth A, Kjølhede M, Sarmon KG, *et al*. Effect of dual trigger on reproductive outcome in low responders: a systematic PRISMA review and meta-analysis. Gynecol Endocrinol 2022;38:213–21.
[64] Tulek F, Kahraman A, Demirel LC. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin improves live birth rates in POSEIDON group 3 and 4 expected poor responders. Gynecol Endocrinol 2022;38:731–5.
[65] Keskin M, Ecemiş T, Atik A, *et al*. Cycle outcomes of dual trigger (GnRH agonist+hCG) versus human chorionic gonadotropin trigger alone in POSEDION group 3–4 poor-responders and normo-responders: a prospective randomized study. J Gynecol Obstet Hum Reprod 2023;52:102633.
[66] Zhou C, Yang X, Wang Y, *et al*. Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. Hum Reprod 2022; 37:1795–805.
[67] American Society for Reproductive Medicine. The use of preimplantation genetic testing for aneuploidy: a committee opinion. Fertil Steril 2024; 122:421–34.