Indian Fertility Society Guideline on Poor Ovarian Response

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INDIAN FERTILITY SOCIETY
GUIDELINE DEVELOPMENT GROUP

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IFS Guidelines on Poor Ovarian Response

This is a clinical practice guideline developed by the Indian Fertility Society (IFS). The draft guideline was released in **March 2024**, providing evidence- based recommendations for the management of poor ovarian response (POR). The guideline was created by a diverse group of experts in reproductive medicine from various regions of India, ensuring a balanced perspective and comprehensive framework for clinicians. It addresses key aspects such as optimizing ovarian response, and enhancing clinical pregnancy rates and live birth rates, while prioritizing patient safety, compliance, and individualized care. This guideline provides **45 recommendations** to help clinicians provide the best care for patients with POR.

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CONTENTS

1. Introduction to the Guideline

This clinical guideline focuses on patients at risk of POR undergoing in vitro fertilisation (IVF). The aim of this guideline is to provide evidence-based recommendations for this specific patient population.

1.1. Scope

The scope of this clinical guideline on POR developed by the IFS encompasses a comprehensive framework, which is aimed at offering evidence-based guidance to clinicians. Drafted by the IFS, this guideline aims to provide healthcare professionals the latest evidence on effective management of POR. The key aspects addressed include optimisation of ovarian response, evaluation of embryo quality, and enhancement of clinical pregnancy rates (CPR) and live birth rates (LBR), while prioritising patient safety, compliance, and individualisation of care. Additionally, this guideline seeks to identify and prioritise knowledge gaps in the management of POR for future research.

Certain topics are beyond the scope of this document, including treatment-associated costs and health economics and consideration of intrauterine insemination (IUI) or other conservative modalities for managing POR.

1.2. Key Outcomes

The outcomes measured and their priority within the guideline are as follows:

Key Efficacy Outcomes:

- Cumulative LBR (Critical)
- LBR (Critical)
- Ongoing pregnancy rate (OPR) (Critical)
- CPR (Critical)
- Miscarriage rates (Critical)

Key Outcomes for Ovarian Response:

- Oocyte retrieval rate (Important)
- Number of metaphase II (MII) oocytes (Important)

Key Outcomes for Embryo Quality:

- Top quality embryo (TQE) rate (Others)
- Blastocyst rate (Others)

Key Safety Outcomes:

- Ovarian hyperstimulation syndrome (OHSS) (Critical)
- Adverse events in the mother (Important)
- Adverse events in the child (Important)

Patient-related Outcomes:

- Cycle cancellation rates (Critical)
- Dropout rates (Others)
- Patient convenience/preference (Important)
- Quality of life (Others)
- Time to pregnancy (Others)

These outcomes were defined per cycle whenever possible to ensure comprehensive evaluation and comparison across treatment cycles.

1.3. Target users of the guideline

Infertility specialists treating patients with POR

2. Tabular Summary of Recommendations

S. No.	Key Question	Recommendation	Strength	Quality
Pre-stimulation management in poor responder				
4.1	Does hormone testing at baseline have value in predicting POR?	The use of AMH levels as a biomarker for predicting POR is recommended.	Strong	⊛⊛⊘⊘
4.2	Does ultrasound imaging at baseline have value in predicting POR?	Assessment of basal AFC through transvaginal ultrasonography (TVUS) is recommended for predicting POR.	Strong	⊛⊛⊘⊘
4.3	Does genetic polymorphism testing have value in predicting POR?	Routine genetic polymorphism testing is not recommended to predict POR.	Strong	⊛⊛⊘⊘
4.4	Does immunological testing at baseline have value in predicting POR?	There is insufficient data to make a recommendation for routine immunological testing at baseline to predict POR and recommend further research.	Strong	
4.5	Does oestradiol pretreatment (priming) improve efficacy and safety of ovarian stimulation in poor responders?	Routine pretreatment with oestrogen in the luteal phase (oestrogen priming) is not recommended for poor responders.	Conditional	⊛⊛⊘⊘
4.6	Does pretreatment with oral contraceptive pills (OCP) improve efficacy and safety of ovarian stimulation in poor responders?	OCP pretreatment is not recommended for improving live births in poor responders.	Strong	⊛⊛⊘⊘
4.7	Does the gonadotropin-releasing hormone (GnRH) antagonist delayed start protocol improve the efficacy and safety of ovarian stimulation in poor responders compared to the conventional antagonist protocol?	Routine use of the GnRH antagonist delayed start protocol is not recommended for poor responders.	Conditional	⊛⊛⊘⊘
4.8	Does antioxidant pretreatment improve efficacy and safety of ovarian stimulation in poor responders?	Pretreatment with antioxidants is not recommended for poor responders due to lack of evidence.	Conditional	⊛⊛⊘⊘
4.9	Does alternative medicine-based therapy improve efficacy and patient-related outcomes in poor responders?	There is insufficient data to make a recommendation for alternative medicine-based therapy for poor responders and recommend further research.	Strong	
4.10.	Do lifestyle-based therapies improve efficacy and patient-related outcomes in poor responders?	There is lack of evidence to recommend specific lifestyle-related interventions to improve outcomes in poor ovarian responders.	Conditional	
Ovarian Stimulation Protocols				
5.1	Is the GnRH antagonist protocol superior to GnRH agonist (GnRH agonist) protocols for poor responders?	The GnRH antagonist protocol and long GnRH agonist protocol are equally recommended for poor responders.	Strong	⊛⊛⊘⊘

		The short GnRH agonist protocol is not recommended over the GnRH antagonist protocol for poor responders.	Conditional	⊛⊛⊘⊘
5.2	Is the mild ovarian stimulation protocol superior to conventional protocols (GnRH antagonist or long GnRH agonist protocol) for poor responders?	Mild stimulation with low-dose gonadotropin and conventional stimulation are equally recommended for poor responders.	Strong	⊛⊛⊘⊘
		Mild stimulation with oral letrozole in combination with low-dose gonadotropin or conventional stimulation is equally recommended for poor responders.	Strong	⊛⊛⊛⊘
		Mild stimulation with oral clomiphene citrate in combination with low-dose gonadotropin or conventional stimulation is equally recommended in poor responders.	Strong	⊛⊛⊛⊘
		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	
5.3	Is the GnRH agonist flare protocol superior to the long GnRH agonist protocol for poor responders?	The GnRH agonist flare protocol is not recommended over the long GnRH agonist protocol for ovarian stimulation in poor responders.	Strong	⊛⊛⊘⊘
5.4	Is DuoStim superior to antagonist/mild stimulation or two conventional (BISTIM) protocols for poor responders?	The DuoStim protocol is not recommended over the GnRH antagonist protocol in poor responders.	Strong	⊛⊛⊘⊘
5.5	Is luteal phase stimulation (LPS) superior to follicular phase stimulation (FPS) for poor responders?	LPS is not recommended over FPS in poor responders.	Strong	⊛⊛⊘⊘
5.6	Is the modified natural cycle protocol superior to the GnRH antagonist protocol for poor responders?	The modified natural cycle protocol is not recommended over the GnRH antagonist protocol for poor responders.	Strong	⊛⊛⊘⊘
5.7	Is the progesterone primed ovarian stimulation (PPOS) protocol superior to the GnRH antagonist protocol for poor responders?	The PPOS protocol is not recommended over the GnRH antagonist protocol for poor responders.	Strong	⊛⊛⊘⊘
Types of Stimulation Drugs				
6.1	What is the safety and efficacy of recombinant FSH (rFSH) compared to that of urinary gonadotropins in poor responders?	The use of either human menopausal gonadotropin (hMG) or rFSH is equally recommended in poor responders.	Strong	⊛⊛⊘⊘
		Mid-follicular addition of hMG in long agonist cycles is recommended for patients hyporesponsive to rFSH.	Conditional	⊛⊛⊘⊘
		The use of urinary FSH over rFSH is not recommended in poor responders.	Conditional	⊛⊛⊘⊘

6.2	What should be the starting dose of gonadotropins to improve safety and efficacy of COS in expected poor responders?	Increasing the dose of gonadotropins beyond standard dose to improve LBR among expected poor ovarian responders is not recommended.	Strong	⊛⊛⊛⊛
6.3	What is the safety and efficacy of recombinant luteinizing hormone (rLH) + rFSH compared to that of rFSH monotherapy in poor responders?	Recombinant follicle stimulating hormone (rFSH) monotherapy is not recommended over rFSH Recombinant human luteinizing hormone (r-hLH) in poor responders.	Conditional	⊛⊛⊘⊘
		Early or mid-follicular initiation of r-hLH is equally recommended in poor responders.	Conditional	⊛⊛⊘⊘
6.4	What is the safety and efficacy of long-acting rFSH (corifollitropin alfa [CFA]) compared to that of rFSH or hMG in poor responders?	CFA and rFSH are equally recommended in poor responders.	Strong	⊛⊛⊛⊘
		CFA and hMG are equally recommended in poor responders.	Strong	⊛⊛⊘⊘
Adjuvant Therapies				
7.1	Is adjuvant use of growth hormone (GH) superior to not using an adjuvant for poor responders?	Adjuvant use of GH in ovarian stimulation is not recommended for poor responders.	Strong	⊛⊛⊘⊘
7.2	Is adjuvant use of testosterone superior to not using an adjuvant for poor responders?	Adjuvant use of testosterone in ovarian stimulation is not recommended for poor responders.	Conditional	⊛⊛⊘⊘
7.3	Is adjuvant use of dehydroepiandrosterone (DHEA) superior to not using an adjuvant for poor responders?	Adjuvant use of DHEA in ovarian stimulation is not recommended for poor responders.	Strong	⊛⊛⊛⊘
7.4	Is adjuvant use of Co-Enzyme Q10 (CoQ10) superior to not using an adjuvant for poor responders?	Adjuvant use of CoQ10 in ovarian stimulation is not recommended for poor responders.	Strong	⊛⊛⊛⊘
7.5	Is adjuvant use of glucocorticoids superior to not using an adjuvant for poor responders?	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	
Monitoring Stimulation Protocols				
8.1	Does the addition of hormonal assessment (oestradiol/progesterone/LH) to ultrasound monitoring improve monitoring efficacy and safety for poor responders?	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	
Criteria for Conversion to Intrauterine Insemination or Cycle Cancellation				

9.1	Should IVF/ICSI treatment be transitioned to IUI or cancelled in case of poor response to ovarian stimulation?	Routine transition to IUI is not recommended for poor responders.	Conditional	⊛⊘⊘⊘
Criteria for Triggering of Final Oocyte Maturation				
10.1	Which is the preferred drug to trigger final oocyte maturation for efficacy and safety in poor responders undergoing IVF/ICSI?	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	⊛⊛⊘⊘
Embryo Transfer				
11.1	Does elective freeze-all embryo transfer improve efficacy in poor responders?	Routine elective freeze-all embryo transfer is not recommended in poor responders.	Strong	⊛⊘⊘⊘
Oocyte Retrieval and Embryology				
12.1	Is follicular flushing superior to no follicular flushing during oocyte retrieval in poor responders?	Routine use of the follicular flushing technique during oocyte retrieval is not recommended in poor responders.	Strong	⊛⊛⊛⊘
12.2	Does routine ICSI improve efficacy or safety in poor responders?	Routine use of ICSI over IVF for non-male factor infertility is not recommended in poor responders.	Strong	⊛⊘⊘⊘
12.3	Does routine pre-implantation genetic testing for aneuploidies (PGT-A) improve efficacy in poor responders?	Routine PGT-A testing is not recommended in poor responders.	Strong	⊛⊘⊘⊘
12.4	Does in-vitro oocyte maturation improve efficacy in poor responders?	Routine in-vitro maturation (IVM) of oocytes is not recommended in poor responders	Strong	⊛⊘⊘⊘
Ovarian Rejuvenation				
13.1	Does intraovarian platelet-rich plasma (PRP) improve efficacy or safety in poor responders?	Intraovarian PRP therapy is not recommended in poor responders.	Strong	⊛⊘⊘⊘
13.2	Does intraovarian stem-cell therapy improve efficacy or safety in poor responders?	Intraovarian stem-cell therapy is not recommended in poor responders.	Strong	⊛⊘⊘⊘
13.3	Does in-vitro activation of ovarian tissue improve safety and efficacy in poor responders?	In-vitro activation of ovarian tissue is not recommended in poor responders.	Strong	⊛⊘⊘⊘

3. Introduction to Poor Ovarian Response

3.1. What is ovarian response?

Ovarian response refers to the quality and quantity of follicular response and oocyte yield during ovarian stimulation. This response is assessed through ultrasound scans to measure follicle development and hormone levels. Ovarian response is critical as a metric of success of ART procedures, as the number of mature oocytes retrieved is strongly associated with live birth. (1)

Success rates of IVF/ICSI still remain low in a sub-population of women who do not respond optimally to ovarian stimulation, known as poor ovarian responders. (2)

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2. Gonda KJ, Domar AD, Gleicher N, Marrs RP. Insights from clinical experience in treating IVF poor responders. Reprod Biomed Online. 2018 Jan;36(1):12–9.

3.2. What is poor ovarian response?

Garcia et al. (1983) first defined the concept of the threshold of "individual ovarian response" to ovarian stimulation and its importance for successful outcomes. (1) Subsequently, various authors have attempted to quantify response and define poor responders in terms of the number of oocytes retrieved in previous cycles, oestradiol levels, response to clomiphene citrate challenge test, follicle stimulating hormone (FSH) levels, basal antral follicle counts (AFC), and newer markers, such as inhibin B and anti-Müllerian hormone (AMH). (2) The Bologna criteria were introduced in the 2011 meeting of the European Society of Human Reproduction and Embryology (ESHRE). (3)

According to the Bologna criteria, POR is diagnosed in the presence of at least two of the following three features in a woman undergoing controlled ovarian stimulation (COS) for IVF:

- Advanced Maternal Age: Women aged ≥40 years or having another risk factor for POR
- History of POR: Defined as the retrieval of ≤3 oocytes with a conventional stimulation protocol
- Abnormal ovarian reserve findings: AFC of <5-7 follicles or AMH levels <0.5–1.1 ng/mL
- The presence of two or more of these criteria is indicative of POR.

The heterogeneous phenotype of patients and uncertainty of clinical response in specific populations of patients with POR introduces methodological challenges in implementing the Bologna criteria. (4) **The POSEIDON (Patient-Oriented Strategies Encompassing Individualized Oocyte Number) criteria, introduced in 2016, further help stratify and categorise patients with POR.** (5)

The POSEIDON classification is based on additional parameters, such as the total oocyte yield from the previous IVF cycle and presence of normal ovarian reserve findings. It is based on the woman's prognosis for live birth through IVF/ICSI and stratifies women into "unexpected" and "expected" poor responders based on the oocyte yield in previous cycles and ovarian reserve. It further classifies women based on age.

Low responders (poor responders) are classified into the following four groups based on the POSEIDON criteria: (6)
Group 1: Patients aged <35 years with sufficient pre-stimulation ovarian reserve findings (AFC ≥5, AMH ≥1.2 ng/mL) and an unexpected poor or suboptimal ovarian response. This group could be further divided into subgroup 1a, comprising patients with <4 oocytes, and subgroup 1b, comprising patients with 4–9 oocytes retrieved after standard ovarian stimulation, who, at any age, have a lower LBR than age-matched normal responders.

Group 2: Patients aged ≥35 years with sufficient pre-stimulation ovarian reserve findings (AFC ≥5, AMH ≥1.2 ng/mL) and an unexpected poor or suboptimal ovarian response. This group could be further divided into subgroup 2a, comprising patients with <4 oocytes, and subgroup 2b, comprising patients with 4–9 oocytes retrieved after standard ovarian stimulation, who, at any age, have a lower LBR than age-matched normal responders.

Group 3: Patients aged <35 years with poor prestimulation ovarian reserve findings (expected poor response) (AFC <5, AMH <1.2 ng/mL).

Group 4: Patients aged ≥35 years with poor prestimulation ovarian reserve findings (expected poor response) (AFC <5, AMH <1.2 ng/mL).

These criteria aid in tailoring and optimising treatment strategies, guiding clinicians in choosing the most appropriate interventions based on individualised patient characteristics, and managing patient expectations.

Primary ovarian insufficiency, a condition occurring in women <40 years of age, characterised by 4 months of amenorrhea or oligomenorrhea with elevated FSH levels (>25 IU/L) measured on two instances at least 4 weeks apart, is beyond the scope of the current guideline.

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3.3. What is the burden of poor ovarian response on assisted reproductive technology procedures like IVF/ICSI?

POR has an estimated incidence of 9–24% among patients undergoing ART procedures. (1) Data from the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology (ASRM/SART) registries indicate that >50% of the 14.1% of initial cycles cancelled may be attributed to poor response. (2) According to the 2011 estimates from the ASRM/SART database, diminished ovarian reserve (DOR) accounted for over 26% of IVF cycles. (3) Over 30% of these patients exhibited POR.

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4. Pre-stimulation management in poor responders

4.1. Does hormone testing at baseline have value in predicting poor ovarian response?

Background

POR occurs in 10–20% women undergoing IVF. A poor ovarian reserve contributes to infertility owing to a poor response to gonadotropin stimulation, which further translates to low success in an IVF cycle. AMH levels and AFC have been investigated as ovarian reserve markers to predict response in poor responders. Both AMH levels and AFC have been found to provide an accurate measure of ovarian follicles. Researchers have made efforts to formulate the Bologna criteria and POSEIDON classification. Ovarian reserve markers play important diagnostic and prognostic roles in POR.

Evidence summary

AMH as a biomarker for predicting POR

A cohort study by Baker et al. (2021) included 472 participants who completed the study (74 with POR and 398 without). (1) POR was defined as ≤4 oocytes retrieved during COS. The mean AMH serum level was 0.99 ng/mL (median 0.76 ng/mL) among poor responders and 2.83 ng/mL (median 2.36 ng/mL) among the normal-to-high responders. The area under the curve (AUC) for predicting ovarian response using AMH levels was 0.852. As a predictor of POR, an AMH cutoff of 0.93 ng/mL demonstrated sensitivity and specificity of 63.5% and 89.2%, respectively. The associated positive and negative predictive values were 52.2% and 92.9%, respectively.

Another cohort study included 523 patients without polycystic ovary syndrome, who underwent their first IVF/ICSI cycle with the PPOS protocol. (2) The patients' AMH levels showed high accuracy in predicting both poor (<4 oocytes) and high response (>15 oocytes), with an AUC of 0.861 (95% confidence interval [CI] 0.825–0.892) and 0.773 (95% CI 0.725–0.817), respectively. The AMH cutoff for poor response prediction was 1.26 ng/mL, with a sensitivity and specificity of 72.0% and 86.4%, respectively. The threshold of 4.34 ng/mL was shown to predict high response with a sensitivity of 67.5% and a specificity of 75.8%. AMH levels were found to be an adequate predictor of both high and poor ovarian response with the PPOS protocol, independent of the medroxyprogesterone acetate (MPA) dose. However, AMH levels do not correlate with pregnancy outcomes in the first frozen embryo transfer cycle in a freeze-all strategy.

A retrospective cohort study evaluated 89,002 women with infertility undergoing their first traditional ovarian stimulation cycle for IVF. (3) POR was defined as the cancellation of oocyte retrieval cycle owing to POR or retrieval of ≤3 oocytes. AFC and AMH levels demonstrated high accuracy on using receiver operating characteristic (ROC) regression to predict POR (AUC 0.862 and 0.842, respectively). Adding age to the AMH alone model improved prediction accuracy (AUC 0.865 vs 0.862), but not significantly.

AMH as a biomarker for predicting poor outcomes

A systematic review and meta-analysis evaluated whether AMH levels are a predictor of implantation and/or clinical pregnancy in women undergoing ART procedures. (4) A total of 525 observational studies were identified, of which 19 were selected (5,373 women). Studies reporting CPRs in women with unspecified ovarian reserve (n=11), DOR (n=4), and polycystic ovary syndrome (n=4) were included in addition to those reporting implantation rates (n=4). The odds ratio (OR) for AMH levels as a predictor of implantation in women with unspecified ovarian reserve (n=1,591) was 1.83 (95% CI 1.49–2.25), with an AUC of 0.591 (95% CI 0.563–0.618). The OR for AMH as a predictor of clinical pregnancy (n=4,324) was 2.10 (95% CI 1.82–2.41), with an AUC of 0.634 (95% CI 0.618–0.650). The predictive ability of AMH levels

for pregnancy was greatest in women with DOR (n=615), with an OR and AUC of 3.96 (95% CI 2.57–6.10) and 0.696 (95% CI 0.641–0.751), respectively.

AMH versus inhibin B

In a meta-analysis by Tan et al. (2011), serum inhibin B was compared with AMH levels as a predictor of POR in patients undergoing IVF-ICSI. (5) The studies used different criteria to establish POR. Fifteen studies on serum inhibin B and 12 studies on AMH were selected. Both basal and stimulated inhibin B levels were significantly lower in poor ovarian responders than in controls. The estimated summary ROC curves suggested that stimulated inhibin B was more accurate than basal inhibin B and AMH in predicting POR.

Recommendation

The use of anti-Müllerian hormone levels as a biomarker for predicting poor ovarian response is recommended.	Strong	⊛⊛⊘⊘

Rationale for Recommendation

AMH levels appear to have the highest predictive value for POR across hormonal biomarkers. They may be tested at any time point within the menstrual cycle.

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4.2. Does ultrasound imaging at baseline have value in predicting poor ovarian response?

Background

Basal AFC is the most evaluated ultrasound marker for predicting ovarian response. It presents the recruitable cohort of follicles in a cycle and correlates it with the ovarian reserve (primordial follicle pool). (1) The present question is aimed at evaluating the efficacy of ultrasound markers (AFC, ovarian volume) in predicting POR.

Evidence Summary

According to a systematic review and meta-analysis of 42 studies by Liu et al. (2023), AFC offers good discriminatory capacity for predicting poor or high ovarian response in IVF treatment. The overall pooled sensitivity and specificity of AFC were 0.73 (95% CI 0.62–0.83) and 0.85 (95% CI 0.78–0.90), respectively. The ROC curve showed an AUC of 0.87 (95% CI 0.84–0.90). There was no significant difference in the AUC of AFC and AMH levels as markers of ovarian reserve (p=0.800). (2)

In a systematic review and meta-analysis of 13 studies, Broer et al. (2009) evaluated AFC and AMH as predictors of POR and pregnancy after IVF. AMH levels and AFC showed similar accuracy and clinical value in predicting poor response. The ROC curves for predicting poor response did not indicate that the performance of AMH levels was superior to that of AFC (p=0.73). Further, there was no significant difference in the ROC curves for both parameters for predicting non-pregnancy (p=0.67). (3)

Through a retrospective cohort study of 9484 patients, Esteves et al. (2021) identified optimal AFC and AMH cut-offs for low or suboptimal oocyte yield (as defined by the POSEIDON criteria). For low oocyte yield, the AFC cut-off was 5, with a sensitivity of 0.61, specificity of 0.81, positive and negative predictive values of 64.1% and 79.4%, respectively, and an AUC of 0.791. For suboptimal oocyte yield, the optimal AFC cut-off value was 12, with a sensitivity of 0.74, specificity of 0.76, and an AUC of 0.81. AFC (p=0.0166) was found to be a significant predictor, and an AUC of 0.917 was obtained for this model. (4)

Kasapoglu et al. (2021) prospectively studied 126 women undergoing ICSI, who were classified as suboptimal and normal responders. The ratio of small antral follicles (2–5 mm) to total antral follicles was positively correlated with ovarian response (R2=0.587, p<001). The results indicated that the small antral follicle ratio could be a more specific predictive marker of ovarian response than AFC. (5)

In a prospective study of 139 women by Sanverdi et al. (2018), antral follicle diameter variance (difference in the diameter of the largest and smallest antral follicle) was a significant predictor of POR (right ovary AUC=0.737, p<0.001 and left ovary AUC=0.651, p<0.05). Variance of >3.5 mm was found to have 75% sensitivity in predicting POR (defined as retrieval of ≤3 oocytes). (6)

A prospective randomised study by Kwee et al. (2007) compared the predictive accuracy of ovarian reserve tests. The AUC for AFC and basal ovarian volume were 0.83 and 0.77, respectively. The highest accuracy of AFC was obtained at a cut-off <6, which yielded a sensitivity of 41%, specificity of 95%, and positive predictive value of 75%. The study concluded that AFC was a superior ovarian reserve measure to ovarian volume in predicting POR. (7)

Recommendation

Assessment of basal antral follicle count through transvaginal ultrasonography is recommended for predicting poor ovarian response.	Strong	⊛⊛⊘⊘

Rationale for Recommendation

Evidence from moderate-quality systematic reviews and meta-analyses and low- and moderate-quality cohort studies indicates that basal AFC determined by TVUS is reliable for predicting POR. Evidence on the role of other parameters, such as antral follicle variance or basal ovarian volume, is scarce. Further, there is no standardised method of estimating size variance in the antral follicles.

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4.3. Does genetic polymorphism testing have value in predicting poor ovarian response?

Background

Increasing evidence suggests that specific genetic characteristics of gonadotropins and their receptors may be linked to an individual's response to ovarian stimulation. There remains a debate regarding the utility of the pharmacogenomic approach in early prediction of POR and individualisation of treatment, particularly for women who, despite a good ovarian reserve, respond poorly to conventional ovarian stimulation.

Evidence Summary

Polymorphisms of different genes involved in ovarian function have been studied, including *FSHR*, *ESR 1*, *ESR2*, *AMH*, *AMHR*, *LHCGR*, androgen receptor, *GDF9*, and *BMP-15*. Different methods have been used to identify these polymorphisms, including single nucleotide polymorphism genotyping assays, polymerase chain reaction-restriction fragment length polymorphism, whole exome sequencing, and single-strand conformation polymorphism sequencing. The available evidence on genetic polymorphisms in ovarian response is usually obtained from cohort studies of small sample sizes. It is therefore difficult to derive any definite conclusions from them. Most studied genetic polymorphisms for ovarian response are associated with *FSHR*.

A systematic review and meta-analysis published in 2014 evaluated the association between *FSHR* Ser680Asn (rs6166) polymorphism and POR. (1) The analysis of nine studies showed that SS genotype carriers were more likely to be poor responders (OR 1.61, p=0.08) than NN and NS genotype carriers. The latter genotypes showed no association with POR (OR 0.93-0.95, p=0.75–0.78). The heterogeneity of these pooled ORs warrants further examination of its sources. Tang et al. (2015) published a meta-analysis of 16 cohort studies (4287 participants) on the effect of *FSHR* Asn680Ser polymorphism on ovarian response. *FSHR* Asn680Ser polymorphism may be a significant biomarker for predicting the number of retrieved oocytes and POR, especially in Asian individuals. Other outcomes, such as exogenous FSH dose, OHSS, and pregnancy rate, were not affected. (2) However, owing to insufficient sample sizes in individual studies, this finding did not translate into a significant difference in clinical outcomes. Kronig et al. (2019) retrospectively studied the relationship between FSH receptor (FSHR) status and IVF cycle outcomes. They concluded that the homozygous *FSHR* Ser/Ser genotype at position 680 was associated with a reduced response to ovarian stimulation; however, there was no difference in the cumulative LBR. (3) A recent retrospective cohort study of 143 individuals showed that although the Ser/Ser polymorphism is linked to a poor response, it does not affect pregnancy per started cycle, ongoing pregnancy per started cycle, ongoing pregnancy per embryo transfer, and live birth per embryo transfer. (4) In 2018, a systematic review and meta-analysis was published on the clinical relevance of genetic variants of gonadotropins and their receptors in COS. It included 33 studies that evaluated COS outcomes in relation to seven polymorphisms of *FSHR*, *LHB,* and *LHCGR*. More oocytes were retrieved from patients with *FSHR* (rs6165) AA homozygotes (five studies, 677 patients, weighted mean difference [WMD] 1.85, 95% CI 0.85–2.85, p<0.001; I2=0%) than with GG homozygotes and AG heterozygotes (four studies, 630 patients, WMD 1.62, 95% CI 0.28–2.95, p=0.020; I2=56%). Moreover, the duration of stimulation was shorter for patients with *FSHR* (rs6165) AA homozygotes than for AG carriers (three studies, 588 patients, WMD −0.48, 95% CI −0.87 to −0.10, p=0.010, I2=44%). More oocytes (21 studies, 2632 patients, WMD 0.84, 95% CI 0.19 to 1.49, p=0.01, I2=76%) and MII oocytes (five studies, 608 patients, WMD 1.03, 95% CI 0.01–2.05, p=0.050, I2=0%) were observed in AA than in GG homozygote carriers. FSH consumption was significantly lower in patients with *FSHR* (rs1394205) GG homozygotes (three studies, 411 patients, WMD −1294.61 IU, 95% CI −593.08 to −1996.14 IU, p=0.0003, I2=99%) and AG heterozygotes (three studies, 367 patients, WMD −1014.36 IU, 95% CI −364.11 to −1664.61 IU, p=0.002, I2=99%) than AA homozygotes. These results support the relevance of specific genotypes on reproductive outcomes. However, further studies are required to determine their clinical application. (5)

Recommendation

Routine genetic polymorphism testing is not recommended to predict poor ovarian response.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

Scientific evidence on the role of genetic polymorphisms for predicting POR is varied with limited robustness, cautioning against the widespread clinical application of this testing. The available evidence is sparse, with limited data on cost considerations and cost-benefit ratio of routine testing. Feasibility and technical challenges of different platforms further complicate implementation.

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4.4. Does immunological testing at baseline have value in predicting poor ovarian response?

Background

Autoimmune causes of ovarian insufficiency or dysfunction maybe suspected in the presence of anti-ovarian antibodies, histological evidence of lymphocytic oophoritis, or an associated autoimmune disorder.

Evidence Summary

No conclusive or relevant evidence could be identified to address the specific key question. However, the absence of evidence does not necessarily indicate the absence of an effect or a definitive answer to the present question. The search included but was not limited to the prognostic role of anti-ovarian antibodies, antithyroid antibodies, anti-adrenal antibodies, antinuclear antibodies, and tissue transglutaminase antibodies. Immunological testing to predict POR at baseline may be evolving, and new research may have been published after the literature search period. The lack of evidence may also be attributed to limited availability of studies, non-standardised testing, or the specific nature of the clinical question. In the absence of direct evidence, clinical recommendations are often guided by expert opinion, consensus statements, and clinical expertise. Clinicians are encouraged to exercise their judgment, considering individual patient characteristics, preferences, and the broader clinical context when making decisions. Further research and ongoing monitoring of the literature are recommended to inform future updates of these guidelines.

Recommendation

There is insufficient data to make a recommendation for routine immunological testing at baseline to predict POR and recommend further research.	**Strong**

4.5. Does oestradiol pretreatment (priming) improve efficacy and safety of ovarian stimulation in poor responders?

Background

The concept of oestrogen priming was first proposed by Fanchin et al. (1) According to the hypothesis, synchronising the growth of early antral follicles could optimise COS and improve cycle outcomes.

Evidence Summary

Reynolds et al. (2013) performed a systematic review and meta-analysis of eight studies comparing ART outcomes between poor responders exposed to controlled ovarian hyperstimulation with and without luteal oestradiol (LE) priming. (2) The review included one randomised controlled trial (RCT) and seven observational studies. The RCT compared the number of oocytes retrieved from 26 patients undergoing GnRH antagonist protocol + LE priming with those from 28 patients undergoing the microdose flare protocol. Four observational studies compared the following between patients undergoing the GnRH antagonist protocol + LE priming and microdose flare protocol: LBR (one study), CPR (two studies), and cancellation rate (one study). The remaining three studies compared GnRH antagonist protocol + LE priming with the GnRH antagonist protocol, GnRH antagonist protocol + letrozole, and prior cycle, while evaluating the CPR, OPR, and cycle cancellation as primary outcomes.

Compared with women undergoing non-LE primed protocols, those exposed to LE priming exhibited a lower risk of cycle cancellation (relative risk [RR] 0.60, 95% CI 0.45–0.78 [one RCT and six observational studies]), with an improved chance of clinical pregnancy in the intention-to-treat (ITT) population (RR 1.33, 95% CI 1.02– 1.72, [one RCT and six observational studies]). The number of mature oocytes retrieved per cycle (1.133, 95% CI 0.099–2.167) and number of zygotes per cycle (0.804, 95% CI 0.037–1.571) were not significantly more in patients treated with an LE protocol. The RCT failed to demonstrate both benefits. Moreover, the effects on clinical pregnancy were not observed in women undergoing embryo transfer (RR 0.92, 95% CI 0.84-1.02, (one RCT and four observational studies]).

Chang et al. (2013) conducted a systematic review and meta-analysis of seven RCTs of poor responders. (3) It included 450 poor responders who underwent LE pretreatment with an antagonist protocol and 606 patients who underwent the antagonist protocol without pretreatment. No significant difference was found in the CPR (RR 1.22, 95% CI 0.89–1.68, six RCTs). However, the analysis demonstrated a significant decrease in cycle cancellation rates (RR 0.37, 95% CI 0.23–0.66). Significantly more oocytes were retrieved in the LE protocol group than in the standard protocol group (p=0.0003; WMD 0.99, 95% CI 0.45, 1.53). Similarly, the number of mature oocytes retrieved was significantly higher with the LE protocol (p<0.00001; 1.31, 95% CI 0.74, 1.87).

Zhang et al. (2022) performed a non-blinded RCT of 552 women with low ovarian response (according to the Bologna criteria) undergoing IVF. (4) In the study group, oral oestrogen valerate (2 mg twice a day) was initiated on Day 7 and continued until Day 2 of the participants' next menstruation. The control group did not receive oestrogen pretreatment. The GnRH antagonist protocol was followed for ovarian stimulation in both groups. The groups showed no significant difference in the number of retrieved oocytes (3.2 [2.8] vs 3.4 [2.6], respectively) and CPR (19.3% [23/119] vs 28.7% [43/150], p>0.05).

Recommendation

Routine pretreatment with oestrogen in the luteal phase (oestrogen priming) is not recommended for poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendation

RCTs on oestrogen priming have failed to conclusively demonstrate its benefits on clinical outcomes, such as pregnancy rate and LBR. There is also considerable variability between studies with regard to the definition of poor responders, comparator groups, protocols for oestradiol priming, dose, and duration of treatment.

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4.6. Does pretreatment with oral contraceptive pills improve the efficacy and safety of ovarian stimulation in poor responders?

Background

OCP pretreatment is administered over varying periods ranging from 12 to 25 days prior to starting COS. (1) It is expected to synchronise the follicular cohort at the start of COS and consequently improve oocyte recovery, availability of embryos, and possibly, LBRs. (2) This intervention may be particularly important for poor ovarian responders because their available follicular cohort at the start of COS may be small and non-synchronous, allowing only a few larger follicles to respond to COS. The duration between OCP cessation and initiation of COS varies between 2 and 7 days. A pill-free duration of 5 days has been proposed as optimal by Cedrin-Durnerin et al. (3) It is hypothesised that a 5-day interval allows for retention of the OCP benefit on follicular cohort synchronisation while enabling recovery of follicular sensitivity to FSH action, which may have been altered by OCP- induced pituitary suppression. Additionally, OCP pretreatment has also been used to schedule COS initiation in patients undergoing IVF and to prevent cyst formation in long GnRH agonist protocols. (4,5)

Evidence Summary

In a Cochrane review, Farquhar et al. (2017) synthesized evidence from 10 RCTs comparing OCP pretreatment with no pretreatment in women undergoing COS for IVF. These RCTs reported outcomes of live births. (6) Eight of these trials included mixed populations, and only two trials (n=80 and n=120) recruited poor responders alone. (7,8) These trials compared OCP pretreatment in antagonist cycles with either no pretreatment in antagonist cycles or with long agonist cycles.

While LBRs were lower in the mixed population group following OCP pretreatment with antagonist cycles (OR 0.74, 95% CI 0.58 to 0.95; six RCTs; 1335 women; I2=0%; moderate-quality evidence), no evidence of a difference in live births was found among poor responders; however, the sample was too small to reach a definite conclusion (OR 1.71, 95% CI 0.61 to 4.79; one RCT; 80 women). Furthermore, poor responders showed no difference in other treatment outcomes like clinical pregnancies (OR 1.85, 95% CI 0.69 to 4.97; one RCT; 80 women) or miscarriage rates (OR 2.05, 95% CI 0.18 to 23.59; one RCT; 80 women). No difference was seen in either oocyte recovery (mean difference [MD] 0.70, 95% CI -0.11 to 1.51; one RCT; 80 women), required gonadotropin dose (MD 20.00 IU/L, 95% CI -165.39 to 205.39; one RCT; 80 women), or stimulation days (MD 0.10 days, 95% CI -0.47 to 0.67; 1 RCT; 80 women) among poor responders with or without OCP pretreatment in antagonist protocol cycles.

On comparing the effects of OCP pretreatment in antagonist and long agonist cycles, no difference was observed in live births in the mixed population (OR 0.89, 95% CI 0.64 to 1.25; four RCTs; 724 women; I2=0%; moderate-quality evidence) or poor responders (OR 1.13, 95% CI 0.43 to 2.98; one RCT; 80 women). No difference was found with regard to clinical pregnancies (OR 1.12, 95% CI 0.44 to 2.83; one RCT; 80 women) or miscarriage rates (OR 1.00, 95% CI 0.13 to 7.47; one RCT; 80 women) between poor responders receiving OCP in antagonist cycle and those not receiving OCP in GnRH agonist cycles.

Bendikson et al. (2006) retrospectively studied 194 cycles of women with DOR undergoing IVF with a GnRH antagonist protocol. (9) Oral contraceptive pretreatment was used in 146 cycles. Pregnancy rates were the same in both groups. Patients receiving OCPs required more gonadotropins (5,890 IU) compared to those who did not (4,410 IU). The authors concluded that although pregnancy outcomes were similar in poor responders undergoing an antagonist protocol with or without OCP, the higher dose of gonadotropins needed for ovarian stimulation should be considered.

Recommendation

Pretreatment with oral contraceptive pills is not recommended for improving live births in poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

In poor responders, OCP pretreatment in antagonist cycles does not improve LBR, clinical pregnancies, or oocyte recovery compared to antagonist cycles without OCP pretreatment or long GnRH agonist cycles. Use of OCPs may increase total gonadotropin dosage.

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4.7. Does the GnRH antagonist delayed start protocol improve the efficacy and safety of ovarian stimulation in poor responders compared to the conventional antagonist protocol?

Background

In poor responders, the FSH levels rise in the late luteal phase and early follicular phase, resulting in early selection and discordance of the follicular cohort. Hence, cycle programming for synchronisation of follicular cohort is challenging in poor responders. Addition of GnRH antagonists in the follicular phase and initiation of ovarian stimulation after a delay of 5 to 7 days, described as the "GnRH antagonist delayed start" protocol, has been proposed to maintain the FSH levels at baseline and reduce variance. The rationale is to suppress FSH levels and obtain a more synchronised cohort of follicles.

Evidence Summary

A meta-analysis by Yang et al. (2020) included data from five RCTs with 514 Bologna poor responders: 256 patients on the delayed start protocol and 258 controls (conventional protocols). Four studies included conventional protocols, with luteal priming and GnRH antagonist flexible protocols, and one study included luteal priming with the microdose flare protocol. CPR was the primary outcome across all studies. The delayed start antagonist protocol increased chance for clinical pregnancy (16.80% vs 7.36% [RR 2.30, 95% CI (1.38, 3.82), p=0.001; I2=0%] and reduced risk of cycle cancellation (16.02% vs 26.36% [RR 0.63, 95% CI (0.45, 0.90), p=0.01; I2=0%]. Significantly more oocytes were retrieved in the delayed start protocol group (mean number of oocytes, 4.00 vs 2.77 [MD, 1.08; 95% CI 0.22–1.95; p=0.01; I2=71%; random effects model] along with a greater number of mature oocytes (MD, 0.85, 95% CI 0.11–1.58; p=0.02; I2=74%; random effects model). (1)

Di et al. (2023) performed a network meta-analysis of 15 RCTs that included 2173 women with POR. (2) Women undergoing the delayed start GnRH antagonist protocol had a 1.90, 2.11, 4.89, and 6.23-fold higher incidence of CPR per initiated cycle and a 30.80, 32.52, 35.49, and 37.72-fold lower risk of cycle cancellation compared to those receiving the long GnRH agonist, GnRH antagonist, GnRH antagonist/letrozole, and short GnRH agonist protocols, respectively. This network meta-analysis included all five trials analysed by Yang et al. (2020).

None of the studies commented on the safety of the delayed start protocol with regard to the adverse impact on the endometrium or long-term effects on the baby. The metanalysis by Yang et al. (2020) demonstrated comparable miscarriage rates between the delayed start GnRH antagonist protocol and other protocols. They observed miscarriage rates of 19.51% and 35.29% with the delayed start GnRH antagonist protocol and conventional COS protocols, respectively (RR 0.55, 95% CI [0.24, 1.23], p=0.15; four RCTs, 58 women [41 subjects:17 controls] I2=17%).

Recommendation

Routine use of the GnRH antagonist delayed start protocol is not recommended for poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendation

The routine use of the GnRH antagonist delayed start protocol is not recommended for poor responders undergoing IVF treatment. The protocol has been studied less than the conventional antagonist protocol. While meta-analyses by Yang et al. (2020) and Di et al. (2023) demonstrated higher CPRs and fewer cycle cancellations with the delayed start antagonist protocol compared to conventional protocols with LE priming and microdose flare, no study has compared the protocol to conventional protocols without priming. Further, the long-term effects of this protocol on the endometrium and baby have not yet been evaluated.

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4.8. Does antioxidant pretreatment improve efficacy and safety of ovarian stimulation in poor responders?

Background

Antioxidants represent a contemporary avenue for the management of POR in the field of ART. They are known for their ability to neutralise reactive oxygen species and reduce oxidative stress. Oxidative stress is implicated in various reproductive disorders, and its impact on oocyte quality and embryo development is gaining increasing interest. Antioxidants have been investigated for their potential to improve ovarian function and enhance reproductive outcomes in POR. Antioxidants, which include vitamins such as vitamin C and E, CoQ10, and other compounds, play a crucial role in mitigating the harmful effects of oxidative stress on the reproductive system. Studies exploring the utility of antioxidant supplementation for poor responders aim to assess whether this intervention can positively influence oocyte quality, embryo development, and ultimately improve the chances of successful pregnancy.

Evidence Summary

The safety and efficacy of antioxidant pretreatment in POR remain uncertain owing to a paucity of studies on this population. We evaluated the effects of antioxidants, including but not limited to vitamin C and E, melatonin, lycopene, and zinc. Research on antioxidant use in ART has primarily focused on broader infertility cohorts, and thus, targeted investigations on individuals with POR are lacking. Studies on the role of CoQ10 have been discussed separately in this guideline. Consequently, definitive recommendations for or against antioxidant pretreatment in this specific context cannot be formulated at this time. Clinicians are advised to exercise caution and evidence-based discretion when considering antioxidant interventions for POR. Given the evolving nature of research, continuous monitoring of emerging literature is essential to inform future clinical decision making and guideline development regarding the safety and efficacy of antioxidant pretreatment in individuals with POR.

Through an RCT, Bahia et al. (2017) evaluated the benefits of melatonin in patients with DOR. (1) The double-blind placebo-controlled trial examined the effect of 3-mg/day melatonin from day 5 of menstruation in the cycle prior to that planned for ovarian stimulation. The paper does not mention the primary outcome that was considered to define the sample size. Thirty-two individuals were enrolled in the melatonin group and 34 in the placebo group. Embryo transfers were performed for 19 and 11 patients in both groups, respectively. No significant differences in CPRs (2/19 vs 1/11) and miscarriage rates (2/19 vs 1/11) were observed between the groups due to low events. The study showed a significantly higher number of patients with MII oocytes (21/32 vs 12/34, p=0.014) and top-quality grade I and II embryos (18/32 vs 9/34, p=0.014).

Recommendation

Pretreatment with antioxidants is not recommended for poor responders due to lack of evidence.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendation

Evidence for the use of melatonin in patients with POR is limited to one small RCT. Although the RCT shows an increase in the proportion of patients with MII oocytes and TQEs in the melatonin group, the impact on clinically relevant outcomes, such as CPRs, LBRs, and cycle cancellation rates, are not reported. Further, there is a limited understanding of the suitable dose and duration of melatonin treatment in ART. There is no information on the long-term safety of this treatment.

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1. Jahromi BN, Sadeghi S, Alipour S, Parsanezhad ME, Alamdarloo SM. Effect of Melatonin on the Outcome of Assisted Reproductive Technique Cycles in Women with Diminished Ovarian Reserve: A Double-Blinded Randomized Clinical Trial. Iran J Med Sci. 2017 Jan;42(1):73–8.

4.9. Does alternative medicine-based therapy improve efficacy and patient-related outcomes in poor responders?

Background

Complementary and alternative medicine is popular for improving ART outcomes owing to the apparent acceptance of naturalness and synergy. We aimed to evaluate specific recommendations that improve outcomes in poor responders undergoing IVF/ICSI.

Evidence Summary

Limited studies have investigated the safety and efficacy of alternate medicine treatments in patients with POR. Further, the available evidence may be influenced by methodological variations and potential biases. The search focused the role of traditional Indian medicine, acupuncture, yoga, meditation, and Chinese and Korean medicine in treating POR. It must be noted that the GDG members lacked expertise in the Eastern systems of traditional medicine, preventing a comprehensive and critical appraisal of the evidence. We reviewed one meta-analysis that aimed to evaluate the benefits of acupuncture for patients with DOR. (1) However, the meta-analysis did not evaluate the impact on clinically relevant outcomes, such as CPRs or LBRs. Consequently, definitive recommendations for or against the use of alternate medicine treatments for POR could not be provided. Clinicians are advised to approach the integration of alternate medicine with caution, considering individual patient characteristics, preferences, and available evidence on conventional medicine.

The scarcity of expertise on traditional medicine within the GDG highlights the need for collaboration between traditional medicine experts and reproductive health researchers to enhance our understanding of the safety and efficacy of alternate medicine in the context of POR. Continuous reviewing of literature and efforts to bridge knowledge gaps would be essential for future guideline development in this domain.

Recommendation

There is insufficient data to make a recommendation for alternative medicine-based therapy for poor responders and recommend further research.	**Strong**

Reference

1. Lin G, Liu X, Cong C, Chen S, Xu L. Clinical efficacy of acupuncture for diminished ovarian reserve: a systematic review and meta-analysis of randomized controlled trials. Front Endocrinol. 2023 Aug;14:1136121.

4.10. Do lifestyle-based therapies improve efficacy and patient-related outcomes in poor responders?

Background

In recent years, there has been an increasing interest in the relationship between nutrition, lifestyle habits, and reproductive health. The role of various endocrine disruptors in the ovarian response remains unclear. The present recommendation is aimed to guide practicing reproductive physicians regarding the role of various lifestyle patterns in treating POR.

Evidence Summary

The safety and efficacy of diet or lifestyle modifications as interventions specifically tailored to patients with POR remain understudied. Limited evidence exists in the targeted population, and the GDG acknowledges the absence of direct studies assessing the impact of these interventions on POR. While findings from the general population may offer insights, the applicability and effectiveness of diet or lifestyle modifications in the context of POR cannot be conclusively determined. Consequently, the GDG has refrained from providing specific recommendations for or against these interventions in POR. Clinicians are encouraged to consider lifestyle factors, such as diet and exercise, as potential contributors to the overall health of patients with POR. Future research endeavors should aim to address this gap in knowledge through well-designed studies, focusing on the safety and efficacy of diet and lifestyle modifications as interventions for POR.

Recommendation

There is lack of evidence to recommend specific lifestyle-related interventions to improve outcomes in poor ovarian responders.	**Conditional**

5. Ovarian Stimulation Protocols
Does the Ovarian Stimulation Protocol Impact Efficacy or Safety in Poor Responders?

5.1. Is the GnRH antagonist protocol superior to the GnRH agonist protocol for poor responders?

Background

Addition of GnRH antagonist to stimulation protocols prevents premature LH surges as well as suppression in the early follicular phase. In poor responders with low ovarian reserves, these endogenous FSH and LH levels without suppression may contribute significantly to the circulating gonadotropin pools.

Evidence Summary

GnRH antagonist versus long GnRH agonist protocol

Papamentzelopoulou et al. (2021) conducted a meta-analysis to compare the efficacy of GnRH antagonist and GnRH agonist protocols in women with POR (as defined by the Bologna criteria). (1) In the included RCTs (four studies) and prospective/retrospective studies (five studies), 1098 patients underwent treatment with the GnRH antagonist ovarian stimulation protocol and 1372 patients with the GnRH agonist protocol. On evidence synthesis, more clinical pregnancies were observed in patients following GnRH agonist protocols (p=0.018, OR=0.748<1, 95% CI 0.588–0.952) than in those following GnRH antagonist protocols. Cycle cancellation rates were, however, lower with GnRH antagonist protocols than with agonist protocols (p=0.044, OR 1.268>1, 95% CI 1.007–1.598).

On evaluation of the RCTs within the above meta-analysis, Prapas et al. (2012) compared the CPR of 162 poor responders undergoing treatment with the long GnRH agonist protocol with that of 168 poor responders undergoing treatment with the GnRH antagonist protocol. (2) The CPR per cycle initiated was higher in the long GnRH agonist group (35.8% vs 25.6%, p=0.03).

In an earlier meta-analysis by Lambalk et al. (2017), six RCTs comparing agonist and antagonist protocols in poor responders were included. (4) Of these, four studies included for evidence synthesis were published before 2011, when there was no consensus on the definition of POR. The meta-analysis showed no significant differences in the OPR per patient (RR 0.87, 95% CI 0.65–1.17, six studies), CPR per patient (RR 0.85, 95% CI 0.66–1.10, six studies), and the number of oocytes retrieved per patient (WMD -0.08, 95% CI -0.59–0.43, six studies). The meta-analysis included the two RCTs described above.

Sunkara et al. (2014) conducted an RCT comparing poor responders on long GnRH agonist, short GnRH agonist, and antagonist protocols. (3) One hundred eleven women were randomised to one of the three regimens. The number of retrieved oocytes was evaluated as the primary outcome, and it was significantly higher in the long GnRH agonist group than in the short GnRH agonist group (4.42 ± 3.06 vs 2.71 ± 1.60), while there was no significant difference between the long agonist and antagonist regimens (4.42 ± 3.06 vs 3.30 ± 2.91). The two other RCTs in the meta-analysis compared microdose-flare agonist protocols with letrozole and antagonist protocols and have therefore not been reviewed further.

GnRH antagonist versus short GnRH agonist protocol

Xiao et al. (2013) performed a meta-analysis, in which they synthesized evidence from 12 studies of poor responders. Seven studies comparing GnRH antagonist protocols (417 participants) to short GnRH agonist protocols (318 participants) were analysed as a subgroup. (5) No difference was observed in the CPR of both groups (RR 1.33, 95% CI 0.88–2.01, I2: 0%, seven studies). The number of retrieved oocytes favoured the short GnRH agonist protocol over the GnRH antagonist protocol (WMD -0.54, -0.98 to -0.10, I2=19%, five studies). This difference was primarily attributed to one study (Malmusi et al., 2005) and was insignificant on excluding the same. Cycle cancellation rates were similar across both protocols (RR 1.08, 95% CI: 0.75–1.57, I2=0, seven studies).

Minoodokht et al. (2022) conducted an RCT of poor responders, in which 96 patients were stimulated using the short GnRH agonist protocol and 96 patients using the GnRH antagonist protocol. (6) The primary outcome of the study was the number of retrieved MII oocytes, which was not significantly different between the two groups (2.99 ± 2.60 vs 3.10 ± 2.70, p=0.76). Similarly, no significant differences were observed in clinical pregnancy (5 [5.21%] vs 5 [5.21%], p=1.0) or LBRs (4 [4.17%] vs 4 [4.17%], p=1.00). Aly et al. (2020) conducted an RCT of poor responders, with 50 patients in the short GnRH agonist group and 50 in the GnRH antagonist group. The primary outcomes were not clearly indicated in the study. There were no significant differences in the number of retrieved oocytes (2 [0-4] vs 2 [0-3]), pregnancy rates (20% vs 18%), or miscarriage rates (44.4% vs 30%) between both groups.

Schimberni et al. (2016) compared a short GnRH agonist protocol (n=75) and a flexible antagonist protocol (n=71) through an RCT. (7) CPRs were significantly higher in the short GnRH agonist group than in the GnRH antagonist group (29.3% vs 14.1%, p=0.0291). Similarly, implantation rates were higher in the short GnRH agonist group (19.2% vs 9.3%, p=0.040).

Recommendations

The GnRH antagonist protocol and long GnRH agonist protocol are equally recommended for poor responders.	**Strong**	⊛⊛⊘⊘
The short GnRH agonist protocol is not recommended over the GnRH antagonist protocol for poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for recommendations

According to the meta-analysis by Lambalk et al. (2017), which synthesized evidence from RCTs, there was no difference in the efficacy of agonist and antagonist protocols in terms of clinical pregnancy, ongoing pregnancy, and number of oocytes retrieved. Although Papamentzelopoulou et al. (2021) observed a higher CPR with GnRH agonist protocols, their meta-analysis included low-quality observational studies. The analysis also suggested higher cycle cancellation rates with the GnRH agonist protocol than with the GnRH antagonist protocol. Long GnRH agonist protocols have demonstrated either similar or better performance than that of antagonist protocols; however, these findings require further validation.

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5.2. Is the mild ovarian stimulation protocol superior to conventional protocols (GnRH antagonist or long GnRH agonist protocol) in poor responders?

Background

Mild stimulation refers to stimulation with oral ovulogens (anti-oestrogens or aromatase inhibitors) alone or with gonadotropins or stimulation with low gonadotropin doses alone. (1) A mild IVF cycle is that in which FSH or hMG is administered at lower doses (≤150 IU/day), for a shorter duration in a GnRH antagonist co-treated cycle, or when oral compounds (anti-estrogens or aromatase inhibitors) are used either alone or in combination with gonadotropins. hCG injection and luteal support are also administered. The objective of mild stimulation is to collect 2–7 oocytes.

The intensity of stimulation has been studied in poor responders. As they may have very few follicles, some studies have pointed to results being similar with mild ovarian stimulation (MOS) and conventional stimulation.

Evidence Summary

Oral ovulation stimulating agents with or without gonadotropins versus conventional stimulation

A metanalysis by Montoya-Botero et al. (2021) included 15 RCTs of low- to- high quality comparing MOS and COS and focusing on outcomes of fresh and cumulative LBRs in patients with POR. Conventional protocols included both agonist and antagonist cycles. (2)

The meta-analysis concluded that cumulative LBR did not differ between the two stimulations (RR 1.15; 95% CI 0.73−1.81; I2=0%, moderate certainty, two studies). There was no significant difference between fresh LBRs across the mild and conventional stimulation groups (RR 1.01; 95% CI 0.97−1.04; I2=0%, n=1001, low certainty, six studies). On sub analysis, there was no significant difference in the fresh LBR of patients who received clomiphene with gonadotropins (RR 1.01, 95% CI 0.97–1.06, one study) and letrozole with gonadotropins with/without antagonist (RR 1.03, 95% CI 0.94–1.14, 12 studies) as compared with the agonist protocol. There was no difference in the CPR (12 trials included, 2355 women, RR 1.00; 95% CI 0.97−1.03; I2=0%, low certainty) and OPR (six trials, 1480 women, RR 1.01; 95% CI 0.98−1.05; I2=0%, low certainty) of MOS and COS groups. The MOS group exhibited a significantly lower oocyte yield (MD −0.80; 95% CI −1.28, -0.32; I^2=83%, n=2516, very low certainty) and higher cycle cancellation rate (RR 1.48; 95% CI 1.08−2.02; I^2=62%, n=2588, low certainty).

In a meta-analysis, Bechtejew et al. (2017) compared oral ovarian stimulating agents (clomiphene or letrozole) with or without gonadotropins and GnRH antagonists with conventional stimulation, which included either GnRH agonist or antagonist protocols. (3) They synthesized evidence from 22 RCTs of women with and without expected POR. In women with expected POR, there was no significant difference in the CPR obtained with clomiphene citrate alone (RR 0.90, 95% CI 0.36–2.26, one study), clomiphene citrate + low-dose FSH (RR 1.48, 95% CI 0.79–2.29, one study), and clomiphene citrate + low-dose FSH + antagonist (RR 0.94, 95% CI 0.68–1.31, three studies) versus conventional stimulation (overall RR 1.02, 95% CI 0.78–1.35). Similarly, there was no significant difference in the CPR obtained with letrozole + low-dose FSH (RR 1.00, 95% CI 0.44–2.28, two studies) or letrozole + low-dose FSH + GnRH antagonist (RR 0.94, 95% CI 0.44–2.03, two studies) versus conventional stimulation (overall RR 0.97, 95% CI 0.5–1.70). There was a significant decrease in the gonadotropin dose used (MD −18 ampules, 95% CI −21 to −15; moderate-quality evidence). None of the studies compared letrozole alone to conventional protocols. The meta-analysis also did not investigate perinatal outcomes and birth defects owing to paucity of data.

Low-dose gonadotropins versus conventional protocols

The metanalysis by Montoya-Botero et al. (2021) compared fresh LBRs in patients with POR receiving low-dose gonadotropins with/without an antagonist with those in patients undergoing conventional stimulation protocols (GnRH agonist and GnRH antagonist). The study found no significant difference between the two groups (RR 1.00, 95% CI 0.90–1.12, two studies). (2)

A meta-analysis by Yousef et al. (2018) evaluated five studies of women with POR and compared the use of lower and higher doses of gonadotropins. There was no difference in the OPR (two RCTs: RR 0.98, 95% CI 0.62–1.57, I2=0), CPR (three RCTs: RR 1.00, 95% CI 0.68–1.51, I2=0), or LBR (one RCT: RR 1.11, 95% CI 0.30–4.12) of both groups. (4)

Recommendations

Mild stimulation with low-dose gonadotropin or conventional stimulation are equally recommended in poor responders.	**Strong**	⊛⊛⊘⊘
Mild stimulation with oral letrozole in combination with low-dose gonadotropin or conventional stimulation are equally recommended in poor responders.	**Strong**	⊛⊛⊛⊘
Mild stimulation with oral clomiphene citrate in combination with low-dose gonadotropin or conventional stimulation is equally recommended in poor responders.	**Strong**	⊛⊛⊛⊘
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**	

Rationale for Recommendations

There are insufficient data to recommend letrozole alone over conventional stimulation in poor responders considering the paucity of studies. More RCTs are needed. However, there is moderate-quality evidence from many meta-analyses and RCTs that oral ovarian stimulation drugs combined with low-dose gonadotropin help achieve comparable CPR, OPR, cumulative LBRs, and fresh LBRs, making it a viable option despite some studies indicating that the number of retrieved oocytes may be low and cancellation rates higher. At the same time, there is strong evidence that lower doses of gonadotropin are used with a shorter duration of stimulation. Safety regarding neonatal outcomes and long-term effects on the baby cannot be commented on due to lack of sufficient data.

There is moderate-quality evidence that lower doses of gonadotropin without oral ovarian stimulation drugs are as efficacious as higher doses in terms of CPR. There is low evidence that LBRs are similar, and therefore, larger studies powered to LBR are needed. The total dose of gonadotropins needed is much lower, and stimulation is administered over a shorter duration.

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5.3. Is GnRH agonist flare protocol superior to long GnRH agonist protocol in poor responders?

Background

The long GnRH agonist protocol in ART cycles reduces the incidence of a premature LH surge, thereby resulting in fewer cycle cancellations and higher pregnancy rates. The short GnRH agonist flare is suggested as an alternative for poor responders. The long agonist regimen can prevent excessive pituitary suppression and the initial flare effect of the GnRH agonist can provide additional gonadotropin stimulation, thereby improving cycle outcomes. The current search was undertaken to compare the two regimens.

Evidence Summary

In a systematic review and meta-analyses by Sunkara et al. (2007), only one RCT compared the GnRH agonist long regimen (29 patients) with the GnRH agonist short regimen (31 patients) in women with POR. (1,2) The study was designed to evaluate the difference in the number of oocytes and reported significantly more oocytes retrieved with the long regimen (WMD 1.35, 95% CI 0.15–2.55). There was no statistically significant difference in clinical pregnancy between the groups (RR 6.55, 95% CI 0.86–50.2). The studies were not powered to detect differences in CPRs. In view of a small sample size, heterogenous nature, they reported inconclusive results and recommended further research.

Sunkara et al. (2014) conducted an RCT of 92 poor responder women. (3) Thirty-one of them underwent COS with the long GnRH agonist regimen (group A), 31 women with the short GnRH agonist regimen (group B), and 30 women with the GnRH antagonist regimen (group C). The number of retrieved oocytes was significantly more with the long GnRH agonist regimen than with the short GnRH agonist regimen (4.42 ± 3.06 vs 2.71 ± 1.60; p<0.01). The duration of stimulation was significantly longer with the long GnRH agonist regimen compared with the short agonist regimen (12.4 ± 2.7 vs 10.5 ± 2.4 days; p<0.005). Also, the total gonadotropin consumption was significantly higher with long GnRH agonist than with the short GnRH agonist (5540.32 ± 1216.1 vs 4819.35 ± 1145.5 IU; p=0.02). The OPR was 8.1% in group A, 8.1% in group B, and 16.2% in group C (p=0.48). The study was not powered to detect significant differences in pregnancy outcomes. Sunkara et al. concluded that the long agonist and the antagonist regimens offer a suitable choice for ovarian stimulation in poor responders. The short GnRH agonist regimen was less effective as fewer eggs were retrieved, and its use for poor responders should be questioned. The inferior outcome with the short agonist protocol could perhaps be explained by the elevated progesterone levels during the early follicular phase because of the initial flare effect of the GnRH agonist, which has been shown to impair follicular recruitment.

Chatillon-Boissier et al. (2012) conducted a prospective, randomised study of 44 poor responders (age 38–42 years, FSH at day 3 > 9.5 IU/L, AFC ≤6, and/or failure of previous stimulation). Thirty-nine cycles were evaluated (20 long agonist protocol, 19 short agonist protocol). At the end of the stimulation, the number of recruited follicles was higher in the long protocol, but the difference was not significant (diameter between 14 and 18 mm: 3.0 ± 2.31 vs 1.88 ± 1.89 and diameter greater than 18 mm: 3.9 ± 2.85 vs 3.06 ± 2.77). The same trend was observed for the number of retrieved oocytes (6.74 ± 2.73 vs 6.38 ± 4.26), total number of embryos (3.16 ± 2.03 vs 2.25 ± 2.11), pregnancy rate per retrieval (21% vs 19%) and per cycle (20% vs 16%), and the number of children born alive. The study did not reveal any difference between the two protocols. (4)

Recommendation

The GnRH agonist flare protocol is not recommended over the long GnRH agonist protocol for ovarian stimulation in poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

A limited number of RCTs has compared GnRH short agonist and long GnRH agonist protocols. The available studies consistently indicate that the long GnRH agonist protocol is associated with higher gonadotropin dose requirements and possibly yields a higher number of oocytes when compared to short GnRH agonist protocols. The available data are insufficient to determine the implications of these findings on CPR, OPR, and LBRs across the two protocols.

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5.4. Is DuoStim superior to antagonist/mild stimulation or two conventional (BISTIM) protocols for poor responders?

Background

Folliculogenesis is a dynamic process, leading to the development and release of a single oocyte. Recently, the concept of a single cohort of antral follicles being recruited under hormonal influences in an ovarian cycle seems to have been challenged by the wave theory of multiple cohorts of follicles undergoing development at different times in a single ovarian cycle. (1) Similar to evidence from large animal studies, human ovaries have two-three cohorts of follicle development, which has paved way to understand newer protocols on ovarian stimulation that initiate folliculogenesis even in the late follicular or luteal phase of the cycle. Experience of random start stimulation protocol in the luteal phase for cancer patients (2,3) prompted its use even in poor responders. Conventional FPS followed by LPS is called dual stimulation. (4) It essentially involves achieving oocyte recovery twice in one ovarian cycle, resulting in a yield in both phases of the ovarian cycle, with the aim of harvesting the maximum from the same cycle. This, however, involves freezing embryos after both stimulations and a frozen embryo transfer in a subsequent endometrial primed cycle. The ideology to obtain a higher number of oocytes and embryos in a single cycle has been backed by similar competence besides euploid status of embryos from the oocytes obtained in LPS. (5) The opportunity to have all this in the same cycle reduced time to pregnancy and patient dropout rates, transformed clinical trials conducted with observational design into a quasi-randomised and recently randomised design. The studies consider the number and days of gonadotropin use, number of competent MII oocytes, fertilisation and blastulation, besides euploidy rate of embryos, clinical pregnancy, miscarriage rate, and liver birth per cycle, per patient.

Evidence Summary

DuoStim versus antagonist/mild stimulation

Historically Kuang et al. were the first to report the use of dual stimulation for poor responders in a pilot study of 38 women defined as poor responders as per the Bologna criteria. (6) Defined as the Shanghai protocol, it involved mild stimulation in the follicular phase, with clomiphene citrate started from day 3 until trigger and letrozole from day 3 for 4 days followed by hMG in an antagonist protocol. This led to oocyte retrieval in stage one, which was followed by LPS using letrozole and hMG. Oocyte retrieval was performed for the second time in the same cycle after dominant follicles matured. The primary outcome was the number of oocytes obtained from both phases in the same menstrual cycle, which was significantly more in the second phase (stage one 1.7 ± 1.0; stage two 3.5 ± 3.2; p=0.001). Twenty-one women underwent 23 cryopreserved embryo transfers, resulting in 13 clinical pregnancies. The study suggested that double ovarian stimulations in the same menstrual cycle provided more opportunities in poor responders, with initiation in the luteal phase resulting in retrieval of more oocytes in a short period. Subsequently, small prospective and retrospective studies were published on dual stimulation in women with POR, comparing ART outcomes between follicular and luteal phases of stimulation (4,7) and confirming the safety and efficacy of DuoStim with a higher number of oocytes and embryos from LPS than from the follicular phase. Ubaldi et al. (2016) published the proof of concept with 43 women with POR undergoing DuoStim and IVF cycle, with PGT-A of embryos demonstrating a similar euploid rate between the embryos from either phase. Vaiarelli et al. from the same unit, however, undertook an observational study where 100 out of the 297 women meeting the Bologna criteria underwent DuoStim. They found a higher number of oocytes after LPS, with similar developmental and chromosomal competence as paired FPS-derived ones. The number of women obtaining one euploid embryo and the cumulative LBR per ITT were not significantly different between women undergoing DuoStim or conventional stimulation, even though the cumulative LBR increased from 7% after FPS to 15% after DuoStim. However, the interval between two stimulations was much shorter after DuoStim than between two conventional stimulations, suggestive of higher dropouts (81%) as only 9% returned for a second stimulation after failed conventional stimulation.

Comparison between DuoStim and conventional antagonist or mild stimulation protocols were reviewed systematically by Sfakianoudis et al. in 2019. (8) Of the nine studies presented in the systematic review, five essentially compared the ART outcomes between DuoStim and conventional stimulation in POR. These studies suggest that DuoStim resulted in a significantly longer duration of stimulation (15.26 ± 4.90 days vs 8.26 ± 3.52. days) and lower cancellation rates (13.1 to 18.10% vs 28.7 to 37.1%) compared to conventional stimulation. All these studies reported significantly more oocytes retrieved following DuoStim in comparison to conventional stimulation (5.83 to 8.8 vs 2.3 to 6.7) besides significantly more MII oocytes (4.73 to 9.23 vs 1.93 to 5.3) with DuoStim. Embryology data, however, did not suggest differences with regard to the fertilisation rate but favoured DuoStim for a greater number of TQEs, perhaps due to a higher number of MII oocytes obtained. There were no significant differences between both stimulation protocols with regard to CPR, OPR, and LBR. The reviewers concluded that the superiority of DuoStim over conventional stimulation is currently uncertain in poor responders given that the benefits in number of oocytes do not translate to a higher CPR or LBR with the DuoStim protocol.

DuoStim versus two consecutive conventional stimulation (BISTIM)

DuoStim was compared with two consecutive conventional stimulations after this systematic review. Of two studies, one was a randomised trial and the other a retrospective study. (9). Both suggested non-superiority of DuoStim over two consecutive conventional stimulations. The BISTIM study, a multi-center open label RCT performed by Massani et al., recruited 88 poor responders (as per Bologna criteria), randomising 44 each to either dual ovarian stimulation (DuoStim) or two conventional ovarian stimulation during IVF cycles. (9) The primary objective was to obtain two more oocytes after DuoStim than the cumulative number of oocytes from two consecutive conventional stimulations with an antagonist protocol. The cumulative number of total oocytes, including mature ones, were no different in the two consecutive ovarian stimulation and DuoStim groups. The total number of embryos transferred was significantly higher in the control group 1.5 (1.1) versus the DuoStim group 0.9 (1.1) (p=0.03). After two cumulative cycles, 78% of women in the control group and 53.8% in the DuoStim group had at least one embryo transfer (p=0.02). There was no statistical difference in the mean number of total and mature oocytes retrieved per cycle in both control and DuoStim groups. The time to the second oocyte retrieval was significantly longer in controls at 2.8 (1.3) months compared to 0.3 (0.5) months in the DuoStim group (p<0.001). The implantation rate was similar between groups. The cumulative LBR was not statistically different, comparing controls versus the DuoStim group, 34.1% vs 17.9%, respectively (p=0.08). The only advantage with DuoStim was the shorter time to second retrieval (by 2 weeks); however, it came at a cost of wastage of more oocytes and embryos, particularly in poor responders, as it involved vitrification and thawing, while a fresh transfer may be feasible after two consecutive ovarian stimulations. The researchers concluded that the benefit of DuoStim in patients with POR, selected by low ovarian reserve markers and not specifically by advanced maternal age, is not confirmed in this RCT.

Recommendations

The DuoStim protocol is not recommended over the GnRH antagonist protocol in poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendations

DuoStim may yield additional oocytes retrieved and higher number of viable embryos for transfer besides reducing the dropouts compared to conventional stimulation protocol for women with POR. However, it does not improve the OPR or LBR when compared to conventional stimulation. Data on cost-effectiveness for increased cost of gonadotropins in same cycle, freezing and thawing embryos have not been studied. Further data on safety and long-term outcome of neonates have not yet been reported.

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5.5. Is luteal phase stimulation superior to follicular phase stimulation for poor responders?

Background

Recent evidence suggests that folliculogenesis occurs in waves within the menstrual cycle, challenging the idea of a single follicle cohort developing only in the follicular phase. This wave-like pattern offers new opportunities for ovarian stimulation, especially in women with DOR. LPS capitalises on these waves by extending stimulation into the luteal phase. By doing so, clinicians aim to recruit additional follicles potentially missed during initial stimulation, improving egg retrieval in DOR patients. Additionally, LPS may enhance synchronisation between follicular and endometrial development, crucial for successful embryo implantation. This approach also holds promise for optimising hormonal conditions within the ovaries, potentially enhancing egg quality. In summary, LPS offers a strategic means to maximise egg quantity and quality, improving outcomes in ART cycles for women with DOR.

Evidence Summary

In a retrospective study of FPS and LPS alongside administration of clomiphene citrate and hMG to poor responders, Li et al. employed mild stimulation. (1) The study confirmed significantly more mature oocytes, more TQEs, and reduced cycle cancellation rate in the luteal group than in the follicular group. In both groups, embryos were frozen on day 3 and transferred in subsequent cycles with endometrial priming using oestrogens and progesterone. The CPRs and LBRs after embryo transfers were comparable in both groups. The findings suggest that LPS may be considered owing to a greater chance of obtaining competent embryos and reduced cycle cancellation rate in poor responders. A major drawback was that the study was not adequately powered and lacked a matching number of samples in the experimental and control groups. The FPS group had three times more participants than the LPS group.

In a systematic review and meta-analysis, Lu et al. analysed studies that compared LPS with FPS. They excluded studies that deployed DuoStim or follicular and luteal stimulation in the same ovarian cycle and women with cancer undergoing ovarian stimulation during luteal phase. (2) Twelve studies (11 retrospective and one RCT) with 4433 patients were included, comprising normal responders, oocyte donors, and poor responders. Seven studies included women defined as poor responders. Only five studies included LBR as an outcome. This review suggested that the CPR and LBR were no different between the FPS and LPS groups. Further, the duration and dosage of gonadotropins were significantly higher with luteal stimulation. The LPS group exhibited significantly more retrieved oocytes than the FPS group. Based on the available studies, the reviewers suggested that luteal stimulation was non-inferior to follicular stimulation. However, given the lack of randomised data on freeze-all policy and limited studies reporting live birth as an outcome, the use of LPS in poor responders remains debatable.

Recommendation

Luteal phase stimulation is not recommended over follicular phase stimulation for poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

LPS results in a greater duration and dosage of gonadotropin treatment for ovarian stimulation in poor responders. It may result in a higher number of mature and competent oocytes retrieved with more good quality embryos for vitrification and subsequent frozen embryo transfer. However, it does not improve the LBR over that obtained with conventional FPS.

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5.6. Is the modified natural cycle protocol superior to GnRH antagonist protocol in poor responders?

Background

Despite high doses of gonadotropins, the overall oocyte yield remains low in most cases of POR. The modified natural cycle has emerged as an effective strategy, in which once a follicle reaches 14-mm size in a natural cycle, GnRH antagonist is added to the treatment with low-dose FSH or hMG (150 U) followed by hCG or GnRH trigger. The aim of the modified natural cycle is to obtain 1 or 2 oocytes with better characteristics, which may convert into a good quality embryo that can be transferred in a more receptive endometrium. Modified natural cycles have been suggested to be more cost-effective, patient-friendly, and equally efficacious as conventional dose IVF in poor ovarian responders.

Evidence Summary

The currently available data on the role of modified natural cycles in poor ovarian responders are inconclusive owing to the use of different definitions of POR, small sample size, and mixed results. Elizur et al. (2005) retrospectively analysed 540 cycles in 433 poor responders (defined as having <4 oocytes at ovum pick-up or serum oestradiol level <1000 pg/mL on the day of hCG). Fifty-two modified natural cycles were compared with 200 antagonist and 288 long agonist cycles. (1) In the modified natural group, Although the modified natural group showed significantly fewer retrieved oocytes than both antagonist and long agonist groups (1.4 ± 0.5 vs. 2.3 ± 1.1 and 2.5 ± 1.1, respectively, $p<0.05$), the implantation and pregnancy rates were similar in all groups (10% and 14.3%, 6.75% and 10.2%, and 7.4% and 10.6%). The authors concluded that the modified natural cycle can be an effective alternative to conventional stimulation in poor responders.

In 2009, a prospective randomised study was performed with 90 low responder women; of them, 45 were randomised to the minimal stimulation (modified natural) group and 45 to the conventional antagonist cycle group. (2) A low responder was defined as a patient who failed to produce ≤3 follicles with a mean diameter of at least 16 mm, with the result that ≤3 oocytes were retrieved despite the use of a high gonadotropin dose (>2500 IU) in previous failed IVF/ICSI cycles. In the minimal stimulation group, 150 U rFSH and antagonist were started on day 6/7 of the cycle when the follicle reached 13–14 mm size. The conventional group received 225 U rFSH from day 3 in a flexible antagonist cycle. The numbers of oocytes, mature oocytes, and embryos transferred were significantly lower in the minimal stimulation group. However, the CPRs per cycle initiated, LBR per embryo transfer, and implantation rates of the minimal stimulation group were similar to those of the conventional group. The dose and days of gonadotropins and GnRH antagonist use were less in the minimal stimulation group. Hence, it was more cost-effective.

Kedem et al. recruited 111 Bologna poor responders for modified natural cycle treatment within 3 months of failed conventional stimulation IVF. (3) These women yielded up to 3 oocytes after receiving a minimum of 300 U FSH in the conventional stimulation cycle. The authors therefore termed these participants as “genuine poor responders.” The LBR in the modified natural cycle group was <1%, and no pregnancies were reported in cycles with only 1 oocyte retrieved. It was concluded that the modified natural cycle does not offer any benefit for genuine poor responders, and oocyte donation may be considered for such patients.

Lainas et al. (2015) retrospectively compared 161 modified natural cycles with 164 high-dose FSH antagonist cycles in poor responders (Bologna criteria). (4) LBRs were higher in the modified natural cycle group than in the high-dose FSH group (OR 4.01, 95% CI 1.14–14.09), after adjusting for basal FSH level, age, and cause of infertility. Though fewer oocytes were retrieved and fewer embryos were formed in the modified natural cycle group, the proportion of cycles with 1 good embryo per started cycle was similar with both modified natural and conventional stimulation. This study was later criticised for faulty statistical methods, few events per variable in regression models, and low LBRs in the whole cohort. (5)

Another retrospective cohort study (2019) included 476 advanced-age poor responders (Bologna criteria), with 189 of them in the modified natural cycle group and 287 in the high-dose ovarian stimulation group. (6) OPRs were significantly lower with modified natural cycles as compared to the high-dose group (5/189, 2.6% vs 29/287, 10.1%; p=0.002). However, after adjusting for relevant confounders and multivariate regression analysis, both regimens were found similar in terms of OPRs. The authors concluded that in advanced-age poor responders, modified natural cycles are a cost-effective and patient-friendly alternative to conventional stimulation.

Recommendation

The modified natural cycle protocol is not recommended over the GnRH antagonist protocol for poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

The modified natural cycle apparently offers a cost-effective and patient-friendly alternative to conventional stimulation, but the pregnancy rates and LBRs remain low. More prospective RCTs with a greater sample are required before adopting this technique as an effective alternative to conventional stimulation in poor responders.

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5.7. Is the progesterone primed ovarian stimulation protocol superior to the GnRH antagonist protocol for poor responders?

Background

Progesterone preparations, both natural and synthetic, can effectively block LH surge during ovarian stimulation for IVF. Progesterone preparations have the advantage of an oral route of administration, fewer side effects, and lower cost compared to GnRH antagonists. Their disadvantages include the requirement of a freeze-all strategy owing to endometrial advancement, adding to overall costs and time to pregnancy. Conventionally, 10-mg MPA has been used either from the early follicular phase (conventional PPOS) or started from day 5 to 7 when the lead follicle reaches 12-14 mm (flexible start PPOS), similar to what is adopted for flexible GnRH antagonist protocols. Other progesterone preparations, e.g., dydrogesterone and micronised progesterone, have also been used.

Evidence Summary

Chen et al. (2019) conducted an RCT (340 women: 170 subjects and 170 controls) comparing the role of progestin to GnRH antagonist in preventing premature LH surges in poor responders undergoing IVF. (1) The study revealed that PPOS prevented premature LH surges more effectively than the GnRH antagonist protocol (0% vs 5.88% $p<0.05$), but there was no significant difference in the average numbers of oocytes and viable embryos (3.7 ± 2.6 vs 3.4 ± 2.4; 1.6 ± 1.7 vs 1.4 ± 1.3, $p>0.05$) and LBR of the two groups (21.8 vs 18.2%, RR 1.25, 95% CI 0.73, 2.13, $p>0.05$). The authors suggested that further well-designed, large clinical trials are needed to compare live birth outcomes and the health economic implications of the two treatment strategies.

Cai et al. (2021) conducted a systematic review and meta-analysis, which included the RCT by Chen et al. (2019) and 15 other case-control studies with a total of 4422 cycles in poor responders (Bologna criteria). (2) They compared PPOS and Chinese minimal stimulation IVF, PPOS and an antagonist protocol, and PPOS and an ultra-short GnRH protocol. Several clinical indicators favoured the use of the PPOS protocol. Patients receiving PPOS exhibited more mature eggs, available embryos, and high-quality embryos. Additionally, the CPR was higher in the PPOS group, along with a lower serum LH level on the day of hCG injection and a reduced cycle cancellation rate. These findings suggest that PPOS is advantageous in terms of ovarian response and pregnancy outcomes for poor ovarian responders, making it a promising choice for IVF/ICSI-embryo transfer. The study concluded that PPOS, with its oral administration of progesterone, is not only effective but also cost-effective, potentially offering a suitable ovulation induction program for this patient population. The authors concluded that PPOS is a promising agent for suppression of LH in during ovulation induction in poor responders. However, the quality of evidence remains low.

Recommendation

The progesterone primed ovarian stimulation protocol is not recommended over the GnRH antagonist protocol for poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendations

The PPOS protocol, despite its robust prevention of premature LH surges compared to the GnRH antagonist, is not recommended over the GnRH antagonist protocol for poor ovarian responders undergoing IVF. While PPOS prevented premature LH surges, it did not significantly differ from the GnRH antagonist in terms of the average number of oocytes, viable embryos, or LBR. The protocol mandates embryo freezing, which requires additional resources and frozen embryo transfer. Additional resources are required for freezing and frozen embryo transfer. The systematic review and meta-analysis suggested that while PPOS may yield more mature eggs and higher-quality embryos, the overall pregnancy outcomes and cost-effectiveness did not favour PPOS over the GnRH antagonist.

Thus, despite its potential benefits for ovarian response and pregnancy outcomes, the recommendation does not support the preference of PPOS over the GnRH antagonist for this patient population undergoing IVF.

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6. Types of Stimulation Drugs
Does the Type of Stimulation Drug Impact Efficacy or Safety in Poor Responders?

6.1. What is the safety and efficacy of recombinant FSH compared to that of urinary gonadotropins in poor responders?

Background

hMGs are available as a combination of roughly equal quantities of FSH and LH and are derived from the urine of menopausal women. They have been used for COS in IVF cycles since 1981. (1) Urinary FSH is also derived from the urine of menopausal women and employs monoclonal antibodies against LH to alter the FSH to LH ratio to 75:1. However, it has protein contamination of 70–95%. Highly purified (HP) FSH and HP-hMG are now available, with protein contamination <5% and FSH bioactivity of 9000 IU/mg of protein. Lately, LH activity in urinary hMG has been derived from urinary hCG. (2) rFSH, on the other hand, has been produced using Chinese Hamster Ovary cell lines by transfecting it with two expression DNA plasmids encoding for alpha and beta subunits of FSH. rFSH has been available for use since 1993.

Compared to rFSH, urinary products have more protein contamination, leading to injection site allergic reactions and batch-to-batch inconsistency, which may result in suboptimal follicular development. On the other hand, the LH activity in hMG is expected to improve FSHR induction on granulosa cells, drive follicular growth in FSH-primed follicles in the late follicular phase, and improve steroidogenesis. These effects may help improve oocyte quality or clinical outcomes, thereby benefiting women deemed to be poor responders. (3)

Evidence Summary

hMG versus rFSH

A small RCT (2012) compared the two preparations in 127 women undergoing IVF (age ≥35 years, POSEIDON groups 2 and 4). (4) The participants being treated with the long agonist protocol were randomised to receive either HP-hMG (n=63) or rFSH (n=64) from day 2/3 of menstruation. More oocytes were obtained in the rFSH group (p<0.001). Further, the LBR per started cycle trended toward improvement with HP-hMG (OR 1.3, 95% CI 0.9-1.8; OR 1.9, 95% CI 0.9–3.9; respectively); however, there was no significant difference between the groups.

A large retrospective cohort study (2022) of 1398 IVF cycles in POSEIDON group 3 and 4 poor responders compared the effectiveness of rFSH (n=251) and hMG (n=1102). (5) It showed oocyte recovery rates of 0.85 ± 0.75 vs 0.83 ± 0.64 (p=0.84), CPRs of 6.8% vs 9.1% (p=0.37), and LBRs of 4% vs 6.2% (p=0.3) in the two groups, respectively. Cycle cancellation rates were 15.4% and 16.8% (p=0.8), respectively.

We found no reported case of OHSS in these studies.

Addition of hMG mid-cycle versus increment of rFSH dose in those with mid-cycle hyporesponsiveness to rFSH

A 2001 RCT defined mid-cycle suboptimal response as serum oestradiol concentrations ≤0.6 pmol/mL (~165 pg/mL) and no ultrasound evidence of follicles with a mean diameter >10 mm on day 8 of stimulation. Forty-three women with sub-optimal response to 300 IU of rFSH in a long agonist protocol on day 8 of stimulation were randomised to receive either replacement of 150 IU of rFSH with 150 IU of hMG (n=20) or a dose increment by 75 units, increasing the total daily dose of rFSH to 375 IU (n=23). (6) Both groups were additionally compared to 40 women who displayed

optimal midcycle response. The average number of oocytes retrieved (11.30 ± 6.91 vs 5.87 ± 2.32) was significantly higher on adding hMG ($p<0.001$). Ten pregnancies were achieved (50%) with hMG addition, eight (34.78%) with rFSH dose increment, and 19 (47.5%) in the control group ($p>0.05$). A trend towards a higher abortion rate was noted in the group with only rFSH-dose increment; however, it was not statistically significant.

Another prospective study (2004) randomised women with hyporesponsiveness to FSH in a GnRH agonist protocol on days 7–10 of stimulation to receive either an rFSH-dose increase alone (group A; n=54) or with addition of 75–150 units rLH (group B; n=54) or 75–150 units hMG (group C; n=20). (7) Hyporesponsiveness was defined as needing increased and/or prolonged FSH stimulation to continue and complete follicular growth. The outcomes in the respective groups were as follows: total cancelled cycles, 2 vs 4 vs 2; mean oocytes retrieved, 8.2 vs 11.2 vs 10.9; number of cycles with OHSS, 6% vs 15% vs 9%; and LBRs per started cycle, 22%, 40.7%, and 18% ($p<0.05$ group B vs groups A and C).

In a third RCT (2005), 68 women with hyporesponsiveness to rFSH in a GnRH agonist downregulated protocol were similarly randomised, and similar live birth outcomes were observed in the three groups. (8)

A 2021 cohort study analysed the effects of IVF cycles stimulated with rFSH alone (n=371), rFSH + midway hMG (n=172), or rFSH and hMG from day 2 (n=139) among 682 POSEIDON group 4 poor responders undergoing COS with an antagonist protocol. (9) The mean number of mature oocytes and available embryos was significantly higher with late supplementation than with early supplementation (5.1 vs 4.6 vs 5.7; $p=0.02$). The LBRs in the three groups were similar after fresh transfer (21.5% vs 255 vs 31%; $p=0.34$) or frozen transfer (15.1% vs 16.4% vs 27.1%; $p=0.2$).

Another retrospective cohort study (2022) analysed 582 IVF cycles in POSEIDON group 3 and 4 patients undergoing IVF stimulation with rFSH supplemented with hMG in the early follicular phase, rFSH supplemented with hMG in the mid-follicular phase, or rFSH without supplementation. (10) The mean oocytes recovered in the respective groups were 2.3, 2.3, and 2.6, respectively ($p=0.32$), and live births per embryo transfer were 21.9%, 11.7%, and 11.6%, respectively ($p=0.035$). The authors observed no benefit of supplementing hMG mid- cycle over using rFSH alone but found a significant benefit on initiating hMG with rFSH in the early follicular phase.

In women with DOR (aged <35 years) undergoing IVF in antagonist cycles, the number of retrieved oocytes was greater with rFSH alone than on adding hMG to rFSH in antagonist cycles (6.5 ± 2.1 vs 5.5 ± 2.3; p 0.001). (11) However, no difference was found in the CPR, miscarriage rate, or LBR of the two groups.

Urinary FSH versus rFSH

A prospective study compared IVF outcomes after COS among 56 women receiving rFSH and 44 receiving urinary FSH. (12) Patients receiving urinary gonadotropins required a higher number of ampoules [31.7 ± 8.6 vs 20.7 ± 6.4 ($p<0.001$)]. No differences in peak oestradiol, day of hCG, endometrial thickness, or total retrieved oocytes were found. A higher number of embryo transfers were observed in the rFSH group (3.4 ± 1.7 vs 1.9 ± 2.2 ($p<0.004$)], but the pregnancy rates were similar across both groups (34.3% and 29.6%; $p>0.05$).

Another randomised study included 30 young infertile patients with POR in two previous consecutive cycles despite normal basal FSH and oestradiol concentrations. They were randomised to receive either rFSH or HP-FSH. (13) An evaluation of the total dose used (3800 IU vs 4600 IU, $p<0.05$) and duration of treatment (10.2 days vs 13.2 days, $p<0.05$) revealed a significantly shorter treatment period and lower total dose of FSH required to induce ovulation successfully in the rFSH group. Total retrieved oocytes (7.2 vs 5.6, $p<0.05$), total good quality embryos (3.4 vs 1.8, $p<0.05$ CPR (33 vs 7%, $p<0.01$), and implantation rates (16 vs 3%, $p<0.01$) were higher in the rFSH group.

Recommendations

The use of either hMG or recombinant FSH is equally recommended in poor responders.	**Strong**	⊛⊛⊘⊘
Mid-follicular addition of hMG in long agonist cycles is recommended for patients hyporesponsive to rFSH.	**Conditional**	⊛⊛⊘⊘
The use of urinary FSH over rFSH is not recommended in poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendations

In an RCT comparing the two preparations among women aged ≥35 years undergoing IVF, both hMG and rFSH yielded comparable LBRs per started cycle. Despite a higher number of oocytes retrieved in the rFSH group, no significant difference was observed in the LBRs of both groups. This finding underscores the similar effectiveness of both treatments in achieving successful outcomes. Further, a large retrospective cohort study of poor responder women in IVF cycles corroborated these results, demonstrating comparable oocyte recovery rates, CPRs, LBRs, and cycle cancellation rates between rFSH and hMG groups. Importantly, the absence of reported cases of OHSS in these studies highlights the safety profile of both treatments. Therefore, an equal recommendation for the use of either allows tailoring of treatment to individual patient needs without compromising on efficacy or safety.

One RCT of women with mid-cycle sub-optimal POR to rFSH in agonist cycles suggests that addition of hMG may help prevent low oocyte recovery and improve LBR to a greater extent than increasing FSH dose or continuing with the existing rFSH dose. Evidence from two other RCTs is equivocal. Low-quality evidence from three cohort studies of antagonist cycles suggests that the effect of hMG supplementation on live births compared to that of existing rFSH dose alone is variable.

The recommendation against using urinary FSH over rFSH in poor responders is supported by small studies. Patients treated with urinary FSH require significantly more ampoules of the medication, indicating less efficient follicular stimulation and perhaps improved oocyte recovery. Whether this translates into more live births is debatable since one or two extra oocytes may not improve LBR significantly in patients with POR.

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6.2. What should be the starting dose of gonadotropins to improve safety and efficacy of controlled ovarian stimulation in expected poor responders?

Background

A gonadotropin dose of 150-225 IU is standard for COS initiation (1). To optimise oocyte recovery, higher doses of 225, 300, 375, 450, and 600 IU have been used in expected poor responders (based on their ovarian reserve findings) with ambiguous effects. (2, 3) This question examines if starting COS with an increased dose would improve clinical outcomes among expected poor responders.

Evidence Summary

Five RCTs on gonadotropin dosing for expected poor responders (n=704) published till 2017 were summarised in a 2018 Cochrane review. (4) The studies were heterogenous owing to different dose comparisons, but none revealed improvement in LBR with a high dose: 450 IU vs 150 IU (OR 0.71 [0.32 to 1.58], n=286); 450 IU vs 300 IU (OR 0.77 [0.19 to 3.19], n=61); 600 IU vs 450 IU (OR 1.33 [0.71 to 2.52], n=356).

A large, open-label, multi-centre RCT, OPTIMIST (Tilborg et al, 2017), recruited 511 women with an AFC <11 between May 2011 and May 2014. (5) The participants were classified into those with AFC ≤7 (n=234) and those with an AFC of 8–10 (n=377). Those with an AFC ≤7 were randomised to receive 450 IU or 150 IU of rFSH and those with an AFC of 8–10 to receive 225 IU or 150 IU of rFSH from day 2 of the cycle. The primary outcome was ongoing pregnancy achieved within 18 months after randomisation and resulting in a live birth. The cumulative LBR with increased and standard dosing was 42.4% (106/250) and 44.8% (117/261), respectively (RR 0.95 [95% CI 0.78–1.15], p=0.58). An increased dose strategy was more expensive (delta costs/woman: €1099 [95% CI 562–1591]) and the standard FSH dosing of 150 IU more cost-effective. In a secondary analysis of the same data, the authors found that clinical pregnancy or live birth outcomes were similar with both dosing regimens, even on adjusting for body mass index and age. (6)

Liu et al. (2022) studied 661 women (aged <43 years) with AFC <10, who were referred for their first IVF cycle. They were randomised to start FSH at increased dosing (n=328) or standard dosing (n=333). Among participants allocated to increased FSH dosing, women with an AFC of 1–6 started with a 300-IU/day dose, while those with an AFC of 7–9 started with a 225-IU/day dose. Participants allocated to standard care started with a 150-IU/day dose. The primary outcome of live birth was observed in 162 (49.4%) and 141 (42.3%) women from the increased and standard dose groups, respectively (RR 1.17 [95% CI 0.99–1.38], risk difference 0.07 [95% CI -0.005, 0.15], p=0.070). The LBR after the first embryo transfer in the increased and standard dose groups was 125/328 (38.1%) and 117/333 (35.1%), respectively (RR 1.08 [95% CI 0.83-1.33], p=0.428). Other secondary outcomes, including biochemical pregnancy, ongoing pregnancy, multiple and ectopic pregnancy, were not significantly different between the groups both from the first and cumulative embryo transfer. (7)

To further examine the safety of a high dose protocol on maternal and neonatal outcomes, Liu et al. secondarily followed up women recruited in their above-mentioned trial who conceived and assessed the antenatal, perinatal, and neonatal outcomes. The occurrence of gestational diabetes mellitus was significantly higher in the increased gonadotropin dose group (24/149, 16.1% vs. 8/128, 6.3%; RR 2.58, 95% CI 1.19 to 5.54, p=0.02) in singleton pregnancies. In women undergoing the first embryo transfer cycle, maternal hypothyroidism occurred more frequently in the increased gonadotropin dose group than in the standard dose group (16.0% vs 6.8%, RR 2.34, 95% CI 1.07-5.11, p=0.03). (8)

Recommendation

Increasing the dose of gonadotropins beyond standard dose to improve live birth rate among expected poor ovarian responders is not recommended.	**Strong**	⊛⊛⊛⊛

Rationale for Recommendation

The 2018 Cochrane review, which summarises evidence from five clinical trials, and two large trials published subsequently do not indicate any benefit of increasing the gonadotropin dose beyond the standard dose of 150-225 IU in terms of improving live births in poor responders. Increasing the dose only added to the overall cost. Additionally, Liu et al. found an increased risk of gestational diabetes and maternal hypothyroidism on increasing the dose. Therefore, the GDG recommends administering the standard dose of gonadotropins for COS in poor responders.

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6.3. What is the safety and efficacy of recombinant LH + recombinant FSH compared to that of recombinant FSH monotherapy in poor responders?

Background

rFSH and rLH are available as a combination (ratio of 2:1) or as separate preparations. They are derived from Chinese Hamster Ovary cell lines and have been used for COS in IVF cycles since 1995 and 2000, respectively.

Recombinant biological products are proteins produced using recombinant DNA technology, which utilises biological processes to produce large molecule drugs that cannot be manufactured using synthetic chemistry. Recombinant gonadotropin products were developed to overcome the limitations of earlier urine derived gonadotropin products as the former can be produced in large volumes with high purity and without variability in composition. This reduces not only the effects of batch-to-batch variability but also adverse allergic reactions. Unlike urinary preparations, the LH activity is derived from the inherent LH molecule rather than from hCG. LH activity is expected to improve FSHR induction on granulosa cells, drive follicular growth in FSH-primed follicles in the late follicular phase, and improve steroidogenesis. These factors have been proposed to contribute to improved oocyte quality and clinical outcomes. This additional LH action may benefit women deemed to be poor responders.

Evidence Summary

rLH + rFSH versus rFSH monotherapy

Conforti et al. (2019) performed a systematic review and meta-analysis to compare the effects of combined rLH and rFSH over rFSH monotherapy in hyporesponders. (1) They synthesized data from four RCTs and one observational study. Improvement in CPR was greater with combined rLH and rFSH therapy than with rFSH monotherapy (RR 2.03, 95% CI 1.27–3.25, I2=0%, four studies). Similar effects were observed in a subgroup with only RCTs (RR 2.02, 95% CI 1.18–3.45, I2=0%, three RCTs). The implantation rate too was better in the combined rLH and rFSH therapy group (OR: 2.62, 95% CI 1.37–4.99, five studies) and in the subgroup of RCTs (OR 2.58, 95% CI 1.09–6.07). Analysis of RCTs indicated that more oocytes were retrieved in the combined rLH and rFSH group than in the rFSH monotherapy group (MD 2.90, 95% CI 1.88–3.92).

Alviggi et al. (2018) systematically reviewed literature on rLH supplementation in six groups of patients. (2) A meta-analysis was not performed. Women with adequate ovarian reserve findings had an unexpected hyporesponse to rFSH monotherapy, and women aged 36–39 years seemed to benefit from this supplementation. The first group, with hyporesponse to rFSH monotherapy and a normal ovarian reserve, included 848 patients from four RCTs. The authors concluded that addition of rLH would be beneficial than continuing rFSH with the same or an increased dosage. However, the inclusion criteria and outcome parameters differed across studies. In the second group with women 36–39 years of age, 10 RCTs (2901 patients) involving agonist and antagonist protocols were analysed. The authors concluded that rhLH exerted a beneficial effect on the implantation rate. No effect on pregnancy rate was observed. Further, no significant effect was observed among women >40 years receiving an agonist or an antagonist regimen.

In a Cochrane review by Mochtar et al. (2017), (3) eight of 36 RCTs included poor responders. On subgroup analysis of low responders for live-birth outcomes, one RCT by Ferraretti et al. (2014) was identified with an OR of 9.33 and 95 % CI of 1.03, 84.2.

On subgroup analysis of the ongoing pregnancy outcomes based on ovarian response, three RCTs, namely by Ferraretti et al. (2004), de Placido et al. (2005), and Ruvolo et al. (2007) were identified. These compared 143 (rLH + rFSH) and133 (rFSH alone) patients, with an OR of 2.06 and a 95 % CI of 1.2, 3.53 favouring the rLH + rFSH group.

There was little or no difference in cancellation rates between the rLH + rFSH and rFSH groups due to a low response (OR 0.77, 95% CI 0.54–1.10; n=2251; 11 studies; I2=16%, low-quality evidence). The evidence suggests that if the risk of cancellation due to low response following treatment with rFSH alone is 7%, it would be between 4% and 7% on using rLH + rFSH.

In a systematic review with meta-analysis by Lehert et al. (2014), data from 43 studies (40 RCTs, 6443 patients) comparing the outcomes of rFSH and rFSH + rLH were included. (4) Of them, 12 studies had a cohort of poor responders. In these, rLH was started on day 1 of stimulation in three studies and mid-cycle in five studies; four articles had no mention of the timing of initiation. This study was graded as having low confidence based on AMSTAR-2 criteria. No significant results were observed in the per protocol population (RR 1.29, 95% CI 0.96–1.73). Significantly higher CPRs were observed with recombinant human FSH (r-hFSH) + r-hLH than with r-hFSH alone in the overall population (RR 1.09; 95% CI 1.01–1.18) and poor responders (n=1179; RR 1.30; 95% CI 1.01–1.67; ITT population); the observed difference was more pronounced in poor responders.

In an RCT by Humaidan et al. (2017), the patients were randomised into two groups administered a 2:1 combination of r-hFSH/r-hLH (n=477) and r-hFSH (n=462). (5) In the ITT population, the mean (standard deviation) number of retrieved oocytes (primary endpoint) (3.3 [2.7]) in the r-hFSH/r-hLH group was not significantly different from that in the r-hFSH group (3.6 [2.82]). The biochemical pregnancy rate, OPR, and LBR did not differ significantly between the groups. A post hoc logistic regression analysis considering baseline characteristics indicated that the incidence of total pregnancy outcome failure (defined as the combination of preclinical miscarriage, clinical miscarriage [early + late] and ectopic pregnancy) was lower in the 2:1 r-hFSH/r-hLH group (6.7%) than in the r-hFSH group (12.4%) with an OR of 0.52 (95% CI 0.33, 0.82; p=0.005).

rLH addition to rFSH in early versus mid-follicular phase

Behre et al. (2015) enrolled 202 patients in their RCT, with rLH initiated in the early follicular phase for 103 patients and in the mid-follicular phase for 98, in addition to administration of standard rFSH in a long agonist protocol across 27 centres. (6) The sample size of the study was powered to evaluate differences in the number of retrieved oocytes as a primary outcome. Women aged 36-40 years were enrolled, and ovarian response was not an inclusion criterion. There was no significant difference in the number of retrieved oocytes retrieved across both groups (9.7 ± 6.9 vs 10.9 ± 6.5, p>0.05).

Revelli et al. (2012) conducted an RCT of 530 women with POR in their first IVF cycle and those undergoing a second IVF attempt. (7) They evaluated the effect of adding rLH (150 IU/day) to the treatment regimen of women undergoing a long agonist protocol from day 1 (early LH exposure; n=264) or day 7 (late LH exposure; n=266). The primary outcome in the study was the number of retrieved oocytes, which was not significantly different between both groups (3.7 ± 2.1 vs 3.5 ± 2.4, p>0.05).

Recommendations

Recombinant follicle stimulating hormone (rFSH) monotherapy is not recommended over rFSH Recombinant human luteinizing hormone (r-hLH) in poor responders.	**Conditional**	⊛⊛⊘⊘
Early or mid-follicular initiation of r-hLH is equally recommended in poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendations

The systematic review and meta-analysis synthesized data from multiple studies, demonstrating that combined rLH and rFSH therapy significantly increased CPR compared to rFSH monotherapy, with sustained effects observed across various subgroup analyses. Moreover, implantation rates were notably higher with combined therapy,

indicating improved embryo implantation potential. Analysis of RCTs consistently showed a higher number of retrieved oocytes with combined rLH and rFSH treatment. This recommendation is further supported by findings from systematic reviews and individual studies, which consistently demonstrate the benefits of rLH supplementation in improving CPRs, particularly in poor responder populations. Notably, an RCT indicated a lower incidence of total pregnancy outcome failure with r-hFSH/r-hLH combination therapy than with r-hFSH monotherapy, emphasising the superiority of combined treatment in enhancing reproductive outcomes in poor responders.

The recommendation equally supporting early or midcycle initiation of rLH in poor responders is backed by evidence from RCTs. Behre et al. enrolled 202 patients initiating rLH either in the early or mid-follicular phase alongside standard rFSH treatment. The study revealed no significant differences in the number of retrieved oocytes between the two groups. Similarly, Revelli et al. investigated the addition of rLH in the treatment regimen of women with POR during IVF cycles, comparing early versus late initiation, and found no significant disparity in the number of retrieved oocytes. These findings indicate that the timing of rLH initiation, whether in the early or mid-follicular phase, does not substantially impact oocyte retrieval outcomes in poor responders. Therefore, both initiation timings can be considered equally effective for optimising IVF outcomes in this population.

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6.4. What is the safety and efficacy of long-acting recombinant FSH (corifollitropin alpha) compared to that of recombinant FSH or hMG in poor responders?

Background

CFA is an injectable, long-acting FSH used to treat infertility. The agent comprises an alpha-subunit, which is identical to that of FSH, and a beta-subunit, which is produced by the fusion of the C-terminal peptide from the beta-subunit of chorionic gonadotropin to the beta-subunit of FSH. (1) CFA has a longer half-life than FSH and thus requires less frequent dosing. A single dose of CFA can initiate and sustain multifollicular growth and replace seven daily injections of rFSH in patients undergoing COS. (2) CFA regimens have been developed with dosages of 100 and 150 µg for patients with body weight ≤60 and >60 kg, respectively. (3) This treatment option may be more convenient and acceptable to patients than conventional long protocols of daily FSH injections. Several comparative clinical trials of mixed populations have evaluated the safety and efficacy of such regimens with equivalent results. The option to restrict the number of injections might be of particular interest for poor ovarian responders, who are likely to require gonadotropin treatment over several days.

Evidence Summary

CFA versus rFSH

Cozzolino et al. (2019) conducted a systematic review and meta-analysis of eight RCTs (2345 women) to evaluate the effectiveness of CFA. (4) Four of these trials included poor responders and were performed by Kolibianakis et al. (2015), Boostanfar et al. (2015), Drakopopulos et al. (2017), and Vuong et al. (2017). The trial by Kolibianakis et al. randomised 79 women ≤45 years of age with a prior poor response (defined as ≤4 oocytes retrieved in a previous IVF cycle) to receive 150 mcg of CFA on day 2 followed by 450 IU of folitropin beta from day 8 or 450 IU of daily rFSH from day 2 till hCG trigger day. (5) The median number of retrieved oocytes was 3 and 2, respectively (95% CI 2-4, 2-3, respectively; p=0.26), and LBRs per oocyte retrieval cycle were 7.9% and 2.6%, respectively (difference +5.3%, 95% CI -6.8 to +18.3). The multicentric trial by Boostanfar et al. randomised 1390 women aged 35–42 years to receive a single injection of 150 µg of CFA or daily 300 IU of rFSH for the first 7 days and then daily rFSH until three follicles reached ≥17 mm in size. (6) The mean (standard deviation) number of recovered oocytes per started cycle was 10.7 (7.2) and 10.3 (6.8), respectively (MD=0.5 [-0.2 to 1.2]), and LBRs were 21.3% and 23.4%, respectively (MD=-2.3% [-6.5 to 1.9]). The trial by Drakopopulos et al. included 152 patients, <40 years old and fulfilling the Bologna criteria for POR, from one tertiary referral centre in Europe and one tertiary referral centre in Asia. (7) Eligible patients were randomised to receive either 150 µg CFA followed by 300 IU HP-hMG (Group A) or daily 300 IU rFSH (Group B) in a fixed GnRH antagonist protocol. An ITT analysis showed that the OPRs did not differ significantly between Group A, 11/77 (14.3%), and Group B, 11/70 (15.7%) (absolute difference: -0.4 [-11.5 to 10.8], OR, 0.9 [0.4-2.4]). Biochemical pregnancies, CPRs, LBRs, and the number of retrieved oocytes were comparable between the two groups. More patients in the CFA group had cryopreserved embryos compared to the rFSH group (22 [28.6%] versus 10 [14.3%], OR 2.4 [1.01-5.5]), and only marginal significance was reached with the lower bound limit for CI being 1.01. Vuong et al. enrolled 400 Asian women aged 35–42 years to receive either 150 µg CFA or daily 300 IU follitropin beta. (8) The two treatments were equivalent with regard to the number of retrieved oocytes (11.4 ± 5.9 vs 10.8 ± 5.8; p=0.338), OPRs, CPRs, LBRs (30.5 vs 32.0%; p=0.83), and obstetric outcomes.

Selman and Rinaldi (2016) conducted an RCT of poor responders, comparing clomiphene citrate and CFA with clomiphene citrate and daily rFSH. (9) They found similar cancellation rates and stimulation outcomes between the groups, emphasising that CFA appears as efficacious as the conventional daily rFSH regimen in poor responders.

CFA versus HP-hMG

The two protocols were compared in a prospective, randomised, non-inferiority, controlled study of 234 patients <40 years and at risk of POR. (10) The first protocol involved a single injection of 150 µg CFA and the second, a daily injection of 300 IU of HP-hMG during the first week of ovarian stimulation. In both groups, if necessary, a daily injection of 300 IU of HP-hMG was dispensed day 8 onward until the criteria for hCG administration were met. The OPR/LBR (15.2% vs 20.2%) (p=0.33) and the cumulative LBR (15.2% vs 22.0%) (p=0.19) per started cycle were not significantly different between the two groups, and the difference estimated between treatments was -5% (95% CI -15.1, 5.0).

In another RCT of 51 IVF cycles with previous poor response, CFA followed by HP-HMG was found to be as effective as daily rFSH + rLH from day 2 in terms of retrieved oocytes, 2PN zygotes, good-quality transferred embryos, and CPR (p>0.05). (11)

Recommendations

Corifollitropin alpha and recombinant FSH are equally recommended in poor responders.	**Strong**	⊛⊛⊛⊘
Corifollitropin alpha and hMG are equally recommended in poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendations

Studies indicate that the clinical outcomes achieved with CFA and daily rFSH or hMG are similar, including LBRs, CPRs, or total number of oocytes retrieved among poor responders or women with advanced age (35–45 years) undergoing IVF. While overall live birth and pregnancy rates with CFA do not significantly differ from those with conventional stimulation protocols, it may be an acceptable alternative to daily rFSH or hMG owing to fewer required injections.

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7. Adjuvant Therapies

Do Adjuvant Therapies Enhance Efficacy or Safety of Ovarian Stimulation in Patients with poor Ovarian Response?

7.1. Is adjuvant use of growth hormone superior to not using an adjuvant for poor responders?

Background

Animal studies show that GH stimulates early follicular growth, improves antrum formation, modifies the growth of developing follicles, stimulates preantral and small antral follicles that lead to the development of healthy granulosa cells, increases the number of mature oocytes, and improves fertilisation rate. (1,2) In women with a poor ovarian reserve, GH supplementation increases the expression of GH, FSH, and LH receptors in granulosa cells. (3)

Evidence Summary

A Cochrane systematic review by Sood et al. (2021) included 16 RCTs (1352 women). Of these, 14 RCTs (1272 women) studied the effects of GH in poor responders. (4) The review compared the use of adjuvant GH to not using an adjuvant in IVF cycles. The LBR (OR 1.77, 95% CI 1.17–2.70; I2=0%; eight trials, 737 participants; very low-certainty evidence) and CPR (OR 1.85, 95% CI 1.35–2.53; I2=15%; 11 trials, 1033 participants; low-certainty evidence) of poor responders taking GH improved. The results, however, must be interpreted with caution, as the included trials were small and few, with significant bias, heterogeneity, and imprecision, downgrading the overall quality of available evidence.

Elkalyoubi et al. (2023) conducted a systematic review and meta-analysis including women >40 years. (5) Subgroup analysis of poor responders (as defined by Bologna criteria) was performed, and the results of 273 participants revealed no significant absolute risk difference (0.05) (95% CI −0.02 to 0.12; I2=25%).

Recommendation

Adjuvant use of growth hormone in ovarian stimulation is not recommended for poor responders.	**Strong**	⊛⊛⊘⊘

Rationale for Recommendation

A comprehensive analysis, including systematic reviews with meta-analysis, consistently suggest that the addition of GH as an adjuvant in ovarian stimulation in poor responders improves CPR and the number of retrieved oocytes. The effects on LBR are unclear owing to studies with varying quality of evidence. However, there is limited evidence on the dose, duration, and timing of GH use. There are limited studies evaluating the short- and long-term adverse effects of GH in the mother and foetus. Considering the gaps in knowledge on established dose, duration, safety, and timing of treatment, use of GH is not justified.

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7.2. Is adjuvant use of testosterone superior to not using an adjuvant for poor responders?

Background

Developing follicles of all stages express ARs. A positive association has been shown between follicular fluid androgen levels and FSH receptor expression. Androgens may promote follicular growth and enhance responsiveness to gonadotropins. (1)

Evidence Summary

The reviewed studies used different definitions of POR and varying doses, durations, and routes of testosterone administration as an adjuvant for poor responders undergoing ART procedures. Katsika et al. (2023) performed a systematic review and meta-analysis of moderate-to-high quality RCTs on testosterone pretreatment in poor responders. (2) Transdermal testosterone gel was used in all studies, with a dose ranging from 10 to 12.5 mg/day for 10–56 days. The probability of pregnancy increased significantly in women pretreated with transdermal testosterone compared to controls. LBR (RR 2.07, 95% CI 1.09–3.92, five studies) and CPR (RR 2.25, 95% CI 1.54–3.30, eight studies) were significantly higher in groups receiving testosterone.

A systematic review and meta-analysis (2019) of testosterone pretreatment of poor responders undergoing IVF synthesized data from seven RCTs with 573 participants. Women receiving testosterone showed higher LBRs (RR 2.29, 95% CI 1.31–4.01, p=0.004), CPRs (RR 2.32, 95% CI 1.47–3.64, p=0.0003), total oocytes (MD 1.28 [95% CI 0.83, 1.73]; p<0.00001), MII oocytes (MD=0.96 [95% CI 0.28, 1.65], p=0.006), and total embryos (MD 1.17 [95% CI 0.67, 1.67]; p<0.00001) in comparison to controls, with no difference in miscarriage rates (p=ns). (3)

A Cochrane systematic review and meta-analysis (2015) synthesized data from 15 RCTs in poor responders. Testosterone pretreatment was associated with higher LBR/OPR (OR 1.88, 95% CI 1.30–2.71; eight RCTs, N=878, I2=27%). (4) However, analysis after excluding studies at high risk of performance bias revealed insignificant differences in live birth or ongoing pregnancy between the two groups (OR 1.50, 95% CI 0.88 to 2.56; five RCTs, N=306, I2=43%). The authors concluded that pretreatment of poor responders with testosterone may improve LBR. They also mentioned that data are insufficient to comment upon the safety of the intervention.

González-Comadran et al. (2012) published a systematic review and meta-analysis with three of the five studies included in Cochrane Review. (5) Their conclusions were similar, implying that transdermal testosterone in poor responders undergoing IVF may be associated with higher LBRs, CPRs, and lower doses of FSH.

Hoang et al. (2021) conducted an RCT of 122 infertile women with POR, who were randomly divided into three groups. The first group received pretreatment with 12.5 mg transdermal testosterone for 4 weeks (n=42), the second group received the same pretreatment for 6 weeks (n=38), and controls received no pretreatment (n=42) in antagonist cycle. CPRs and OPRs were significantly higher in patients treated with testosterone. However, no difference was noted between the 4- and 6-week treatment groups. (6)

Recommendation:

Adjuvant use of testosterone in ovarian stimulation is not recommended for poor responders.	**Conditional**	⊛⊛⊘⊘

Rationale for Recommendation

Analysis of RCTs included in systematic reviews and meta-analyses indicates that adjuvant use testosterone may improve OPR or LBR in poor responders. However, the definition of poor responders and dose and duration of

testosterone pretreatment varied across studies. Further, data on the side effects and safety of the intervention are limited. Well-designed RCTs are required to evaluate the dose and duration of treatment and its safety to determine the suitability of testosterone as standard of care in poor responders.

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7.3. Is adjuvant use of DHEA superior to not using an adjuvant for poor responders?

Background

DHEA, an androgen precursor, is primarily produced by the ovaries (10–30%) and adrenal glands (70–90%). Its levels steadily decline with age, decreasing by approximately 10–20% per decade and reaching a nadir after the age of 80 years.

Studies utilising the Cre-lox conditional knockout strategy have been instrumental in elucidating the in vivo roles of the AR in the female reproductive system. These investigations have revealed that female mice lacking functional AR exhibit diminished fertility, characterised by defective folliculogenesis, reduced corpus luteum formation, and diminished uterine response to gonadotropins. These findings underscore the significance of the androgen-AR pathway in granulosa cell development and its essential role in optimising female reproductive performance.

Considering these discoveries, the use of DHEA pretreatment in patients diagnosed with DOR or POR has gained popularity as an adjunctive therapy aimed at improving pregnancy outcomes in subfertile women undergoing IVF. However, it is worth noting that the use of DHEA for this subgroup of patients remains off-label, despite its widespread adoption in many IVF centres.

Evidence Summary

Zhang et al. (2023) published a meta-analysis and meta-regression analysis to investigate the efficacy of DHEA pretreatment in women with POR undergoing IVF. (1) Thirty-two studies were included in this meta-analysis, comprising 14 RCTs, 11 self-controlled studies, and seven case-control studies. Pooled analysis of all studies indicated that the group with DHEA pretreatment had a higher CPR (RR 1.34, 95% CI 1.17–1.55, p<0.001) and LBR (RR 1.86, 95% CI 1.21–2.86, p=0.005), significant increase in AMH levels (WMD 0.34, 95% CI 0.17–0.51, p<0.001), lower total gonadotropin doses and days of stimulation, increased peak oestradiol levels on hCG day (WMD 88.43, 95% CI 45.15–131.71, p<0.001), more retrieved oocytes (WMD 0.99, 95% CI 0.41–1.56, p=0.001) and transferred embryos (WMD 0.27, 95% CI 0.01–0.52, p=0.040), lower miscarriage rates (RR 0.51, 95% CI 0.36–0.72, p<0.001), and similar endometrial thickness as the control group.

However a subgroup analysis of 14 RCTs alone found no significant difference in the CPR (RR 1.18, 95% CI 0.98–1.41, p=0.081), LBR (RR 1.59, 95% CI 0.87–2.93, p=0.134), AMH levels (WMD 0.1, 95% CI -0.14 to 0.34, p=0.416), peak oestradiol levels on hCG day (WMD -33.21, 95% CI -222.59 to 156.17, p=0.731), number of retrieved oocytes (p=0.123), and transferred embryos (p=0.274) between the two groups. DHEA pretreatment group had a significantly greater AFC (WMD 1.18, 95% CI 0.17–2.19, p=0.022), reduced basal FSH level (WMD -1.99, 95% CI -2.52 to -1.46, p<0.001), and reduced need for gonadotropin doses (WMD -382.29, 95% CI -644.82 to -119.76, p=0.004), days of stimulation (WMD -0.90, 95% CI: -1.34 to -0.47, p<0.001), and miscarriage rates (RR 0.46, 95% CI: 0.29 to 0.73, p=0.001).

A meta-regression analysis was performed to identify the source of variance in the main outcomes. Univariate analysis showed that after DHEA supplementation, women with lower FSH levels experienced a greater increase in serum FSH levels (b=-0.94, 95% CI -1.62 to-0.25, p=0.014) and women with higher baseline AMH levels experienced a higher increase in serum AMH levels (b=-0.60, 95% CI -1.15 to -0.06, p=0.035). The number of retrieved oocytes was greater in relatively younger women (b=-0.21, 95% CI -0.39 to -0.03, p=0.023) and in studies with small sample sizes (b=-0.003, 95% CI -0.006 to -0.0003, p=0.032).

This systematic review and meta-analysis of RCTs concluded that DHEA pretreatment did not improve CPR and

LBR among patients with POR. These findings contradict those of previously published meta-analyses as none of the prior reviews analysed RCTs alone and because additional evidence from newer and larger RCTs was included in the final data synthesis. Univariate regression analysis showed that younger women with lower FSH and higher AMH levels could achieve greater improvement with DHEA pretreatment. The findings indicate the need for further research on subgroups of POR likely to benefit from DHEA pretreatment and the relationship between basal levels of androgens and effect size of DHEA supplementation. The impact of DHEA on endometrium and receptivity is unknown and less studied. The limitations of the review are inclusion of trials with small sample sizes and heterogeneity in the definition of POR, dose and duration of DHEA use, and stimulation protocols. Only one case-control study by Chen et al. defined POR using the POSEIDON criteria. This study showed that women with DHEA pretreatment had significantly more retrieved oocytes, but without a significant benefit on CPRs or LBRs.

A Cochrane review by Nagels et al. (2015) involving eight RCTs compared DHEA supplementation with placebo or no treatment in women with POR undergoing assisted reproduction. (2) Pretreatment with DHEA was associated with higher LBRs or OPRs (OR 1.88, 95% CI 1.30–2.71; eight RCTs, N=878, I2=27%, moderate-quality evidence). However, a sensitivity analysis excluding trials at high risk of performance bias showed a reduced effect size that no longer reached significance (OR 1.50, 95% CI 0.88–2.56; five RCTs, N=306, I2=43%). There was no evidence of a difference in miscarriage rates (OR 0.58, 95% CI 0.29–1.17; eight RCTs, N=950, I2=0%, moderate quality evidence).

Recommendation

Adjuvant use of DHEA in ovarian stimulation is not recommended for poor responders.	**Strong**	⊛⊛⊛⊘

Rationale for Recommendation

There is a lack of evidence from RCTs to support routine DHEA pretreatment of women with POR to improve pregnancy rates and LBRs. The observed effects were limited to an increase in AFC and reduction in FSH levels, total gonadotropin dose, and duration of stimulation. Heterogeneity in the definition of POR, protocols used, DHEA dose and duration, conflicting findings, methodological limitations, and concerns about bias underscore the need for more well-designed studies to establish the safety and efficacy of DHEA supplementation in this context, warranting cautious clinical implementation.

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7.4. Is adjuvant use of Co-Enzyme Q10 superior to not using an adjuvant for poor responders?

Background

CoQ10 is essential for oxidative phosphorylation and energy generation and is a component of the electron transport chain. CoQ10 is chiefly self-synthesized in the human body, while a small amount is obtained from exogenous supplements. As the third-most consumed dietary supplement, CoQ10 has attracted interest owing to its crucial role in antioxidation, immune system regulation, and especially in improving oocyte quality. (1,2)

Evidence Summary

Zhu et al. (2023) synthesized evidence through a network systematic review on transcutaneous electrical acupoint stimulation (TEAS), DHEA, CoQ10, and GH for POR undergoing IVF embryo transfer. (3) Of the included studies, the one by Xu et al. (2018) evaluated the effects of CoQ10 supplementation in poor responders. Compared with the control group, CoQ10 (OR 2.22, 95% CI: 1.05 to 4.71) and DHEA supplementation (OR 1.92, 95% CI: 1.16 to 3.16) showed an improvement in CPR.

A Cochrane review by Showell et al. (2020) evaluated the role of CoQ10 from two studies on poor responders. (4) The review did not provide a subgroup analysis, and hence, these studies were analysed separately.

An RCT by Xu et al. (2018) evaluated 169 participants (76 treated with CoQ10 and 93 controls). (5) The study was powered to detect a 50% difference in good quality embryos between the CoQ10-treated and untreated group. The CoQ10 group had more retrieved oocytes (4, interquartile range 2–5), higher fertilisation rate (67.49%)m and more high-quality embryos (1, interquartile range 0–2); $p<0.05$. The CoQ10-treated group had significantly lesser cycle cancellations when compared to the control group (8.33% vs 22.89%, p=0.04). There was no significant difference in the CPRs (34.85 vs 25.00, p=0.24), LBR per transfer (31.82 vs 21.88, p=0.33), or cumulative LBRs (28.95% vs 15.94%, p=0.08) of the two groups. However, the study may have had detection (subjective primary outcome) and attrition biases.

A prospective RCT by Caberello et al. (2016) evaluated 78 poor responders aged 36–40 years (Bologna criteria). (6) They were randomised to Group 1, 600 mg Co Q10 twice a day for 12 weeks, and Group 2, no treatment for 12 weeks. There was no significant inter-group difference in the number of MII oocytes retrieved (1.82 ± 0.82 vs 1.87 ± 0.76; p=0.77), implantation rate (26.2% vs 21.4%; p=0.75), and CPR (fetal heartbeat at 7 weeks) (15.4% vs 12.8%; p=0.64).

Recommendation

Adjuvant use of CoQ10 in ovarian stimulation is not recommended for poor responders.	**Strong**	⊛⊛⊛⊘

Rationale for Recommendation

Despite the potential benefits of CoQ10 on reproductive outcomes, the available evidence is sparse to recommend it as an established adjuvant. Studies have not conclusively demonstrated its benefits for CPR and LBR. Further studies are required to establish its benefits, optimal dose, and duration of therapy.

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7.5. Is adjuvant use of glucocorticoids superior to not using an adjuvant for poor responders?

Background

Glucocorticoids exert direct effects on ovarian cyclic physiology and steroidogenesis by modulating the functions of various cellular components, including granulosa cells, oocytes, cumulus cells, and luteal cells. Previous research has suggested that glucocorticoids may have beneficial effects on ovarian response to stimulation. For instance, a study demonstrated that dexamethasone could directly influence follicular development and oocyte maturation. This influence may occur via 11β-hydroxysteroid dehydrogenase (11β-HSD) regulation in granulosa cells or indirectly by elevating serum GH and intrafollicular IGF-1 levels.

Moreover, the activity of 11β-HSD in ovarian follicular fluid has been proposed as a potential predictive marker for IVF outcomes. These findings collectively highlight the potential role of glucocorticoids as adjuvants in enhancing ovarian function and response to stimulation in the context of ART.

Evidence Summary

The safety and efficacy of adjuvant glucocorticoids in patients with POR remain largely unexplored. There are currently no studies addressing this specific population. The limited available evidence on the use of glucocorticoids in ART primarily focuses on other patient groups. Given the lack of targeted investigations in individuals with POR, no definitive recommendations can be formulated at this time. Consequently, clinicians should exercise caution and prudence when considering the use of glucocorticoids as adjuvants in POR patients, emphasising the importance of evidence-based practices and the need for further research to elucidate the potential benefits and risks associated with this intervention in this specific population. Continuous monitoring of emerging literature is essential to inform future clinical decision making and guideline development.

Recommendation

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**

8. Monitoring Stimulation Protocols

8.1. Does the addition of hormonal assessment (oestradiol/progesterone/LH) to ultrasound monitoring improve monitoring efficacy and safety for poor responders?

Background

Monitoring of IVF and ICSI is essential to achieve optimal ovarian response and reduce cycle cancellations among poor responders. There is no good-quality evidence to support or refute the need for combined monitoring (using TVUS and hormonal assessment) during ovarian stimulation. A Cochrane meta-analysis by Kwan et al. (2021) showed that combined monitoring with TVUS and assessment of serum oestradiol levels is as effective as that with TVUS alone. However, the applicability of the evidence was limited owing to an unavailability of RCTs and low methodological quality of the available studies. (1) Combined monitoring is associated with more inconvenience and higher costs to patients. In a retrospective cohort study of 4502 IVF/ICSI cycles with follicular-phase GnRH agonist protocol, low LH levels (≤0.5 mIU/mL) on the day of trigger were associated with more retrieved oocytes and available embryos. However, there was no difference in pregnancy rates. (2) In a low-quality RCT by Depalo et al., 213 women underwent IVF with follicular-phase LH administered on day 2, day after antagonist administration, and on trigger day. The study indicated that the trend of decreasing LH levels from baseline was associated with an improved pregnancy rate. However, there was no significant difference in the LH levels of the study groups (fixed and flexible antagonist protocols). (3) Elevated progesterone levels in the late follicular phase affect the endometrium by advancing the window of implantation, thereby affecting CPRs in fresh embryo transfer cycles. (4) The aim of the guideline is to review the evidence and formulate recommendations on hormonal monitoring during ovarian stimulation (oestradiol, LH, and progesterone levels) in poor responders.

Evidence Summary

No study has evaluated the addition of oestradiol, progesterone, or LH testing for monitoring ovarian stimulation in poor responder populations.

Recommendation

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**

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9. Criteria for Conversion to Intrauterine Insemination or Cycle Cancellation

9.1. Should IVF/ICSI treatment be transitioned to IUI or cancelled in case of poor response to ovarian stimulation?

Background

In cases of POR, patients and healthcare providers are confronted with a challenging decision: to proceed with oocyte retrieval, transition to IUI, or cancel the cycle? Decision making presents a significant challenge for both counselling physician and patient, who must weigh several factors to determine the most suitable course of action.

Evidence Summary

Fujii et al. (2017) systematically reviewed literature on the continuation of IVF or conversion to IUI in low responders. (1) Data from seven retrospective studies and one RCT were evaluated. These studies involved the use of GnRH agonist (one study), GnRH antagonist (one study), or a GnRH agonist and antagonist protocols. In only one RCT (Elzeiny et al.), significantly higher CPRs were observed on continuing IVF (12% IUI vs 40% IVF). (2) Two retrospective studies by Norian et al. (5.2% IUI vs 25.7% IVF) and Nicopoullos et al. (3.6% IUI vs 9.1% IVF) showed significantly higher CPRs with IVF than with IUI. (3,4) Norian et al. additionally reported an OR of 3.6 (95% CI 1.8–7.4) in favour of continuing IVF. Elzeiny et al. demonstrated a significantly higher LBR (6% IUI vs 40% IVF) on continuing IVF. Norian et al.'s was the only retrospective study to reveal significant results (4.1% IUI vs 19.8% IVF).

Shohieb et al. (2012), Biljan et al. (2000), and Shahine et al. (2009) found no difference in the CPR or LBR of patients whose treatment was changed to IUI or continued with IVF.

The risk of multiple pregnancies appears to be similar among poor responders who continued with oocyte retrieval and whose treatment was transitioned to IUI. The definition of poor response varied across studies.

Recommendation

Routine transition to intrauterine insemination is not recommended for poor responders.	**Conditional**	⊛⊘⊘⊘

Rationale for Recommendation

In cases of a single follicular response among poor responders, transition to an IUI cycle may help mitigate the risk of obtaining no embryos at transfer. The RCT suggests significantly better outcomes in patients continuing IVF than in those transitioning to IUI. While some observational studies indicate that continuation of oocyte retrieval improves outcomes, others show comparable pregnancy and LBR outcomes with IUI conversion. The risk of multiple pregnancies appears similar across both modalities, emphasising the significance of individualised decision making.

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10. Criteria for Triggering of Final Oocyte Maturation

10.1. Which is the preferred drug to trigger final oocyte maturation for efficacy and safety in poor responders undergoing IVF/ICSI?

Background

Controlled ovarian hyperstimulation in ART typically involves triggering of final oocyte maturation and resumption of meiosis using different agents. A bolus injection of hCG administered at a dose of 5000-10,000 IU approximately 36 h before oocyte retrieval has been the standard trigger. However, alternative mechanisms have emerged to more closely mimic natural physiological processes. GnRH agonist has been shown to effectively trigger ovulation by stimulating the release of endogenous LH and FSH, offering a more physiologically relevant approach. Recent studies have compared the efficacy of hCG and GnRH agonist triggers in IVF cycles.

A newer approach, particularly beneficial for patients with empty follicle syndrome and low responders, involves a dual trigger. This method combines a single dose of GnRH agonist with hCG administration. Additionally, a modified version, known as the double trigger, involves the co-administration of GnRH agonist and hCG 40 and 34 h before ovum-pick up, respectively. The dual and double trigger techniques offer advantages, such as prolonging the interval between ovulation activation and oocyte retrieval as well as inducing an FSH peak through GnRH agonist activity.

Evidence Summary

A meta-analysis by Sloth et al. (2022) included seven studies, with two RCTs, four cohort studies, and one case-control study. (1) The analysis comprised 2474 and 1140 low responders in the dual trigger and hCG groups, respectively. The dual trigger group exhibited notably higher pregnancy rates (six studies, (OR [95% CI], 1.62 [1.00, 2.62], p=0.05) and LBRs (three studies, OR [95% CI], 2.65 [1.66,4.24], p<0.0001), without significant difference in the pregnancy rates (RR 1.62, 95% CI 1.00–2.62, I2=58%, six studies) and implantation rates (RR 1.14, 95% CI 0.93–1.39, I2=40%, seven studies). The meta-analysis acknowledged the presence of certain limitations, such as the retrospective nature of five of the seven studies and substantial heterogeneity in POR definitions, choice of GnRH agonist for triggers, and protocols.

Zhou et al. (2022) performed an RCT to determine the efficacy of the dual trigger technique among advanced-age women (>35 years). The primary outcome was the number of retrieved oocytes, and it was not significantly different across the the hCG trigger (3.60 ± 2.71), agonist trigger (3.81 ± 3.38), and dual trigger groups (4.08 ± 2.79) (p>0.05). The study further demonstrated significantly higher LBRs in the hCG trigger group than in the agonist trigger (19/68 [27.9] vs 10/71 [14.1], p=0.044) and dual trigger (28/86 [32.6] vs 10/71 [14.1], p=0.007) groups. The dual trigger and agonist trigger groups displayed significant differences in the OPR (31/89 [34.8] vs 13/74 [17.6], p=0.013) and miscarriage rates (4/33 [12.1] vs 8/21 [38.1], p=0.027). On further analysis, it was noted that the study population had a mix of poor and normal responders.

Similarly, another RCT by Haas et al. (2019) recruited 11, 10, and 12 low responders in the hCG, agonist, and dual trigger groups. The dual trigger group resulted in significantly more TQEs than in the hCG or GnRH agonist trigger groups (1.1 ± 0.9 vs 0.3 ± 0.8 and 0.5 ± 0.7; p<0.02). The OPR remained similar across the three groups. (3) Conversely, Keskin et al. (2023) observed that dual trigger conferred no additional benefits for POR, with higher LBRs observed in the hCG trigger group (39.2% vs 19.2%; p=0.026). (4)

In a large observational study, Mutlu et al. (2022) evaluated the outcomes of 1283 cycles in 1010 poor ovarian

responders (according to Bologna criteria). Compared to the hCG trigger group, the dual trigger group exhibited significantly more retrieved and mature oocytes, as well as improved clinical pregnancy per embryo transfer (27.5% vs 19.9%, p=0.010) and live birth per embryo transfer (21.6% vs 14.9%, p=0.011). (5)

Tulek et al. (2022) focused on 1068 women (POSEIDON groups 3 and 4). They observed significantly more retrieved oocytes and MII oocytes, and 2PN embryos and a greater oocyte maturation rate, fertilisation rate, implantation rate, CPR, and LBR in the dual-trigger group. (6) Ren et al. (2022) evaluated patients with DOR and noted higher fertilisation rates in the dual trigger group, without improvement in cumulative LBRs. (7)

Recommendation

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**	⊛⊛⊘⊘

Rationale for Recommendation

Despite heterogeneity across studies, triggering oocyte maturation with concomitant injections of GnRH agonist and hCG in GnRH antagonist cycles appears to improve the number of retrieved oocytes, fertilisation rate, and embryo quality, consequently increasing LBRs among poor responders.

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11. Embryo Transfer

11.1. Does elective freeze-all embryo transfer improve efficacy in poor responders?

Background

The freeze-all strategy is gaining worldwide popularity as an alternative to conventional fresh embryo transfer. The freeze-all strategy was initially a "rescue" strategy for women at high risk of OHSS, and its application has now been extended as a scheduled strategy to improve implantation rate. However, the procedure does not increase LBRs in all infertile couples. It is therefore crucial to identify the subgroups of patients who would benefit from the freeze-all strategy.

Evidence Summary

Le et al. (2022) compared the outcomes of elective frozen transfer and fresh embryo transfer in a cohort of 7,236 IVF cycles and 10,283 embryo transfers (n=5,639 elective frozen transfer group; n=4,644 fresh embryo transfer group). (1) They analysed outcomes in poor responders (1-3 oocytes) with 351 IVF cycles and 387 embryo transfers. The cumulative LBR was 14.3% and 17.7% (p=0.584) in the elective frozen and fresh embryo transfer groups, respectively.

A retrospective cohort study by Roque et al. (2018) evaluated 433 participants with POR (as defined by the Bologna criteria), of whom 277 underwent fresh embryo transfer and 156 followed the freeze-all policy. (2) The primary objective of the study was to determine differences in OPRs. The groups revealed no significant difference in OPR (9.6% vs 10.1%, respectively; RR 0.95; 95% CI 0.52–1.73), CPR (14.1% vs 13.7%, respectively; RR 1.03; 95% CI 0.63–1.67), and implantation rate (9.6% vs 9.8%, respectively; p=0.82).

Another retrospective cohort study, by Xue et al. (2018), evaluated the impact of 256 fresh and 303 frozen embryo transfers on live birth among poor responders (as per Bologna criteria). (3) Both treatment groups showed similar LBRs per cycle (12.1% vs 16.2%, p=0.172) and per transfer (15.9% vs 20.9%, p=0.182).

Recommendation

Routine elective freeze-all embryo transfer is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for recommendation

No meta-analysis or RCT has compared the outcomes of fresh and frozen embryo transfers in poor responders. However, observational studies revealed consistent agreement regarding the impact of fresh versus frozen transfers on the LBR and CPR among poor responders.

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12. Oocyte Retrieval and Embryology

12.1. Is follicular flushing superior to no follicular flushing during oocyte retrieval in poor responders?

Background

The number of retrieved oocytes is directly related to the success of IVF cycles. Follicular flushing involves aspiration of a follicle, followed by introduction of a culture medium, and re-aspiration of the follicle. It has been proposed as a method to increase the number of retrieved oocytes during follicular aspiration. However, follicular flushing may increase the operating time and decrease the quality of oocytes in poor responders as the number of follicles is limited. Follicular flushing may also result in the collection of more oocytes and improved chances of pregnancy compared to those with aspiration alone.

Evidence Summary

Through a Cochrane systematic review and meta-analysis of 11 RCTs, Georgiou et al. (2022) compared the use of follicular flushing to no flushing. (1) In a subgroup of poor responders, follicular flushing was found to have no significant impact on LBR compared to the outcomes with aspiration alone (OR 0.60, 95% CI 0.25 to 1.47; two RCTs; n=130; I2=44%; high-quality evidence).

Similarly, a meta-analysis by Neumann et al. (2018) evaluated the role of follicular flushing in women with POR. (2) The analysis included three RCTs, including two that were included in the Cochrane review. The analysis showed no significant difference in the mean number of cumulus oocyte complexes (WMD -0.45, 95% CI -1.14 to 0.25, I2=70%, three studies), MII oocytes (WMD -0.09, 95% CI -0.40 to 0.59, I2=64%, three studies), and embryos (WMD -0.41, 95% CI -1.29 to 0.47, I2=90%, two studies) with or without follicular flushing.

Recommendation

Routine use of the follicular flushing technique during oocyte retrieval is not recommended in poor responders.	**Strong**	⊛⊛⊛⊘

Rationale for recommendation

While a recent RCT by Lainas et al. (2023) suggests potential benefits of follicular flushing during oocyte retrieval for poor responders, the overall evidence from two systematic reviews and meta-analyses paints a more inconclusive picture. The procedure also increases treatment duration, potentially impacting overall patient experience. Given the conflicting findings and substantial body of evidence highlighting limited benefits, the routine use of follicular flushing in POR is not recommended.

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12.2. Does routine ICSI improve efficacy or safety in poor responders?

Background

ICSI may be preferable over IVF owing to a potentially higher likelihood of fertilisation and increased number of available embryos. It has been suggested for treating couples with unexplained infertility and women with poor response and advanced age.

Evidence Summary

Mete et al. (2022) retrospectively compared the outcomes of ICSI and IVF in patients with <4 oocytes and diagnosis of non-male factor infertility. (1) The authors evaluated the LBR, implantation rate, and fertilisation rate of the IVF non-male factor group (Group 1, n=77); ICSI non-male factor group (Group 2, n=65); and ICSI male factor group (Group 3, n=49). Similar LBRs (26.8%, 30.6%, 31.1%, respectively; p=0.643) and implantation rates (20.42%, 28.49%, 23.33%, respectively; p=0.407) were observed across the groups. Fertilisation rate per collected cumulus oocyte complex was significantly higher in Group 1 than in the other two groups (85.68%, 72.58%, 73.33%, respectively; p=0.004).

A larger retrospective cohort study by Supramaniam et al. (2020) compared a POR cohort with 62,641 stimulated fresh cycles (11.0%), 33,436 (53.4%) IVF cycles, and 29,205 (46.6%) ICSI cycles. (2) ICSI did not confer any benefit on the live birth outcome when compared to the conventional IVF per treatment cycle (adjusted OR 1.03, 99.5% CI 0.96–1.11, p=0.261) and adjusted for confounders (female age, number of previous ART treatment cycles, number of previous live births through ART, oocyte yield, stage of transfer, method of fertilisation, and number of embryos transferred).

Recommendation:

Routine use of ICSI over IVF for non-male factor infertility is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendation

There is no RCT evaluating the benefits of ICSI over IVF for non-male factor infertility in poor responders. The largest study to date (Supramaniam et al., 2021) showed no significant improvement in the reproductive outcomes of patients with POR using ICSI, indicating that routine use may not be justified.

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12.3. Does routine preimplantation genetic testing for aneuploidies improve efficacy or safety in poor responders?

Background

PGT-A may play a crucial role in patients with POR undergoing ART treatment. Successful pregnancies are challenging to achieve in POR owing to DOR and a lower oocyte yield. PGT-A enables identification of euploid embryos, which have the correct number of chromosomes, thereby increasing likelihood of successful implantation and reducing risk of miscarriage in POR. By selecting euploid embryos for transfer, PGT-A optimises the chances of achieving a healthy pregnancy, mitigating the adverse outcomes associated with advanced maternal age and DOR. Additionally, PGT-A can help avoid multiple embryo transfers, reducing the risk of multiple gestations and associated complications. Overall, PGT-A can enhance embryo selection and promote successful implantation, serving as a valuable tool to improve reproductive outcomes in POR.

Evidence Summary

Fouks et al. (2022) performed a retrospective cohort study of women aged <40 years, with 154 participants diagnosed with POR, 383 participants diagnosed with DOR, and their propensity-matched controls (n=572 and n=764 for the two groups, respectively) who underwent PGT-A. (1) Participants with POR and their propensity-matched controls had similar aneuploidy rates (41.1% vs 44%, RR 1.02; 95% CI 0.91–1.14). Similarly, patients with DOR and their propensity-matched controls also exhibited similar aneuploidy rates (42.2% vs 41.7%; RR 1.06; 95% CI 0.95–1.06). LBRs were not significantly different in the DOR and non-DOR groups (60.6% vs 56.1%) and the POR and non-POR groups (64.1% vs 54.1%), respectively.

Karlikaya et al. (2021) retrospectively studied 331 participants who met the POSEIDON group 1 criteria (Cohort A), 133 participants who met POSEIDON group 3 criteria (Cohort B), and 323 participants who had a non-low prognosis (Cohort C). (2) Participants in all three groups underwent PGT-A. The cancellation rate in cycles without a euploid blastocyst was significantly lower in Cohort C than in Cohorts A and B (8.4% vs 12.8% and 16.5%; p= 0.034). The euploidy rate between the three cohorts was not significantly different (61.7% [145/235] for Cohort A vs 53.5% [68/127] for Cohort B vs 62% [625/1008] for Cohort C; p=0.13).

In a retrospective cohort study by Deng et al. (2020), participants with POR were stratified into PGT-A (n=241) and non-PGT (n=112) groups. (3) The LBR per retrieval (6.6% vs 5.4%, p=0.814) or CPR per retrieval (7.1% vs 8.9%, p=0.526) did not differ between the PGT-A and non-PGT groups. Miscarriage rates per retrieval (0.4% (1/241) vs 3.6% (4/112), p=0.036) and miscarriage rates per pregnancy (5.9% (1/17) vs 40% (4/10), p=0.047) were significantly lower in the PGT-A group than in the non PGT-A group.

Recommendation

Routine preimplantation genetic testing for aneuploidies is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendation

The studies provide inconsistent evidence on the benefits of PGT-A in poor responders, indicating that routine use may not be justified. Aneuploidy rates in patients with POR appear to be no different from those in matched controls. The decision to pursue PGT-A should be individualised, considering patient preferences, age, values, and the specific clinical context.

The utility of PGT-A is further constrained by the limited number of embryos available for transfer in such cases,

further exacerbated by the challenges associated with ovarian response. Additionally, the invasive nature of PGT-A procedures introduces an additional layer of concern as the risk of embryo damage may offset the potential benefits, emphasising the need for careful consideration in clinical decision making for individuals with POR.

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12.4. Does in-vitro oocyte maturation improve efficacy or safety in poor responders?

Background

Some poor responders have lower ovarian sensitivity. In some studies of these patients, gonadotropin and hCG priming yielded immature oocytes, which were then cultured to maturity through IVM. This method is a potential treatment alternative for poor responders with ovaries resistant to gonadotropin stimulation. (1,2)

Evidence Summary

In a prospective cohort study, the number of mature oocytes was compared between 146 patients receiving rescue IVM (n=50) or DuoStim (n=96). (2) Women with POR (defined as AMH level of ≤1.5 ng/mL and basal AFC ≤6 (Cimadomo et al., 2018), women aged ≥40 years, or all) were included. The following outcomes were superior in the DuoStim group: mature oocytes (81.49% vs 68.82%, p=0.009), available embryos (74.89% vs 53.33%, p=0.004), and TQEs (60.27% vs 33.33%, p=0.001). These outcomes were greater in the LPS of the DuoStim group than in the IVM group: mature oocytes (59.76% vs 29.09%, p<0.001), available embryos (61.65% vs 19.83%, p<0.001), and TQEs (60.83% vs 17.24%, p<0.001). No significant differences in the rates of biochemical pregnancy, clinical pregnancy, implantation, and LBRs were observed between the groups: 10.00 (1/10) vs 24.62 (16/65), p=0.534; 10.00 (1/10) vs 21.54 (14/65), p= 0.671; 10.00 (1/10) vs 16.92 (11/65) p=0.926, respectively. The study concluded that IVM and DuoStim offer more competent oocytes and viable embryos in the shortest possible time for women with poor prognosis and that DuoStim may be more efficient.

In a prospective cohort study, 440 poor responders comprising women with less <5 MII oocytes and at least 1 immature oocyte (MI or PI oocyte) were included. (3) The outcomes of patients who were transferred embryos derived from mature (MII) oocytes alone were compared to those of patients who were transferred embryos derived from rescue spontaneous maturation oocytes with or without those derived from matured oocytes (RSM group). No differences were observed in pregnancy (16.7% vs 16.5% for MII and RSM groups, respectively) or miscarriage rates (25.5% vs 29.4% for MII and RSM groups, respectively). A non-significant trend of a lower implantation rate in the RSM group was noted (15.4% vs 10.5% for MII and RSM groups, respectively). In 17 cycles, only embryos derived from RSM oocytes were available for transfer, and two pregnancies were achieved. The implantation rate was 4.7%, mean number of transferred embryos was 1.3, and the high-quality embryo rate was 22.7%. The study concluded that rescue spontaneous maturation did not contribute to ICSI outcomes in poor-responder cycles.

Recommendations

Routine use of in-vitro maturation of oocytes is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendations

One low-quality prospective cohort study concluded that IVM can reduce cycle cancellation rates in poor responders, with reproductive outcomes (clinical pregnancy, implantation, and live birth) non-inferior to those obtained with dual stimulation. One low-quality cohort study showed that the pregnancy and implantation rates did not improve in patients who were transferred embryos derived from IVM (with or without those from mature oocytes) compared to those who were transferred embryos derived only from mature oocytes. Both studies were of low quality with contradicting conclusions. No systematic reviews or RCT has evaluated the role of IVM in poor responders.

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13. Ovarian Rejuvenation

13.1. Does intraovarian platelet-rich plasma improve efficacy or safety in poor responders?

Background

Autologous platelets are believed to promote the development of isolated human primordial and primary follicles in the preantral stage. Recent data suggest that ovarian injection of PRP can effectively increase ovarian reserve markers, improve ovarian angiogenesis, follicle formation, menstrual cycle recovery, and ovarian function and contribute to increased egg production. (1–3)

Evidence Summary

A systematic review and meta-analysis by Xualing et al. (2023) synthesized evidence from 10 studies with 793 participants with POR. (4) The included studies had quasi experimental before and after designs. Intraovarian injection of PRP was found to have significant therapeutic effects. On comparing the levels before and 2 months after treatment, improvements were observed in AMH levels (standardised MD 0.44, 95% CI [0.07,0.81], p=0.02), AFC (MD=1.15, 95% CI [0.4,1.90], p=0.003), oocyte count (MD=0.91, 95% CI [0.40, 1.41], p=0.0004), and embryo number (MD=0.78, 95% CI [0.5,1.07], p<0.0001). However, there was significant heterogeneity in the preparation, dose, and technique of intraovarian PRP treatment across studies.

A systematic review by Panda et al. (2020) involved data analysis of 663 poor responders treated with an intraovarian infusion of PRP (four studies). (5) Three of four studies had a quasi experimental before and after design, whereas one study was a non-RCT. Two studies were not included in the earlier meta-analysis. The authors did not provide a pooled analysis of data across studies. PRP intervention was found to be beneficial in terms of improvement in ovarian reserve parameters, such as serum AMH and AFC levels and decreased serum FSH levels. The outcomes of ICSI were evaluated in three studies. They improved in terms of the total number of oocytes retrieved, number of good quality embryos, and cycle cancellation rate after intraovarian PRP infusion.

Recommendation

Intraovarian platelet rich plasma therapy is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendation

The current evidence on the role of PRP in poor responders is limited and inconclusive. There is a need for well-powered RCTs and standardised protocols to evaluate the efficacy of PRP in different subgroups of poor responders. Current studies show considerable variations in the method of preparation of PRP, effective dose, technique of administration, and activation of platelets. Measures of efficacy and the duration of follow-up are also inconsistent across studies. There is no evidence on the benefits of intraovarian PRP on cumulative LBRs, fresh LBRs or CPRs, as most studies limit the outcomes to markers of ovarian reserve.

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13.2. Does intraovarian stem cell therapy improve efficacy or safety in poor responders?

Background

Intraovarian stem cell therapy holds promise to overcome the limitations of ovarian stimulation. By harnessing the regenerative potential of stem cells within the ovary, this innovative approach aims to rejuvenate ovarian function and enhance follicular development. Stem cells have the capacity to differentiate into various cell types, including granulosa cells, which play a crucial role in follicular growth and oocyte maturation. By introducing stem cells directly into the ovary, it is possible to replenish the pool of ovarian follicles and improve responsiveness to stimulation protocols.

Evidence Summary

A non-randomised, open-label, parallel-group investigation by Zafardoust et al. (2023) included 180 women with POR. The study group, comprising 90 individuals, underwent collection, isolation, and culture of menstrual blood-derived stem cells (MenSC), with subsequent intravaginal injection into each ovary. The MenSC-treated group demonstrated a significantly higher rate of spontaneous pregnancies (22.5% vs 7.4%), with 10 live births in the study group versus four in the control group. Following IVF, women aged <40 years in the MenSC group exhibited a significantly higher LBR (25% vs 9.1%). Additionally, MenSC therapy increased serum AMH levels with a 135% rise in antral follicles, contrasting the decline in the control group. The treatment exhibited favourable tolerability and safety profile (1).

A prospective interventional pilot study by Tandulwadkar et al. (2020) evaluated the use of autologous bone marrow-derived stem cells (BMDSC) in 20 women (POSEIDON groups 3 and 4). Bone marrow aspiration from the posterior superior iliac spine was performed, BMDSCs were separated, and the final stem cell concentrate from 5–13 million cells/mL was prepared using a flow cytometer. Intraovarian instillation was guided either by TVUS or laparoscopically. The IVF cycle was performed 6 weeks later using the mini long agonist protocol. The increase in total AFC was statistically significant (p=0.0001), but the increase in AMH values was not (p=0.584). The mean number of oocytes retrieved after COS was 4 ± 1.654. The mean number of Grade A and B embryos frozen on day 3 was 2.5 ± 1.051, and there was a statistically significant difference between preinstallation and postinstillation AFC (3.35 ± 0.98 vs 5.7 ± 1.75) (p=0.0001) (2).

Herraiz et al. (2018) evaluated the use of BMDSCs in 17 women with POR (defined as per the Bologna criteria). Following treatment with granulocyte-colony stimulating factor, BMDSCs were mobilised from peripheral blood, and a volume of whole apheresis containing $50x10^6$ CD133+ cells was prepared for infusion. Intraarterial catheterisation was performed, and the prepared volume was injected into the ovarian artery to reach one ovary. The other ovary served as the control. The primary outcome measures were improvement in AMH levels, AFC, and number of mature oocytes. Secondary outcomes included the number of treatment cycles, cancellation rate, number of obtained embryos and euploid embryos assessed by comparative genomic hybridisation array, cumulative pregnancy rate, and cumulative LBR. Significant improvement in AFC was noted 2 weeks after treatment. Ovarian function improved in 81% of women. In patients who underwent IVF, the number of antral follicles and oocytes increased in the treated ovary. However, the embryo euploidy remained low. Posttreatment, cancellation rates were lower. Five pregnancies were achieved after two IVFs and three natural conceptions. The authors concluded that autologous stem cell ovarian transplantation optimised the mobilisation and growth of existing follicles, oocyte quantity, and pregnancy in POR patients (3).

Recommendation

Intraovarian stem-cell therapy is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendation

The above studies on intraovarian stem cell therapy reveal poor study design, heterogeneity in source of stem cells, its type and concentration, route of delivery, timing, and outcomes measured. Although it appears to be a promising treatment for women with POR, there remain challenges and limitations to its use, such as ethical and legal issues, long-term safety and efficacy, and cost-effectiveness. More RCTs and long-term follow-up studies are needed to establish the efficacy, safety, cost effectiveness and standards for intraovarian stem cell therapy.

Research Recommendations

Intraovarian stem cell therapy is still an experimental and unproven treatment that should be offered only in the context of well-designed clinical trials or under compassionate use protocols. Patients should be fully informed of the potential benefits and risks of this treatment, and informed consent should be obtained before this procedure.

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13.3. Does in-vitro activation of ovarian tissue improve safety and efficacy in poor responders?

Background

A small pool of quiescent primordial follicles remains even in the ovaries of menopausal patients or those with primary ovarian insufficiency. These follicles can potentially be activated to yield more oocytes. In vitro activation of residual dormant follicles by chemical treatment or mechanical disruption of ovarian tissue can reinitiate menstrual cycles and pregnancies in a fraction of amenorrhoeic women with premature ovarian insufficiency. Primordial follicle activation can be achieved using inhibitors of PTEN or activators of PI3K/AKT to produce mature and competent oocytes. Ovarian fragmentation increases actin polymerization, leading to an interruption in intracellular Hippo signalling, which, in turn, promotes cell proliferation and activation of primordial follicles. (1–4)

Evidence Summary

Díaz-García et al. (2022) enrolled 34 patients with POR in an RCT and randomised one ovary to receive ovarian fragmentation and the other to serve as the control. (5) The primary outcome of the study was to compare the number of MII oocytes between the two ovaries, which were not significantly different (23 vs 33) between the two groups. The control group had 18 embryo transfers that resulted in a pregnancy rate of 20% and LBR of 18.7% per cycle. These findings were not significantly different from those in the intervention group, in which 11 embryo transfers resulted in a 13.3% pregnancy rate and 6.7% LBR per cycle.

Lunding et al. (2019) evaluated the benefits of autotransplantation of fragmented ovarian cortical tissue in 20 patients with DOR. (4) The study included women (aged 30–39 years) with infertility, preserved menstrual cycles, indication for IVF/ICSI, and repeated serum measurements of AMH ≤5 pmol/L. Ovarian cortical fragments were prepared and transplanted into one ovary, whereas the other served as control. There was no significant difference in the number of matured follicles in the biopsied versus control ovaries (1.0 vs 0.7 follicles, p=0.35). The authors observed that only 4 follicles developed in the graft site, of which only 1 resulted in the retrieval of an MII oocyte that fertilised. However, this oocyte failed to develop further into an embryo.

Recommendation

In-vitro activation of ovarian tissue is not recommended in poor responders.	**Strong**	⊛⊘⊘⊘

Rationale for Recommendation

There is limited evidence to review the efficacy and safety of in-vitro activation of ovarian tissue. The evidence is restricted to one small, randomised trial, a few cohort studies, and case series that indicate a possible benefit of mechanical activation on the number of antral follicles in poor responders. The RCT showed no significant difference in the primary or secondary outcomes. Further, the effects on LBR and CPR have not yet been adequately studied.

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Annexure 1:
Methodology for Guideline Development

The development of the clinical guideline on POR by the IFS was initiated with the aim of providing evidence-based recommendations to healthcare professionals in the field of reproductive medicine.

The Indian Fertility Society (IFS) developed a guideline for poor ovarian response. The guideline was developed using a predefined, systematic and rigorous process which included the following steps:

1) The executive committee of the IFS commissioned the guideline based on the need for a clinical guideline on Poor Ovarian Response.
2) An expert committee of IFS executive members defined the scope, key questions, outcomes and objectives of the guidelines.
3) A Guideline Development Group (GDG) was formed to:
    a. Identify population, intervention, comparator and outcomes (PICO) against key questions
    b. Formulate keywords against each PICO
    c. Conduct structured search for evidence for key questions
    d. Review and identify relevant evidence for structured searches
    e. Evaluate quality of evidence
    f. Prepare evidence tables for review and discussion
    g. Developing recommendations based on evidence
    h. Prepare a draft guideline
4) The GDG circulated the drafted guideline to internal and external stakeholders for review.
5) The GDG reviewed the feedback and suggestions from stakeholders, documenting the outcome in the Stakeholders Review Report.
6) The GDG prepared the final draft of the guideline and presented it to executive committee for approval.
7) The Indian Fertility Society published the approved guideline, making it accessible to healthcare professionals.

This guideline provides evidence-based recommendations for managing poor ovarian response, aiming to improve patient outcomes in fertility treatment.

Objectives, Scope, Key questions, and Outcomes

The objectives, scope, key questions, and relevant outcomes were outlined by an expert committee. The committee finalized on 37 key questions. Key outcomes prioritised within the guideline include efficacy, safety, and patient-related outcomes. Efficacy outcomes encompass critical measures such as cumulative live birth rate, fresh live birth rate, ongoing pregnancy rate, and miscarriage rates. Safety outcomes of paramount importance include OHSS, and adverse outcomes attributable to the stated interventions. Patient-related outcomes include cycle cancellation rates and patient convenience/preference

Forming the guideline Development Group

The IFS executive committee called for experts in the field across India to form the guideline development group (GDG). The group of experts was selected as members of the GDG based on their expertise, experience, and geographical representation to ensure a balanced perspective.

Experts in the fields of patient advocacy, genetics, embryology and gynaecology were included in addition to reproductive medicine specialists to enhance diversity in the guideline development group.

PICO statements and identification of keywords

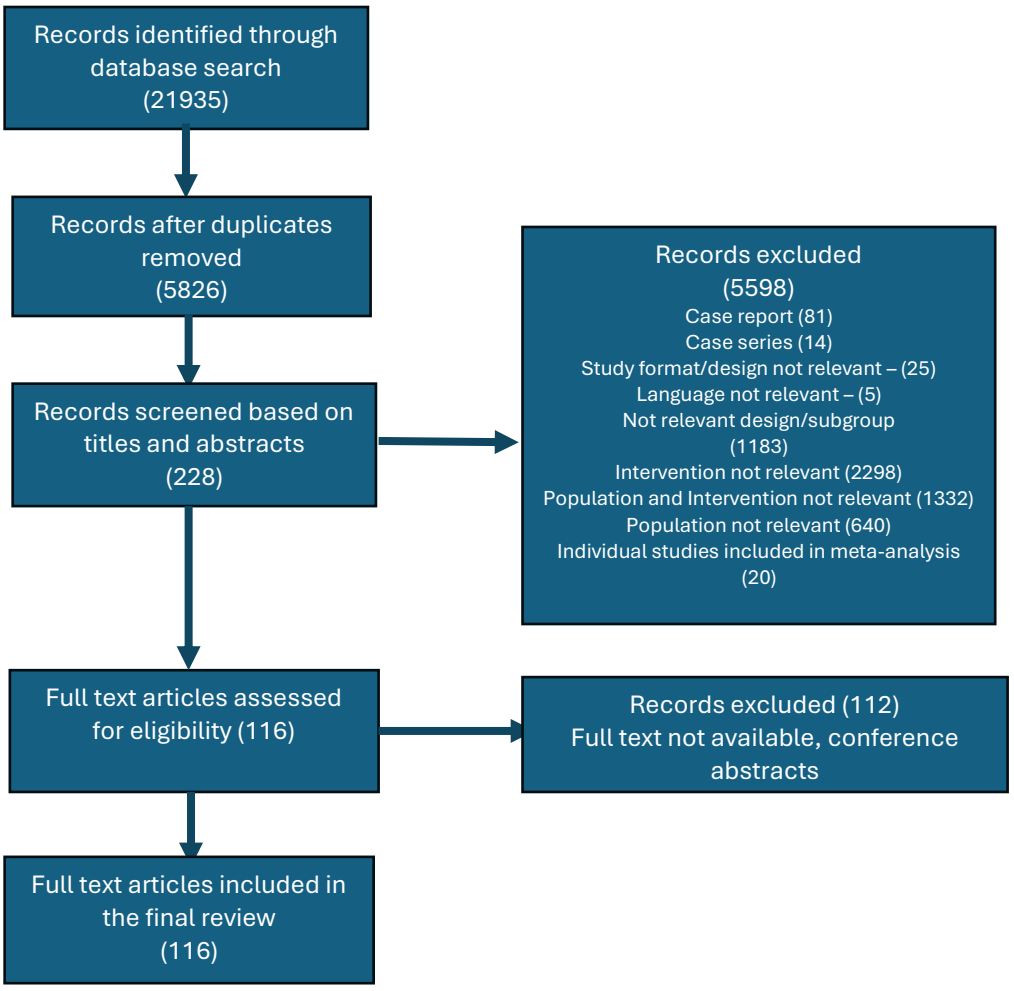
The guideline development group established the population, intervention, comparators and key outcomes against each key question. Keywords were then identified based on the population and interventions of interest. These keywords were used to conduct structured literature searches across databases, including PUBMED/MEDLINE, Cochrane Library, EMBASE and Scopus, covering literature up to 31 October 2023. Searches were

performed, in duplicate, by two independent experts to ensure consistency. Studies identified were classified as meta-analyses, randomised controlled studies, and observational studies based on study design.

Relevance checks on searched literature

The outcomes of the literature search were subjected to checks to exclude duplicates, study designs which were not relevant (case series, case reports, review articles etc) and relevance. Articles which were not in English were excluded from the review. The initial relevance checks were performed on the titles and abstracts to ensure alignment to the defined PICO's. Full text articles were obtained at the end of the relevance check to evaluate quality of evidence.

PRISMA flowchart



Evaluation of quality of evidence

The quality of evidence was assessed using predefined checklists by two independent GDG members. Systematic reviews and meta-analysis were evaluated using the AMSTAR-2 checklists. Randomized controlled trials, cohort and case control studies were evaluated for selection bias, performance bias, detection bias and attrition bias using structured checklists. The GRADE framework was then used to evaluate the quality of evidence from relevant studies. The GRADE criteria for evaluating the quality of evidence, takes into consideration study design, inherent biases, effect size, impact of confounders, and other pertinent quality-related concerns.

Preparation of evidence tables

Studies identified as relevant were included into evidence tables which summarized the study design, population of interest, key interventions and comparators, key outcomes, conclusion by the authors and the quality of the study. The evidence for each key question was independently reviewed by two experts from the GDG and then summarized. The experts then used this evidence for each of the key questions to draft recommendations.

Development recommendations based on evidence

The formulation of recommendations by the GDG followed the GRADE approach to evaluate the strength of evidence. The recommendations were presented to GDG members and discussed to reach a consensus. Recommendations classified as either "strong" or "conditional" based on the certainty of evidence and consensus of experts and stakeholders. Each recommendation was accompanied by a rationale for the recommendations outlining the considerations during formulation, including the balance between desirable and undesirable effects, certainty of evidence, acceptability by stakeholders, feasibility, and impact on health equity and resource utilisation.

Quality of Evidence:

The quality of evidence for recommendations is based on GRADE and is according to the following criteria:
High ⊛⊛⊛⊛: Recommendations supported by high-quality meta-analyses including well designed randomised controlled trials (RCTs).
Moderate ⊛⊛⊛⊘: Recommendations supported by good quality RCTs or meta-analysis with multiple randomised controlled trials with some potential methodological concerns
Low ⊛⊛⊘⊘: Recommendations supported by RCTs with some methodological concerns or high-quality cohort studies.
Very low ⊛⊘⊘⊘: Recommendations supported by cohort studies with some methodological concerns, case-control studies or other study designs not indicated above

Strength of Recommendations:

The strength of recommendations is determined by considering factors such as:
Certainty of Evidence: The level of confidence in the evidence supporting the recommendation.
Harm versus Potential Benefit: The balance between potential harms and benefits associated with the recommendation.
Resources Required for Implementation: The feasibility and resource implications of implementing the recommendation.
Acceptability to Key Stakeholders: The degree to which the recommendation is acceptable to patients, healthcare providers, and other relevant stakeholders.
Impact on Health Equity: The potential impact of the recommendation on health disparities and equity.

Based on the strength, recommendations are categorised into four levels:

Strongly Recommended: Recommendations supported by high-certainty evidence, with clear benefits outweighing potential harms, feasible resource implications, and broad stakeholder acceptability.
Conditionally Recommended: Recommendations supported by moderate- certainty evidence with uncertainties regarding benefits and harms or variability in resource implications or stakeholder acceptability.
Conditionally Not Recommended: Recommendations supported by low- certainty evidence or potential for harm outweighing benefits, significant resource implications, and limited stakeholder acceptability.
Strongly Not Recommended: Recommendations supported by very low- certainty evidence or clear evidence of harm outweighing potential benefits, substantial resource implications, and strong stakeholder opposition.

Development of a draft guideline

The outcomes from structured reviews of the evidence and recommendations for each key question was summarized by the members of the GDG to create a draft guideline, March 2024

Stakeholder review

The Indian Fertility Society draft guideline for poor ovarian response was opened for stakeholder review between 27-Feb-2024 and 07-May-2024. Over this period stakeholders were invited to review the document through social media campaigns and direct emails. The draft document was displayed on the IFS website. Comments, suggestions and feedback was collected through the online portal and email.

Comments and feedback obtained from stakeholders was reviewed by members of the GDG. Changes to the guideline were made based on the review in relevant cases. A detailed summary of the feedback, comments and the response by the GDG was documented in the stakeholder's summary report which was included in the final draft of the guideline.

Review and Approval of the final draft of the guideline

The final draft of the guideline was presented for review and approval – May 2024

Publication of the guideline on Poor Ovarian Response

The IFS guideline on poor ovarian response was published on the website of the Indian Fertility society for public dissemination – June 2024

Guidelines were launched in ESHRE 2024, Amsterdam on 9th July 2024.

Annexure 2: List of reviewers

The Indian Fertility Society (IFS) guideline for poor ovarian response was opened for stakeholder review between 27 February 2024 and 7 May 2024. All reviewers, their comments and reply of the guideline development group are summarized in the review report which is a separate document and is available as online annexure. The list of representatives and experts that provided comments are summarized below:

Representative	Organizations/Groups
Ameet Patki	President, Indian Society of Assisted Reproduction (ISAR)
Gedis Grudzinskas	Past Editor (Clinical), Reproductive BioMedicine Online
Gitanjali Bhasin	Non-governmental organization/Patient representative
Hrishikesh Pai	Immediate past president, Federation of Obstetric and Gynecological Societies of India (FOGSI); The International Federation of Gynecology and Obstetrics (FIGO) Representative
Jane Stewart	Deputy Director Education, International Federation of Fertility Societies; Past Chair, British Fertility Society
Linda Giudice	Immediate Past President, International Federation of Fertility Societies (IFFS), Past President, American Society for Reproductive Medicine (ASRM)
Nandita Palsheker	Past President, FOGSI
Raj Mathur	Past Chair, British Fertility Society
Ying Cheong	Coordinator SIG Reproductive Endocrinology, European Society of Human Reproduction and Embryology (ESHRE)

Reviewer	Country
Abha Maheshwari	Scotland
Alberto Vaiarelli	Italy
Baris Ata	Turkey
Carlos Calhaz-Jorge	Netherlands
Aanchal Garg	India
Animesh Agrawal	India
Bindu Bajaj	India
Shalini Raman	India
Monica Verma	India
Ethiraj Balaji Prasath	Singapore
Michael Grynberg	France
Jayant Mehta	UK
Neelam Potdar	United Kingdom
Ratna Chattopadhyay	India
Shalini Chawla Khanna	India
Siladitya Bhattacharya	UK
Soumya Ranjan Panda	India
Sujoy Dasgupta	India
Yoni Cohen	Israel

Annexure 3: List of Abbreviations

Abbreviations	Definitions
11β-HSD	11β-Hydroxysteroid dehydrogenase
2PN	pronuclear-stage embryos
AFC	antral follicle count
AKT	Ak strain transforming, protein kinase B
AMH	anti-Müllerian hormone
AMHR	anti-Müllerian hormone receptor
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
AR	androgen receptor
ART	assisted reproductive technology
ASRM	American Society for Reproductive Medicine
AUC	area under the curve
BMDSC	bone marrow derived stem cells
BMP-15	bone morphogenetic protein 15
CD	cluster of differentiation
CFA	corifollitropin alfa
CI	confidence interval
CoQ10	coenzyme Q10
COS	controlled ovarian stimulation
CPR	clinical pregnancy rate
DHEA	dehydroepiandrosterone
DNA	deoxyribonucleic acid
DOR	diminished ovarian reserve
DuoStim	double ovarian stimulation/dual ovarian stimulation
FPS	follicular phase stimulation
FSH	follicle stimulating hormone
FSHR	follicle stimulating hormone receptor
GDG	Guideline Development Group
GH	growth hormone
GnRH	gonadotropin-releasing hormone
GPP	Good Practice Point
GRADE	Grading of Recommendations, Assessment, Development, and Evaluations
hCG	human chorionic gonadotropin
hLH	human luteinising hormone
hMG	human menopausal gonadotropin
HP	highly purified
ICSI	intracytoplasmic sperm injection
IGF-1	insulin like growth factor-1
IFS	Indian Fertility Society
IUI	intrauterine insemination
IVF	in-vitro fertilisation
IVM	in-vitro maturation

LBR	live birth rate
LE	luteal oestradiol
LH	luteinising hormone
LPS	luteal phase stimulation
MII	metaphase II
MD	mean difference
MenSC	menstrual blood derived stem cells
MOS	mild ovarian stimulation
MPA	medroxyprogesterone acetate
OCP	oral contraceptive pills
OHSS	ovarian hyperstimulation syndrome
OPR	ongoing pregnancy rate
OR	odds ratio
PGT-A	preimplantation genetic testing- aneuploidy
PICO	patient/population, intervention, comparison, and outcomes
POR	poor ovarian response
POSEIDON	Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number
PPOS	progesterone primed ovarian stimulation
PRP	platelet-rich plasma
RCT	randomised controlled trial
rFSH	recombinant follicle stimulating hormone
r-hFSH	recombinant human follicle stimulating hormone
r-hLH	recombinant luteinising hormone
rLH	recombinant luteinising hormone
ROC	Receiver operating characteristic
RR	relative risk
SART	Society for Assisted Reproductive Technology
TEAS	transcutaneous electrical acupoint stimulation
TQE	top quality embryo
TUVS	transvaginal ultrasonography
WMD	weighted mean difference

Annexure 4: Evidence tables - Separate Document

Annexure 5: Stakeholder Consultation - Separate Document

Annexure e: Literature Review and List of Excluded Studies - Separate Document

Annexure e: Literature Review