Guideline on Poor Ovarian Response

BY THE INDIAN FERTILITY SOCIETY

Annexure 3: EVIDENCE TABLES

Contents

4 Evidence based Recommendations on Pre-Stimulation Management

4.1. Is There a Value of Hormone Testing at Baseline in Predicting Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Tan R, Pu D, Liu L, Liu J, Wu J. Comparisons of inhibin B versus antimüllerian hormone in poor ovarian responders undergoing in vitro fertilization. Fertil Steril. 2011 Oct;96(4):905-911.	Systematic Review/Meta-analysis	Patients undergoing IVF.	None	The basal serum inhibin B level was statistically significantly lower in poor responders than in normal responders (p<0.002; SMD: 0.94; 95% CI, 0.34 to 1.53). Similarly, the stimulated inhibin B concentration was statistically significantly lower in controls (p< 0.02; SMD: 1.36; 95% CI, 0.25 to 2.47). The sensitivity and specificity of AMH in predicting poor response both showed heterogeneity. After excluding the need for subgroup analysis from the study characteristics analysis, the Spearman correlation coefficients between sensitivity and specificity for poor response were judged to be sufficient to estimate summary ROC curves (0.754, p<0.000), although heterogeneity arose due to the threshold effect. The curves exhibit a high accuracy in predicting poor ovarian response. The estimated summary ROC curves of the three indicators for the prediction of poor response was compared. Stimulated inhibin B had more accurate predictability than AMH for poor response (Z	Both basal and stimulated inhibin B serum levels are lower in poor ovarian responders than in controls. The stimulated inhibin B level is more accurate than AMH in predicting poor ovarian response. Because ART is costly and not universally successful, determining the factors that predict a successful outcome in each patient is important. However, further work is necessary to establish multivariate logistic regression model indicators that offer efficient prognostic value.	Low

				= 2.37, p<0.05). Also, a statistically significant difference was observed in predictability between stimulated inhibin B and the basal state (Z=4.77, p<0.05). Compared with basal inhibin B, AMH seemed to be a superior predictor (Z=3.80, p<0.05).		
Baker VL, Glassner MJ, Doody K, Schnell VL, Gracia C, Shin SS, Behera MA, Le Saint CM, Alper MM, Pavone ME, Zbella EA, Coddington CC, Marshall LA, Feinberg RF, Cooper AR, Straseski JA, Broyles DL. Validation study of the Access antimüllerian hormone assay for the prediction of poor ovarian response to controlled ovarian stimulation. Fertil Steril. 2021 Aug;116(2):575-582.	Cohort Study (Prospective and Retrospective Study)	Women aged 21-45 years planning controlled ovarian stimulation for in vitro fertilization.	NA	Data were available for 472 participants who completed the study (74 with POR and 398 non-POR). The mean AMH serum level among those with POR was 0.99 ng/mL (median 0.76 ng/mL) compared with 2.83 ng/mL (median 2.36 ng/mL) among the normal-to-high responders. For confirmation of the 0.93 ng/mL AMH level cutoff as a predictor of POR, a receiver operating characteristic analysis gave an area under the curve of 0.852, with corresponding sensitivity and specificity of 63.5% and 89.2%, respectively. The associated positive predictive value was 52.2%, and the negative predictive value was 92.9%. The AMH plasma values demonstrated a strong correlation with AMH serum values with an r value of 0.9980. The previously established AMH cutoff of 1.77 ng/mL for antral follicle count >15 resulted in a sensitivity of 83.8% (95% confidence interval [CI] 77.7–88.5) and a specificity of 59.9% (95% CI 54.2–65.4).	This study validated the previously established AMH cut point for the prediction of POR. Because this cut-point may vary depending on the assay used, the specific AMH assay should be reported in the literature whenever possible.	Low
Huang J, Lin J, Gao H, Wang Y, Zhu X, Lu X, Wang B, Fan X, Cai R, Kuang Y. Anti-müllerian Hormone for the Prediction of Ovarian Response in Progestin-Primed Ovarian	Cohort Study (Prospective and Retrospective Study)	523 patients without polycystic ovary syndrome who underwent their first in vitro fertilization/intracytoplasmic sperm injection cycle	PPOS regimen for ovarian stimulation	AMH showed a high accuracy for the prediction of both poor and high response with an AUC of 0.861 (95% CI: 0.825–0.892) and 0.773 (95% CI: 0.725–0.817), respectively. The AMH cutoff value for poor response	Study demonstrates that AMH is an adequate predictor of both high and poor ovarian response in PPOS protocol, independent of the dose of MPA. However, AMH does not	Moderate

Stimulation Protocol for IVF. Front Endocrinol (Lausanne). 2019 May 28;10:325.	prediction was 1.26 ng/mL with a sensitivity of 72.0% and a specificity of 86.4%, while 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%.The AUC values of AFC were comparable to those of AMH for prediction of poor and high response (AUC = 0.843 [95% CI: 0.806–0.876] and 0.797 [95% CI: 0.751–0.839]; p AMH vs. AFC = 0.374 and 0.420, respectively).Basal FSH and age, however, performed significantly worse than AMH. The AUC values of basal FSH for poor and high response were 0.773 (95% CI: 0.731–0.811; p AMH vs. FSH = 0.001) and 0.673 (95% CI: 0.621–0.723; p AMH vs. FSH = 0.021), and those of age were 0.656 (95% CI: 0.609–0.700; p AMH vs. FSH < 0.001) and 0.659 (95% CI: 0.606–0.710; p AMH vs. age < 0.001), respectively. The curves revealed that the AUC values of AMH were comparable between hMG + MPA (4 mg/d) and hMG + MPA (10 mg/d) protocol: 0.829 (95% CI: 0.778–0.880) vs. 0.886 (95% CI: 0.834–0.981) for poor response, p = 0.125; and 0.770 (95% CI: 0.704-0.835) vs. 0.814 (95% CI: 0.709–0.919) for high response, p = 0.485.No significant differences, however, were observed among the AMH quartiles for all the analyzed pregnancy parameters, including biochemical pregnancy rate (p = 0.084), clinical pregnancy rate (p = 0.158), implantation rate (p = 0.144), early miscarriage rate (p = 0.346), multiple pregnancy rate	correlate with pregnancy outcomes in the first FET cycles in a freeze-all strategy.

				(p = 0.132), and ectopic pregnancy rate (p = 0.278).Age and the number of embryos transferred were significantly related to clinical pregnancy in unadjusted analysis (p = 0.010 and p = 0.042, respectively). In adjusted analysis, the only independent variable was found to be age (p = 0.011).Women ≥41 years had a significantly lower incidence of clinical pregnancy than women <30 years (OR = 0.27, 95% CI: 0.10–0.80).		
Wang X, Jin L, Mao YD, Shi JZ, Huang R, Jiang YN, Zhang CL, Liang XY. Evaluation of Ovarian Reserve Tests and Age in the Prediction of Poor Ovarian Response to Controlled Ovarian Stimulation-A Real-World Data Analysis of 89,002 Patients. Front Endocrinol (Lausanne). 2021 Aug 30;12:702061.	Cohort Study (Prospective and Retrospective Study)	A total of 89,002 women with infertility undergoing their first traditional ovarian stimulation cycle for in vitro fertilization	Every patient that met the inclusion criteria underwent the first in vitro fertilization cycle. The stimulation protocol and the dose of gonadotropin were determined by the reproductive endocrinologist. In all cases, the dose of gonadotropin was chosen to optimize the number of oocytes retrieved while minimizing the risk of ovarian hyperstimulation syndrome (OHSS).Before the cycle, venous blood was collected on days 2–4 of the menstrual cycle, and the AFC was measured through a transvaginal ultrasound examination by a reproductive endocrinologist or an experienced sonographer. Within one centre, these posts are filled by relatively permanent personnel. Since all the five reproductive centres are large artificial reproductive technology centres of China and each centre has its own personnel training and assessment process, thus, the results of	In this retrospective cohort, the frequency of POR in the first IVF cycle was14.8%. Age, AFC, AMH, and bFSH were used as predicting factors for POR, of which AMH and AFC were the best indicators when using a single factor for prediction (AUC0.862 and 0.842, respectively). The predictive values of the multivariate model included age and AMH (AUC 0.865), age and AFC (AUC 0.850), age and all three ORTs (AUC0.873). Compared with using a single factor alone, the combinations of ORTs and female age can increase the predictive value of POR. Adding age to single AMH model improved the prediction accuracy compared with AMH alone (AUC 0.865 vs. 0.862), but the improvement was not significant. The AFC with age model significantly improved the prediction accuracy of the single AFC model (AUC 0.846 vs. 0.837). To reach 90% specificity for POR prediction, the cutoff point for age was 38 years old with a sensitivity of40.7%, 5 for AFC with a sensitivity of 55.9%,	AFC and AMH demonstrated a high accuracy when using ROC regression to predict POR. When testing is reliable, AMH can be used alone to forecast POR. When AFC is used as a prediction parameter, age is suggested to be considered as well. Based on the results of the cutoff threshold analysis, AFC ≤ 5 and AMH ≤ 1.18 ng/ml should be recommended to predict POR more accurately in IVF/ICSI patients.	Very Low

			the AFC were reliable. AFC is defined as the number of2–10 mm diameter follicles in two ovaries. After standard venipuncture, the blood sample was completely coagulated andthe sample was centrifuged. Then 1 ml serum was removed to a new tube, frozen at 2–8°C within 24 h after blood collection and tested in an independent laboratory of each IVF center within 2days. Kangrun Biotech Reagent Automatic SMART6500 immunoassay analyzer was used to detect levels of AMH and sex hormones in serum and plasma samples. The published total imprecision of the AMH assay kit was 2.4–5.2% .	and 1.18 ng/ml for AMH with a sensitivity of 63.3%.		
Tal R, Seifer DB, Tal R, Granger E, Wantman E, Tal O. AMH Highly Correlates with Cumulative Live Birth Rate in Women with Diminished Ovarian Reserve Independent of Age. J Clin Endocrinol Metab. 2021 Aug 18;106(9):2754-2766.	Cohort Study (Prospective and Retrospective Study)	A total of 34 540 index retrieval cycles of women with AMH <1 ng/mL. A total of 34 540 (25.9%) cycles with AMH <1 ng/mL out of 133 442 autologous index retrieval cycles were analyzed.	COS	The MLR demonstrated that: Age (OR 0.84, 95% CI 0.83-0.85, P < 0.00001), AMH (OR 1.39, 95% CI 1.18-1.64, P < 0.0001), Maximal early follicular FSH (OR 0.98, 95% CI 0.97-0.99, P < 0.0001), White race (OR 1.29, 95% CI 1.17-1.42, P < 0.0001), FSH dosage (OR 0.99, 95% CI 0.99-1.00, P < 0.0001), Number of embryos transferred (OR 1.57, 95% CI 1.52-1.63, P < 0.0001). These were independent predictors of cumulative live birth. The probability of cumulative live birth increased with AMH, White race, and the number of embryos transferred, but decreased with age. The effects of maximal early follicular FSH (OR 0.98) and FSH dosage (OR 0.99) were clinically insignificant. The covariates BMI and infertility etiology were not	Serum AMH is highly correlated with CLBR in women with DOR independent of age. The addition of AMH to current age-based prognostication counseling particularly in women with DOR would provide more informative and personalized CLBR prediction prior to ART.	High

		independent predictors of CLBR and were not included in the MLR model. The MLR model was statistically significant (P < 0.0001) with ROC curve analysis showing an AUC of 0.762 (95% CI 0.756-0.769), indicating that the model had a moderately good ability to discriminate between women who did and women who did not achieve a live birth. The AUC of age alone as a predictor of live birth is 0.703 (95% CI 0.697-0.709), while the AUC of AMH is 0.629 (95% CI 0.623-0.635).When the MLR model included only age and AMH together, the predictive ability for CLBR improved beyond that of age alone, and it had similar good discriminative ability for CLBR (AUC of 0.720, 95% CI 0.712-0.727) to that of the combined MLR model. Including additional baseline pretreatment parameters in the model (i.e., addition of maximal FSH and race to age and AMH) did not further improve the discriminative ability of the model (AUC 0.724, 95% CI 0.717-0.731, P < 0.0001) beyond that of combined age and AMH. Within each age group, AMH was strongly correlated with the probability of CLBR. The linear regression correlation coefficients (R) were as follows: Women <35, R = 0.954 (P < 0.0001)Women 35-37, R = 0.938 (P < 0.0001)Women 38-40, R = 0.871 (P = 0.001)Women 41-42, R = 0.888 (P = 0.001)Women >42, R = 0.877 (P < 0.001)Notably, the correlation coefficients for the relationship

				between AMH and CLBR were greatest in women <35 years old and those 35-37 years old and were somewhat lower at older ages. This indicated that the influence of AMH level on the probability of CLBR in women with DOR was greatest at younger ages and diminished as a woman becomes older, although it remained significant also in the oldest age group (>42 years old).	

4.2. Is there a value of Ultrasound Imaging at Baseline in Predicting Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Liu Y, Pan Z, Wu Y, Song J, Chen J. Comparison of anti-Müllerian hormone and antral follicle count in the prediction of ovarian response: a systematic review and meta-analysis. J Ovarian Res. 2023 Jun 27;16(1):117.	Systematic Review/Meta-analysis	Adult infertile women	Patients receiving COS for IVF/ICSI	Comparison of the summary estimates for the prediction of poor or high response showed significant difference in performance for AMH compared with AFC [poor (sensitivity: 0.80 vs 0.74, P<0.050; specificity: 0.81 vs 0.85, P<0.001); high (sensitivity: 0.81 vs 0.87, P<0.001)]. However, there were no significant differences between the ROC curves of AMH and AFC for predicting high (P=0.835) or poor response (P=0.567).	The present meta-analysis demonstrated that both AMH and AFC have a good predictive ability to predict poor or high responses in IVF treatment	High
Broer SL, Mol BW, Hendriks D, Broekmans FJ. The role of antimullerian hormone in prediction of outcome after IVF: comparison with the antral follicle count. Fertil Steril. 2009 Mar;91(3):705-14.	Systematic Review/Meta-analysis	NA	None	Sensitivities and specificities for predicting poor ovarian response based on AMH were found to vary between 40% and 91% for sensitivity and between 64% and 100% for specificity across the studies. However, there was evidence of heterogeneity in both sensitivity and specificity (P-values for the chi-square test were 0.04 and 0.001, respectively). For predicting non-pregnancy, the sensitivities and	The present meta-analysis has shown that AMH has at least the same level of accuracy and clinical value for the prediction of poor response and nonpregnancy as AFC. Clinical applicability depends on the way abnormal test results might alter patient	Very Low

				specificities from each study were summarized. Like the prediction of ovarian response, heterogeneity was observed for sensitivity, but specificity was homogeneous (chi-square test: p=0.11). Sensitivity ranged from 19% to 66%, and specificity ranged from 55% to 89%. Comparing the estimated summary ROC curves for predicting poor ovarian response, no significant improvement in performance was observed for AMH compared to AFC (P=0.73). The overall accuracy for predicting non-pregnancy was poor for both tests, and there was no significant difference between the ROC curves for predicting non-pregnancy between the two tests (P=0.67).	management.	
Kwee J, Elting ME, Schats R, McDonnell J, Lambalk CB. Ovarian volume and antral follicle count for the prediction of low and hyper responders with in vitro fertilization. Reprod Biol Endocrinol RBE. 2007 Mar 15;5:9.	Randomised study	One hundred and ten regularly menstruating patients, aged 18–39 years, participated in this prospective study, randomized, by a computer designed 4-blocks system study into two groups	One hundred and ten regularly menstruating patients, aged 18–39 years, participated in this prospective study, randomized, by a computer designed 4-blocks system study into two groups	The best prediction of ovarian reserve (Y) was seen in a multiple regression prediction model that included, AFC, Inhibin B-increment in the EFORT and BOV simultaneously (Y = -3.161 + 0.805 × AFC (0.258-1.352) + 0.034 × Inh. B-incr. (0.007-0.601) + 0.511 BOV (0.480-0.974) (r = 0.848, p < 0.001). Univariate logistic regression showed that the best predictors for poor response were the CCCT (ROC-AUC = 0.87), the bFSH (ROC-AUC = 0.83) and the AFC (ROC-AUC = 0.83). Multiple logistic regression analysis did not produce a better model in terms of improving the prediction of poor response. For hyper response, univariate logistic regression showed that the best predictors were AFC (ROC-AUC = 0.92) and the inhibin B-increment in the EFORT (ROCAUC = 0.92), but AFC had better test characteristics, namely a sensitivity of 82% and a specificity 89%. Multiple logistic regression analysis did not produce a better model in terms of predicting hyper response.	AFC performs well as a test for ovarian response being superior or at least like complex expensive and time-consuming endocrine tests. It is therefore likely to be the test for general practise	Moderate

Mutlu I, Demirdag E, Cevher F, Erdem A, Erdem M. Dual trigger with the combination of gonadotropin-releasing hormone agonist and standard dose of human chorionic gonadotropin improves in vitro fertilisation outcomes in poor ovarian responders. J Obstet Gynaecol. 2022;42(5):1239-1244.	Cohort Study (Prospective and Retrospective Study)	1283 cycles of 1010 poor responder patients according to Bologna criteria	GnRH antagonist protocol with rFSH + HMG (maximum 375 IU) Trigger: rhCG 250mcg (control group) vs rhCG 250mcg + 0.2mg triptorelin (dual trigger group)	**Mean number of retrieved oocytes** (4.5 ± 2.4 vs. 3.1 ± 2.3, p<0.001), **the mean number of mature oocytes retrieved** (3.4 ± 2.0 vs. 2.3 ± 1.9, p<.001) and the mean number of fertilised oocytes (2.5 ± 1.8 vs. 1.6 ± 1.6, p<.001) **were significantly higher in the dual trigger group as compared to the standard hCG trigger group. The fertilisation and implantation rates were significantly higher in the dual trigger group than in the standard hCG group** (73.6% vs. 69.6%, p=.009 and 18.7% vs. 14.6, p=.039, respectively). The maturation rates were not different between groups (76.4% in the hCG group vs. 76.7% in the dual trigger group, p=.847). **The mean number of transferred embryos (1.75 ± 0.58 vs. 1.57 ± 0.60, p<.001), the mean number of top-quality embryos transferred (1.73 ± 0.62 vs. 1.55 ± 0.63, p<.001) and blastocyst transfer rate (8.2% vs. 3.8%, p=.007) were significantly higher in the dual trigger group than in hCG trigger group.** ET cancellation rates were higher in hCG trigger group (35% vs. 29.2%, p=.03). **Clinical pregnancy rate (CPR) per cycle (19.4% vs 13%, p=.002), live birth rate (LBR) per cycle (15.3% vs 9.7%, p=.003) and CPR per ET (27.5% vs 19.9%, p=.010), LBR per ET (21.6% vs 14.9%, p=.011) were significantly higher in the dual trigger group** as compared to the standard hCG trigger group.	The present study results demonstrated that dual trigger with a standard dose of hCG and GnRHa could improve the clinical pregnancy and live birth rates in poor ovarian responders in GnRH antagonist ICSI cycles. These results could encourage us to use a dual trigger for improving IVF outcomes in PORs. With data accumulation, dual trigger with a combination of GnRHa and a standard dose of hCG might replace the traditional ovulation trigger with hCG in poor ovarian responders.	Low
Esteves S et al. Antral follicle count and anti-Müllerian hormone to classify low-prognosis women under the POSEIDON criteria: a classification agreement study of over 9000	Cohort Study (Prospective and Retrospective Study)	Eligible patients were consecutive infertile women between 22 and 46 years old who had their first IVF/ICSI cycle in the study centres. Included were all patients who (i) had had their ovarian reserve assessed by both AFC	Ovarian reserve assessments were carried out during a natural menstrual cycle 1–3 months before starting stimulation using standardized protocols. AFC was determined on the early follicular phase using two-dimensional (2D) transvaginal ultrasonography	A significant regression equation was found between ovarian markers and low oocyte yield (n = 9484, χ^2 = 2520.14; P < 0.0001), with an R^2 of 0.407. Both AFC and AMH were significant predictors, and the female's age had an interaction effect (P < 0.0001).Likewise, a significant	The study shows a strong agreement between AFC and AMH to classify patients according to the POSEIDON criteria. Using the POSEIDON	Moderate

patients. Human Reproduction 2021; 36(6):1530–1541.	and AMH, (ii) had been treated with standard ovarian stimulation using exogenous gonadotropins and (iii)had had an oocyte collection. Each patient contributed only one IVF/ICSI cycle.	performed by the physicians from study center according to the practical recommendations for standardized use of AFC. All doctors performing AFC assessments had formal training in ultrasonography and reproductive medicine and a minimum of 5 years of experience in the field. AMH serum values were based on the modified Beckman Coulter generation II enzyme-linked immunosorbent assay. Blood was collected during the daytime, preferably in the morning and during the early follicular phase. Samples were collected either at the clinic or at the reference laboratories partnered with each institution. Serum was isolated, and the specimens were stored at 4C and analysed the next day. AMH values were obtained from the reports provided by the reference laboratories. The two protocols used for standard ovarian stimulation were (i) long GnRH agonist protocol or (ii) GnRH antagonist protocol. Patients received daily subcutaneous injections of (i) recombinant FSH, (ii) recombinant FSH combined with recombinant LH (2:1 ratio) or hMG, or (iii) highly purified hMG. Initial daily gonadotropin doses varied between 150 and 450 IU. Ovarian response was primarily monitored using serial transvaginal ultrasonography and estradiol measurements and gonadotropin doses were adjusted as needed. Both fixed and flexible GnRH antagonist protocols were used. Subcutaneous administration of (i) recombinant hCG (250 mcg) or (ii) GnRH agonist (0.2 mg	equation was found between both ovarian markers and suboptimal oocyte yield (n = 9484, χ^2 = 3476.87; P < 0.0001), with an R^2 of 0.316; female age was also shown to have an interaction effect (P = 0.04).For low oocyte yield, the optimal AFC cutoff value was 5, with a sensitivity of 0.61, a specificity of 0.81, positive and negative predictive values of 64.1% and 79.4%, and an AUC of 0.791. Moreover, the optimal AMH cutoff value was 1.27 ng/ml, with a sensitivity of 0.66, a specificity of 0.72, positive and negative predictive values of 56.7% and 79.4%, and an AUC of 0.751. For suboptimal oocyte yield, the optimal AFC cutoff value was 12 with a sensitivity of 0.74, a specificity of 0.76, and an AUC of 0.81. Accordingly, the optimal AMH cutoff was 2.97 ng/ml, with a sensitivity of 0.69, a specificity of 0.66, and an AUC of 0.80. Both AMH (P < 0.001) and AFC (P = 0.0166) were significant predictors; however, none of the other clinical parameters (age, BMI, infertility factor, and infertility duration) showed an interaction effect. An AUC of 0.917 was obtained for this model. The effect of AMH was more significant than that of AFC (False Discovery Rate LogWorth: 206.00 vs 1.42; P < 0.00001 and P = 0.037, respectively).	thresholds, an acceptable and similar performance was obtained for both biomarkers in predicting low oocyte yield (AUC0.75–0.79), but the sensitivity and positive predictive values were low. Although this evidence overall supports either AFC or AMH for classifying these patients, one in four women will have discordant AFC and AMH values when both biomarkers are used. Clinicians should adopt the biomarker that best reflects their clinical setting when classifying patients according to the POSEIDON criteria.

			triptorelin) was used for triggering final oocyte maturation. Oocyte retrieval was carried out by transvaginal ultrasound-guided puncture of follicles 35–37 h after the trigger injection. The collected follicular fluid was analyzed in the IVF laboratory and the total number of retrieved oocytes was recorded. The study included only data up to the number of collected oocytes as this information—in addition to female age and ovarian marker's results—is required for classifying the patient according to the POSEIDON criteria. Two indicators of interest were created—POSEIDON_AFC and POSEIDON_AMH—to classify patients based on the ovarian biomarker result.			
Sanverdi I, Ozkaya E, Kucur SK, Bilen D, Eken MK, Bilgic BE. Antral Follicle Diameter Variance Within Each Ovary May Be a Predictor For Poor Response In Cases With Normal Ovarian Reserve. Exp Clin Endocrinol Diabetes. 2018 Sep;126(8):521-527.	Cohort Study (Prospective and Retrospective Study)	Age (Years)Duration of infertility (years)FSH (mIU/ml)Estradiol (pg/ml)Day 5 estradiol level (pg/ml)Peak estradiol level (pg/ml)Antral follicle count, Endometrium (mm)# of follicles > 14 mm (right)# of follicles < 14 mm (left)Smallest antral follicle (right) (mm)Smallest antral follicle (left) (mm)Starting gonadotropin dose (U)Total gonadotropin dose (U)Duration of stimulation (days)# of total oocytes# of mature oocytes, Largest antral follicle (right) (mm)Largest antral follicle (left) (mm)AFC Variance (right) (mm)AFC Variance (left) (mm)	COS using Antagonist protocol using r-FSH & r-HCG as trigger	Significant differences were observed between cases with and without clinical pregnancy in terms of basal AFC and the variance in antral follicle diameter in both the right and left ovaries, as well as the diameter of the largest antral follicle in the left ovary ($P < 0.05$). The variance in antral follicle diameter in both the right (AUC = 0.737, $P < 0.001$) and left (AUC = 0.651, $P < 0.05$) ovaries was a significant predictor of poor ovarian response. However, basal serum FSH, estradiol levels, and AFC failed to predict poor response ($P > 0.05$). Variance did not predict clinical pregnancy ($P > 0.05$). A variance > 3.5 mm was found to have a sensitivity of 75% in predicting poor response. Other significant predictors for poor response included day 5-estradiol level (AUC = 0.676, $p< 0.001$) and estradiol level on the trigger day (AUC = 0.854, $p< 0.001$).In a multivariate regression analysis, both AFC and the variance in antral follicle diameter in the right	Increased antral follicle diameter variance early in the follicular phase may be a determinant for the asynchronous follicular growth which resulted in poor ovarian response in cases with normal ovarian reserve	Low

				ovary were found to be significantly associated with clinical pregnancy, while peak estradiol and the variance in antral follicle diameter in the right ovary were significantly associated with poor response. Among the 38 poor responders, 29 (76.3%) women had an antral follicle diameter variability > 3.5 mm [OR: 2.9, 95% CI (1.3-6.8), p = 0.011].		

4.3. Is There a Value of Genetic Polymorphism Testing in Predicting Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Pabalan N, Trevisan CM, Peluso C, Jarjanazi H, Christofolini DM, Barbosa CP, Bianco B. Evaluating influence of the genotypes in the follicle-stimulating hormone receptor (FSHR) Ser680Asn (rs6166) polymorphism on poor and hyper-responders to ovarian stimulation: a meta-analysis. J Ovarian Res. 2014 Dec 20;7:285.	Systematic Review/Meta-analysis	9 Studies on poor responders Klinkert 2006 105 Livshyts 2009 274 Boudjenah 2012 427 Binder 2012 259 Mohiyiddeen 2013 504 de Castro 2003 102 de Castro 2004 170 Huang 2014 1250 Yan 2013 450	FSH receptor genotype in poor responders, hyper responders VS normal responders	Our findings showed that SS genotype carriers were most likely to be poor responders (OR 1.61, p = 0.08) compared to the NN and NS genotypes, which showed no associations (OR 0.93-0.95, p = 0.75-0.78). The heterogeneity of these pooled ORs warranted examining its sources. The outlying studies in each of the three N680S genotypes was noted. Omitting these outliers erased the heterogeneity of the recalculated pooled outcomes. It also materially altered the SS effects where carriers became slightly unlikely to be poor responders (OR 0.90, p = 0.52). The S allele carrier effect was modulated for poor responders (OR 1.24, p = 0.39) in the Non-Hispanic Caucasian (NHC) subgroup. The likelihood of the S allele carriers (OR 1.47, p = 0.02) and the unlikelihood of the N allele carriers (OR 0.64, p = 0.007) were significant in these hyper-response findings. Confined to NHC retained significance of the S allele effects (OR 1.57, p = 0.01) but not among the N allele carriers (OR 0.68, p = 0.18).	In summary, this is a meta-analytical confirmation of the FSHR SS genotype role in COH response. Hyper-responder analysis strengths lie in the non-heterogeneity and robustness of its results. Non-robustness and heterogeneity of the poor-responder results compose its limitations. Thus, poor response findings require caution as to the interpretation as a susceptibility marker for ovarian response.	Low
Tang H, Yan Y, Wang T, Zhang T, Shi W, Fan R, Yao Y, Zhai S.	Systematic Review/Meta-	16 Studies on poor response included in	N/A	Sixteen cohort studies comprising a total of 4287 subjects were included.	In summary, this meta-analysis of	Moderate

Effect of follicle-stimulating hormone receptor Asn680Ser polymorphism on the outcomes of controlled ovarian hyperstimulation: an updated meta-analysis of 16 cohort studies. J Assist Reprod Genet. 2015 Dec;32(12):1801-10.	analysis	the Analysis Perez Mayorga 2000 Sodu 2002 De Castro 2003 Behre 2005 Jun 2006 Klinkert 2006 Loutradis 2006 Achrekar 2009 Huang 2010 Sheikhha 2011 Boudjenah 2012 Genro 2012 Mohiyiddeen 2013 Mohiyiddeen 2013 Yan 2013 Huang 2015		The number of retrieved oocytes was significantly fewer in subjects with the SS genotype at position 680, compared to subjects with the NN or NS genotype (WMD = -1.36, 95% CI = -1.85 to -0.87). A lack of association was detected between the genotypes (SS genotype vs. NN or NS genotype) and clinical outcomes such as exogenous FSH dose (WMD = 98.96 IU, 95% CI = -22.33 to 220.24), poor response (OR = 1.08, 95% CI = 0.71–1.64), ovarian hyperstimulation syndrome (OHSS) (OR = 1.58, 95% CI = 0.41–6.07), and clinical pregnancy rate (OR = 1.10, 95% CI = 0.86–1.40). However, poor ovarian response and the number of retrieved oocytes were significantly influenced by the Asn680Ser polymorphism in the Asian subjects. In addition, no publication bias was detected.	currently available studies suggested that FSHR Asn680Ser polymorphism might be a significant biomarker for predicting the number of retrieved oocytes and poor response, especially in Asian subjects. Other outcomes such as exogenous FSH dose, OHSS, and pregnancy rate were not influenced by FSHR Asn680Ser polymorphism. However, it does not translate into statistically significant differences in these clinical outcomes, due to insufficient sample size in the meta-analysis. Further investigations will be required to confirm these findings.	
Alviggi C, Conforti A, Esteves SC, Andersen CY, Bosch E, Bühler K, Ferraretti AP, De Placido G, Mollo A, Fischer R, Humaidan P; International Collaborative Group for the Study of r-hLH (iCOS-LH). Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review. Fertil Steril. 2018 Apr;109(4):644-664.	Systematic Review/Meta-analysis	7 studies reviewed effects in hypo responders 1483 Participants Fernandez Ramirez Berkkanooglu et al. Barrenetxea et al. Musters et al. Ferraretti et al. Younis et al. Humaidan et al.	**Barrenetxea et al. 2008:** n=42+42; rFSH w/wo LH; rLH started on stimulation day 7; rLH dosage 150 IU/d **Berkkanoglu et al. 2007:** n: 97; 46 rFSH+LH; rLH started on stimulation day 7; rLH dosage 75 IU/d **Musters et al. 2012:** n 116 vs. 118; rFSH+rLH; rLH started on stimulation day 5; rFSH–rLH ratio 2:1 **Ferraretti et al**.- Described in Cochrane review **Younis et al.**- Described in Cochrane review **Humaidan et al. 2017:** n=939**,** n= 462; rFSH+rLH; rLH started on stimulation day 1; rFSH–rLH	**Barrenetxea et al. 2008:** no differences between the two groups in pregnancy rate, pregnancy rate per oocyte retrieved, miscarriage rate, or implantation rate. **Berkkanoglu et al. 2007:** The clinical pregnancy rates were similar in the three groups (27.1%, 27.5%, and 21.8% for groups A (rFSH), B (rFSH +rLH), and rFSH +HCG, respectively). **Musters et al. 2012:** The ongoing pregnancy rates and numbers of oocytes retrieved were similar in the two groups. **Ferraretti et al**.- Described in Cochrane review **Younis et al.**- Described in Cochrane review	Despite differences in study design, r-hLH dosage, and r-hLH starting day, current evidence suggests that the following groups of ART women may benefit from r-hLH supplementation during OS: 1) patients with sufficient prestimulation ovarian reserve parameters that have an unexpected hypo response to FSH monotherapy—in these cases r-hLH can be	Very Low, no meta-analysis performed, Studies were not evaluated for bias

			ratio 2:1	**Humaidan et al. 2017:** Women with moderate or severe BSC had a higher live birth rate when supplemented with r-hLH than when treated with r-hFSH alone (moderate BSC: 11% vs. 7.5% [P<.05]; severe BSC 9.6% vs.4.5% [P<.05]), Conversely, women with a mild BSC had a higher live birth rate when stimulated with r-hFSH alone than when supplemented with r-hLH (10.6% vs. 32.7%; P<.05).	started either during the mid-follicular phase to rescue the ongoing cycle or on stimulation day 1 in a subsequent cycle; and 2) women 36–39 years of age—the positive effect in terms of implantation rate and oocyte/embryo quality observed in donor cycles was supported by a single small RCT, so further research is required before any definitive conclusion can be drawn. The effect of r-hLH supplementation in preventing OHSS remains to be established. Although the effect of LH supplementation on ART has been studied in a number of trials, in which conclusions have been drawn from subgroup analyses. Finally, it remains to be established in which of the low-prognosis categories defined by the Poseidon group (70) that r-hLH supplementation could be beneficial.	
König TE, van der Lee J, Schats R, Lambalk CB. The relationship between FSH receptor polymorphism status and IVF cycle outcome: a retrospective observational study. Reprod Biomed Online. 2019	Cohort Study (Prospective and Retrospective Study)	334 women in the Asn/Asn group (28.2%), 617 in the Asn/Ser group (52.1%) and 234 in the Ser/Ser group (19.7%).	Genotyping women undergoing IVF for FSH receptor gene polymorphism at position 680, into Asn/Asn, Asn/Ser, and Ser/Ser. Followed by Controlled ovarian stimulation in long GnRH agonist, short GnRH agonist and	Basal FSH concentration was highest in the Ser/Ser group (P = 0.006). The number of oocytes (P = 0.01) and number of embryos (P = 0.02) were lowest in the Ser/Ser group. The Asn/Asn group showed a significantly lower live birth rate. Live birth rates	FSHR gene polymorphism at position 680 is associated with a different ovarian response to ovarian stimulation. There was	Moderate

Aug;39(2):231-240			GnRH antagonist protocol, followed by IVF. ICSI and embryo transfer. And comparison of results in the three types of polymorphisms.	were 21.9% versus 31.1% and 27.6% (P = 0.009), for Asn/Asn, Asn/Ser and Ser/Ser, respectively. Logistic regression analysis, however, showed no significant difference in cumulative live birth rate between the three genotypes either unadjusted or when adjusted for age.	no difference in the cumulative live birth rate. Further studies are needed to determine whether it is possible to use this individual genetic pre-disposition as a pre-cycle evaluation to predict the extremes of ovarian responses. To increase the specificity and sensitivity of a biomarker to predict ovarian response, other candidate genes need to be analysed together. Genome-wide association studies in a large sample of women undergoing ovarian stimulation may identify new candidate genes relevant to ovarian stimulation that could lead to the development of personalized treatment protocols and may have the potential to increase the probability of live birth.	
Bayraktar B, Güleç EŞ, Kutbay YB, Köse C, Gür EB, Demir A. Does Follicle-Stimulating Hormone Receptor Polymorphism Status Affect In vitro Fertilization-Intracytoplasmic Sperm Injection Results and Live Birth Rate? A Retrospective Study. J Hum Reprod Sci. 2022 Jan-Mar;15(1):58-63	Cohort Study (Prospective and Retrospective Study)	The study was retrospective and included patients who applied to the University of Health Sciences Tepecik Training and Research Hospital in vitro fertilization (IVF) Unit during 2018 and 2019. 143 Patients	Controlled ovarian hyperstimulation and in vitro fertilization-ET protocols During COH, patients who used GnRH antagonist or long GnRH agonist protocols were evaluated. Our IVF unit uses the antagonist protocol. Following the GnRH antagonist protocol in our clinic; on the 2nd or 3rd day of the menstrual cycle, the number of antral follicles is evaluated by transvaginal ultrasound (TVUS). Blood samples are taken for basal FSH and E2. Considering	A total of 143 patients who met our criteria were included in the study. 14% (n = 20) of the patients are also homozygous natural (Asn/Asn) type; 44.7% (n = 64) of the heterozygous mutant (Asn/Ser) type; 41.3% (n = 59) of them were homozygous mutant (Ser/Ser) type. There was no statistically significant difference between the groups in terms of pregnancy rate per started cycle, ongoing pregnancy per started cycle, ongoing pregnancy per embryo transfer, and live birth per embryo transfer. A significant difference was	Ser/Ser polymorphism is characterised by a poor ovarian response. Despite this, polymorphisms in the FSHR gene do not seem to affect the results of pregnancy per started cycle, ongoing pregnancy per started cycle, ongoing pregnancy per embryo transfer and live birth per embryo transfer.	Moderate

	the patient's age, BMI, and the number of antral follicles (AF), 150–300 IU recombinant (GONAL-f®; Merck-Serono, Darmstadt, Germany) or (Puregon®; NV Organon, Oss, The Netherlands) or urinary (Fostimon®; IBSA Institut Biochimique SA, Lugano, Switzerland) FSH is started. On the 6th day of the cycle, 0.25 mg cetrorelix (Cetrotide®; Merck-Serono, Idron, France) is started. FSH and GnRH antagonists are continued until the day of the human chorionic gonadotropin (hCG) administration.	observed between peak E2 and peak progesterone levels between Asn/Ser and Ser/Ser groups, and the levels of these hormones were lower in the Ser/Ser group (P = 0.018 and P = 0.016, respectively). Ovarian responses were classified as poor (≤3 oocytes), normal (4-20 oocytes), and hyperresponse (≥20 oocytes) according to the oocyte count. Accordingly, the number of patients with poor response was higher in the Ser/Ser group (P = 0.011).	

4.4. Is There a Value of Immunological Testing at Baseline in Predicting Poor Ovarian Response?

No evidence

4.5. Does Estradiol Pre-Treatment (Priming) Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Zhang Y, Zhang C, Shu J, Guo J, Chang HM, Leung PCK, Sheng JZ, Huang H. Adjuvant treatment strategies in ovarian stimulation for poor responders undergoing IVF: a systematic review and network meta-analysis. Hum Reprod Update. 2020 Feb 28;26(2):247-263.	Systematic Review/Meta-analysis	In the network meta-analysis, 19 RCTs that included 2677 women was selected. Of these RCTs, in addition to the control group, one study evaluated a comparison of HCG and rLH treatments (49 women). The remaining RCTs offered one adjuvant treatment	1. Artini, P.G., et al., DHEA supplementation improves follicular micro-environment in poor responder patients 2. Bassiouny, Y.A., et al. Does the addition of growth hormone to the in vitro fertilization/intracytoplasmic sperm injection antagonist protocol improve outcomes in poor responders RCT 3. Bastu, E., et al. A randomized, single-blind, prospective trial comparing three different gonadotropin doses with or	Compared with controls, DHEA and CoQ10 treatments resulted in a significantly higher chance of clinical pregnancy [odds ratio (OR) 2.46, 95% CI 1.16 to 5.23; 2.22, 1.08-4.58, respectively]. About the number of retrieved oocytes, HCG,	The present network meta-analysis of RCTs demonstrates that the COS protocol that included GH adjuvant agents in patients with POR was the optimal adjuvant treatment in terms of outcome measures, including the collected oocytes number, embryo number and oestradiol levels on the HCG Day. Moreover, adjuvant treatment with GH significantly reduced the total gonadotrophin required in COS. Adjuvant treatments in poor ovarian response 13 of intraovarian insulin-like growth factor-1 (Zhou et al.,	High

	in each intervention: testosterone (two trials; 51 women), DHEA (two trials; 82 women), letrozole (two trials; 68 women), oestradiol (one trial; 50 women), rLH (three trials; 516 women), hCG (one trial; 47 women), clomiphene (two trials; 75 women), GH (four trials; 334 women), CoQ10 (one trial; 76 women) and progesterone (0 trial).	without addition of letrozole during ovulation stimulation in patients with poor ovarian response. 4. Bayoumi, Y.A., et al., Addition of growth hormone to the microflare stimulation protocol among women with poor ovarian response. 5. Bosdou, J.K., et al. Transdermal testosterone pretreatment in poor responders undergoing ICSI: RCT 6. Choe, S.A., et al., Increased proportion of mature oocytes with sustained-release growth hormone treatment in poor responders: a prospective RCT 7. Dakhly, D.M.R., et al., The addition of growth hormone adjuvant therapy to the long down regulation protocol in poor responders undergoing in vitro fertilization: RCT 8. Davar, R., N. Neghab, and E. Naghshineh, Pregnancy outcome in delayed start antagonist versus microdose flare GnRH agonist protocol in poor responders undergoing IVF/ICSI: An RCT. 9. Ebrahimi, M., F. Akbari-Asbagh, and S.M. Ghalandarpoor Letrozole+ GnRH antagonist stimulation protocol in poor ovarian responders undergoing intracytoplasmic sperm injection cycles: an RCT 10. Ferraretti, A.P., et al.	oestradiol and GH treatments had the highest number of oocytes retrieved [weighted mean difference (WMD) 2.08, 0.72 to 3.44; 2.02, 0.23 to 3.81; 1.72, 0.98 to 2.46, compared with controls, respectively]. About the number of embryos transferred, testosterone and GH treatment led to the highest number of embryos transferred (WMD 0.72, 0.11 to 1.33; 0.67, 0.43 to 0.92; compared with controls, respectively). Moreover, GH resulted in the highest oestradiol level on the HCG Day (WMD 797.63, 466.45 to 1128.81, compared with controls). Clomiphene citrate, letrozole and GH groups used the lowest dosages of gonadotrophins for ovarian stimulation (WMD 1760.00, -2890.55 to -629.45; -1110.17, -1753.37 to -466.96; -	2013). Adjuvant treatment using GH also improved the effects of gonadotrophin on granulosa cells (Bachelot et al., 2002). The beneficial effect of GH on clinical outcomes was demonstrated in a meta-analysis published by the Cochrane group (Harper et al., 2003) and confirmed in several meta-analysis studies (Kolibianakis et al., 2009; Kyrou et al., 2009; Li et al., 2017). However, in the current meta-analysis, the results did not show that adjuvant treatment with GH improved the pregnancy rate significantly in poor ovarian responders using the Bologna criteria. It is possible that the response to GH varies in different subgroups of patients with POR. Therefore, more detailed research on the application of GH is needed to better understand the auxiliary role of GH in patients with POR. In the current meta-analysis, adjuvant treatment using exogenous androgens (DHEA or transdermal testosterone) had beneficial effects. DHEA resulted in the best clinical pregnancy rate, and testosterone produced the highest number of embryos. Pretreatment with trans dermal DHEA or testosterone has been proposed as a safe and effective means to increase the concentration of intraovarian androgens (Balasch et al., 2006; Casson et al., 2000). Theoretically, intraovarian androgens promote cellular sensitivity to FSH in growing follicles (Hillier and De Zwart, 1981; Vendola et al., 1998) and may thereby increase oocyte yield and oocyte maturity during ovarian stimulation, subsequently improving the pregnancy rate. Although oestradiol levels on the HCG Day were low in the DHEA groups, the clinical pregnancy rate was highest,

	LH pretreatment as a novel strategy for poor responders 11. Humaidan, P., et al., Efficacy and safety of follitropin alfa/lutropin alfa in ART :RCT 12. Kotb, M.M.M., A.M.A. Hassan, and A.M.A. AwadAllah Does dehydroepiandrosterone improve pregnancy rate in women undergoing IVF/ICSI with expected poor ovarian response according to the Bologna criteria RCT 13. Madani, T., et al. Efficacy of low dose hCG on oocyte maturity for ovarian stimulation in poor responder women undergoing intracytoplasmic sperm injection cycle: RCT 14. Mak, S.Z.J., et al. Effect of mid-follicular phase recombinant LH versus urinary HCG supplementation in poor ovarian responders undergoing IVF- a prospective double-blinded randomized study 15. Pilehvari, S., et al., Comparison Pregnancy Outcomes Between Minimal Stimulation Protocol and Conventional GnRH Antagonist Protocols in Poor Ovarian Responders. 16. Saharkhiz, N., et al., The effect of testosterone gel on fertility outcomes in women with a poor response in in vitro fertilization cycles: A pilot	875.91, -1433.29 to -282.52; compared with controls, respectively). CoQ10 led to the lowest global cancelation rate (OR 0.33, 0.15 to 0.74, compared with controls).	and the cycle cancelation rate was lowest. A previous meta-analysis review demonstrated that pretreatment with transdermal testosterone, but not DHEA, increased clinical pregnancy and live birth rates (Bosdou et al., 2012). Two papers included in the present review showed that testosterone significantly increased clinical pregnancy rates, although only DHEA and not testosterone had a better prospect for improving pregnancy probability after the Bologna criteria was applied. About adjuvant treatment using CoQ10, data were obtained from only one study, which showed that the addition of CoQ10 may have a beneficial effect on the ovarian response (Xu et al., 2018). In the current network meta-analysis, the results show that CoQ10 treatment had the lowest cycle cancelation rate and achieved the second highest clinical pregnancy rate, indicating that the prospects are good for using CoQ10 in the POR population. However, these results need to be confirmed in further prospective studies. HCG and rLH have long been used as adjuvant agents for increasing the production of endogenous intraovarian androgens (through the addition of LH activity). In the only eligible study in the present network meta-analysis, HCG obtained the highest number of retrieved oocytes. However, neither rLH nor HCG was associated with better clinical outcomes, including the clinical pregnancy rate, the number of embryos and the cycle cancelation rates. These results are consistent with those of several previous meta-analyses (Bosdou et al., 2012; Gizzo et al., 2015), although the RCTs included in those meta-analyses were

	RCT 17. Siristatidis, C., et al. Mild Versus Conventional Ovarian Stimulation for Poor Responders Undergoing IVF/ICSI 18. Xu, Y., et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: RCT 19. Younis, J.S., I. Izhaki, and M. Ben-Ami effect of LH supplementation to the GnRH antagonist protocol in advanced age: a prospective RCT	vastly different. However, these results are inconsistent with the results obtained from studies on exogenous androgens (transdermal testosterone and DHEA). This inconsistency may be because the interventions have overall differential effects or because different adjuvant agents act through different molecular mechanisms. Moreover, various parameters, such as the types of substances, the timing of treatment and the duration of treatment, are likely to be important determinants that affect the efficacy of these interventions. Previous studies have proposed that luteal phase oestradiol priming may improve the synchronization of the pool of follicles available for COS, resulting in more favorable responses to COS (Fanchin et al., 2003a, Fanchin et al., 2003b). In the current network meta-analysis, oestradiol treatment increased the oocyte number significantly. As only one RCT was included in the present network meta-analysis, more rigorous RCT studies are still needed to determine whether adjuvant treatment with oestrogen is beneficial. Based on the results in some meta-analysis studies, a mild ovarian stimulation strategy involving clomiphene or letrozole obtained pregnancy outcomes like those of conventional COS protocols (Bosdou et al., 2012; Song et al., 2016). However, in the current network meta-analysis, although there were no significant differences compared with the control group, SUCRA values showed that cotreatment using clomiphene or letrozole with gonadotrophin, especially clomiphene, led to the worst clinical outcomes, including the lowest pregnancy rates, the lowest oocyte numbers, the lowest 0

		embryo numbers and the highest cycle cancelation rates. Therefore, it is not recommended using clomiphene or letrozole for mild stimulation regimens as the first-line adjuvant treatment for patients with POR. All adjuvant treatment groups used a lower dosage of gonadotrophin for ovarian stimulation, especially for clomiphene letrozole and GH. Studies have shown that a higher dosage of FSH has a detrimental effect on egg and oocyte quality, thus increasing the incidence of chromosomally abnormal embryos and significantly decreasing live birth rates in subfertile patients (Baart et al., 2007). Moreover, a higher dosage of gonadotrophins may increase the total consumption of ovarian follicles, which is not beneficial for patients with POR. Indeed, clinical studies have confirmed that higher dosages of FSH resulted in an increased number of follicle recruitments but low-quality embryos (Hohmann et al., 2003). Taken together, previous studies and the findings suggest that the optimal COS protocol for patients with POR is supplementation with appropriate adjuvant agents to improve clinical outcomes rather than simply increasing the FSH dosage. In conclusion, based on the available evidence, for patients with POR, COS protocols that use adjuvant treatment with DHEA, CoQ10 and GH produced better clinical outcomes in terms of pregnancy achievement and a lower dosage of gonadotrophin required for ovulation induction than were achieved in the control group. However, adjuvant treatment using clomiphene led to the lowest pregnancy rates, even though the total dosage of gonadotrophins was the most economical. These findings suggest that supplementation with

					adjuvant treatment during COS is the optimal management for patients with POR. However, the application of mild COS combined with letrozole, or clomiphene has no beneficial effect. More high-level RCT studies using Bologna standard are clearly necessary for future meta-analyses to better guide clinical practice.	
Reynolds KA, Omurtag KR, Jimenez PT, Rhee JS, Tuuli MG, Jungheim ES. Cycle cancellation and pregnancy after luteal estradiol priming in women defined as poor responders: a systematic review and meta-analysis. Hum Reprod. 2013 Nov;28(11):2981-9. doi: 10.1093/humrep/det306. Epub 2013 Jul 25. PMID: 23887073; PMCID: PMC3795468.	Systematic Review/Meta-analysis	Different definitions of Poor responders **Chang et al. (2012)** ,5 oocytes retrieved or maximum E2 , 500 pg/ml in previous cycle or previous cycle cancellation due to poor follicular recruitment **DiLuigi et al. (2011)** Prior poor response (at least one of the following: ≤4 mature follicles, ≤4 oocytes retrieved, peak E2 ≤ 1000 pg/ml or prior IVF cycle cancelled for poor response), or predicted poor response [at least one of the following: age .40 years, FSH ≥ 10 mIU/ml or poor response in prior gonadotrophin cycle (E2 , 500 pg/ml)] **Dragisic et al. (2005)** One or more of the following: ≤4 oocytes retrieved	Oral micronized 17B-estradiol 2 mg twice daily-two studies One 0.1 mg transdermal E2 patch every other day - 6 studies	Primary outcome-CPR of all women starting a cycle RR (RR **1.33, 95% CI 1.02–1.72) (favours LE)** NNT (number needed to treat was **11** **CPR women underwent OPU after excluding cancellations** (RR 0.925, 95% CI 0.841–1.016).No significant difference Secondary Outcomes Pooled RRs from random effects models revealed **a significantly decreased chance of cycle cancellation for poor responders utilizing an LE protocol** (RR 0.60, 95% CI 0.45–0.78) The **number of mature oocytes retrieved per cycle** (WMD1.133, 95% CI 0.099–2.167)	Despite its limitations, until the results of an adequately powered, well-designed, multi-centre RCT are available on the effect of LE priming in ART, our systematic review and meta-analysis support the use of LE priming prior to COH in poor responders	High

	in previous stimulation, basal FSH . 12 mIU/ml or E2 , 500 pg/ml in previous stimulation **Elassar et al. (2011a,b)** One or more of the following: two or more prior ovarian stimulation cycles at a starting dose of gonadotrophins .300 IU with a yield of ,5 oocytes, or prior cycle cancellation due to low follicular recruitment (≤3 follicles, ≤15 mm, after 10 days of stimulation) **Weitzman et al. (2009)** At least one of the following: age ≥ 40 years, previous poor response to stimulation (≤4 follicles or oocytes), Day 3 FSH ≥ 10 mIU/ml or previously cancelled cycle for inadequate ovarian response **Shastri et al. (2011)** At least one of the following: history of previously cancelled cycles, poor response to stimulation or (,3 dominant follicles or E2 , 500 pg/ml or	and **number of zygotes per cycle(WMD0.804, 95% CI 0.037–1.571) were not significantly improved in patients treated with an LE protocol.** Live birth rate was excluded as a variable fromour meta-analysis as only one study (Hill et al., 2009) included this as an outcome variable.

		basal FSH . 12 mIU/ml) **Hill et al. (2009)** At least one of the following: ≤5 oocytes retrieved, poor-quality oocytes or embryos, cycle cancellation due to poor response, or anticipated poor responder (basal FSH . 12 mIU/ml or basal antral follicle count ≤5) **Ata et al. (2011)** Definition not included				
Chang X, Wu J. Effects of luteal estradiol pre-treatment on the outcome of IVF in poor ovarian responders. Gynecol Endocrinol. 2013 Mar;29(3):196-200.	Systematic Review/Meta-analysis	**Dragisic KG, et al 2005**- 66 vs. 66, 1. Four or fewer oocytes retrieved in previous stimulation; or 2. Basal follicular-stimulating hormone levels > 12 mIU/Ml; or 3. Low E2 level on the day of hCG administration (< 500pg/ml) in previous stimulation **Frattarelli JL,et al 2008- 60 vs. 60,** Poor responders(women who has a history of poor responder) **Hill MJ, et al 2009- 57 vs. 228** A history of poor response in a prior cycle (≤ 5 oocytes	**Dragisic KG, et al 2005-** One 0.1mg transdermal E2 patch every other day **Frattarelli JL,et al 2008-** Oral micronized 17β-estradiol 2mg twice a day **Hill MJ, et al 2009-** Oral micronized 17β-estradiol 2mg twice a day **Weitzman VN, et al 2009-** E2 patch (0.1mg) every other day **Shastri SM, et al 2011-** One 0.1mg transdermal E2 patch every other day **Ata B, et al 2011-** 0.1mg of estradiol per day **Chang EM, et al 2012-** Oral estradiol valerate 4 mg	The luteal estradiol protocol resulted in a significantly **higher duration of stimulation** compared with the standard protocol. In addition, the **number of oocytes retrieved, and mature oocytes retrieved** were significantly higher in the **luteal estradiol protocols** than those in the standard protocols. The **cycle cancellation rate (CCR)** in the luteal estradiol protocols was lower than the standard	In conclusion, our meta-analysis demonstrated that the number of oocytes retrieved, and mature oocytes retrieved were significantly higher in luteal estradiol pre-treatment protocols than the standard protocols in poor responder IVF patients. But the duration of stimulation was also higher in the luteal estradiol pre-treatment group. Meanwhile, the CCR was lower, and CPR had a trend of increase, although it is not a significant difference. These results may be helpful to our clinical practice. More studies including larger samples are needed in future.	Very Low

	retrieved, poor-quality oocytes, poor-quality embryos, or cyclic cancellation due to poor response) **Weitzman VN, et al 2009: 45 vs. 76**, 1. Age ≥ 40 years or 2. Previous poor response to stimulation with gonadotropins or 3. Elevate day 3 FSH level of ≥ 10 mIU/mL, or 4. Previously cancelled cycle due to inadequate ovarian response **Shastri SM, et al 2011, 117 vs. 69,** Poor responders (1. history of previously cancelled cycle, or 2. poor response to stimula-tion, or 3. basal FSH levels > 12 mIU/mL) and age < 35 years **Ata B, et al 2011,** 19 vs.38, Anticipated poor responders **Chang EM, et al 2012,** 86 vs. 69, Patients with a history of poor response, oocytes retrieved and /or a maximum E2 level < 500 pg/ml	protocols. Moreover, no significant difference was found in the **clinical pregnancy rate (CPR).**

Zhang S, Tang Y, Wang X, Zong Y, Li X, Cai S, Ma H, Guo H, Song J, Lin G, Lu G, Gong F. Estrogen valerate pretreatment with the antagonist protocol does not increase oocyte retrieval in patients with low ovarian response: a randomized controlled trial. Hum Reprod. 2022 Jun 30;37(7):1431-1439.	Randomized Controlled Trial	552 , 276 vs 276	The estrogen pre-treatment group received tab estradiol valerate 2 mg twice daily from day 7 after ovulation till day 2 while control group received no pre-treatment. Both groups received 300 IU of Recombinant FSH in antagonist cycle.	1. **Number of oocytes retrieved,** Absolute MD, 0.18 (0.67, 0.32), p-value 0.49 2. **Number of MII oocytes,** Absolute MD, 0.23 (0.69, 0.23), p-value 0.16 3. **Number of superior quality embryos** , Absolute MD, 0.23 (0.69, 0.23), p-value 0.19 4. **Clinical pregnancy rates per first transfer cycles** , RR, 0.67 (0.43, 1.05), p-value 0.08	Estrogen valerate pretreatment with an antagonist protocol did not increase oocyte yield in patients with low ovarian response. Like the number of retrieved oocytes, there was no significant difference in clinical pregnancy rate between estrogen pretreatment group and control group. More research is needed on whether patients with low ovarian response need pretreatment and which pretreatment is more appropriate.	Moderate

4.6. Does OCP Pre-Treatment Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Li J, Sun Y, Mo S, Wang S, Luo W. Effects of oral contraceptive for different responder women before 19 GnRH antagonists: a systematic review and meta-analysis. Gynecol Endocrinol Off J Int Soc Gynecol 20 Endocrinol. 2021 Nov;37(11):977–86.	Meta-Analysis	Fifteen studies with 5326 in vitro fertilization (IVF)/intracytoplasmic sperm injection (ICSI) cycles were summarized.	Compare the efficacy of oral contraceptive pill (OCP) pretreatment for gonadotropin-releasing hormone antagonist (GnRH-ant) protocol, especially for different responder women	The clinical pregnancy rate, moderate or severe ovarian hyper-stimulation syndrome (OHSS) rate, and miscarriage rate was not found to be significantly different between patients with and those without OCP pretreatment, even after sensitivity analyses. In addition, there were still no statistically significant differences for the subgroups analyses of hyper-responders, poor responders, and normal responders. No significant differences were	This meta-analysis did not find an unequivocally beneficial effect of OCP pretreatment for different responder women with using a GnRH-ant protocol. The clinician should weigh the advantages and disadvantages of OCP pretreatment and guide the treatment scheduling considering the patient's own situation.	Low

				detected in the duration of ovarian stimulation, gonadotropin dose consumed, endometrial thickness on day of oocyte collection, or number of oocytes.		
Kim CH, Jeon GH, Cheon YP, Jeon I, Kim SH, Chae HD, et al., Comparison of GnRH antagonist protocol with or without oral contraceptive pill pretreatment and GnRH agonist low-dose long protocol in low responders undergoing IVF/intracytoplasmic sperm injection. Fertil Steril. 2009 Nov;92(5):1758–60.	Randomized Controlled Trial	82 low responders, aged 28 to 41 years, who were defined as patients with repeated day 3 levels of FSH >8.5 mIU/mL, and/or antral follicle count ≤5 and were eligible to undergo IVF/ICSI	GnRH antagonist multiple-dose protocol (MDP) with or without oral contraceptive pill (OCP) pretreatment and GnRH agonist low-dose long protocol (LP) in 82 patients undergoing IVF/intracytoplasmic sperm injection (ICSI) **Group A** (MDP with OCP)**Group B** (MDP without OCP) **Group C** (GnRH agonist low-dose LP)	Total dose and days of rhFSH required for COS were significantly higher in group C than in group A or B. The number of mature oocytes, fertilized oocytes, and grade I, II embryos were significantly lower in group B than in group A or C. However, significant differences were not found among three groups regarding clinical pregnancy rate per patients randomized, implantation rate, and live birth rate per patients randomized	GnRH antagonist MDP with OCP pretreatment was at least as effective as GnRH agonist low-dose LP in low responders and can benefit the low responders by reducing the amount of FSH and the number of days of stimulation required for follicular maturation.	Moderate
Kim CH, You RM, Kang HJ, Ahn JW, Jeon I, Lee JW, et al., GnRH antagonist multiple dose protocol with oral contraceptive pill pretreatment in poor responders undergoing IVF/ICSI. Clin Exp Reprod Med. 2011 Dec;38(4):228–33.	Randomized Controlled Trial	120 poor responders were randomized into three groups according to controlled ovarian stimulation (COS) options	GnRH antagonist MDP after OCP pretreatment (group 1), GnRH antagonist MDP without OCP pretreatment (group 2) GnRH agonist luteal low-dose LP without OCP pretreatment (group 3)	There were no differences in patients' characteristics among three groups. Total dose and days of rhFSH used for COS were significantly higher in group 3 than in group 1 or 2. The numbers of mature oocytes, fertilized oocytes and grade I, II embryos were significantly lower in group 2 than in group 1 or 3. There were no significant differences in the clinical pregnancy rate and implantation rate among three groups.	GnRH antagonist MDP with OCP pretreatment is at least as effective as GnRH agonist low-dose LP in poor responders and can benefit the poor responders by reducing the amount and duration of FSH required for follicular maturation.	Moderate

4.7. Does "GnRH Antagonist Delayed Start Protocol" Improve Efficacy and Safety of Ovarian Stimulation in Poor Responders Compared to Conventional Antagonist Protocol?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Yang S, Liu N, Li Y et al. Efficacy of the delayed start antagonist protocol for controlled ovarian stimulation in Bologna poor ovarian responders: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021 Feb;303(2):347-362.	Systematic Review/Meta-analysis	5 RCTs yielding 514 patients were eligible, of which 5, 5, and 4 studies were included in analyzing the cycle cancellation rate, the clinical pregnancy rate, and the miscarriage rate, respectively.	Maged 2015- 80 vs. 80 Delayed start Antag vs flexible antag Afatoonian 2017- 30 vs. 30 Delayed start Antag vs flexible antag Asharfi 2018 60 vs. 60 Delayed start Antag vs flexible antag Davar 2018 58 vs. 62 Delayed start Antag vs MDF agonist Zarie 2018 21 vs 21 Delayed start Antag vs flexible antag	Primary outcomes **Cycle cancellation rate**; Risk ratio;0.63(0.45,0.90) **Clinical pregnancy rate;** Risk ratio;2.30(1.38,3.82) **Miscarriage rate: Risk ratio;**0.55(0.24,1.23) Secondary outcomes Number of oocytes retrieved; Mean difference ;1.28(0.77,1.79) Number of MII oocytes retrieved; Mean difference; 1.04(0.64,1.45) Number of embryos obtained; Mean difference; 0.17(-0.15,0.50) Number of transferred embryos; Mean difference; 0.11(-0.12,0.34) Endometrial thickness; Mean difference; 0.88 (0.60,1.15) E2 level; Mean difference; 274.49 (153.35,395.63) Gn consumption; Mean difference; -532.25 (-689.42, -375.08) stimulation length; Mean difference; -0.44(-1.21,0.32)	In POR patients defined by Bologna criteria, delayed start antagonist protocol could improve ovarian response by inhibiting premature FSH rise and improve clinical pregnancy rate by optimizing embryo quality and increasing endometrial receptivity. To confirm the validity of these conclusion and explore its scope of application, more powered, standardized-designed multi-centre RCTs are needed. The new trial is recommended to use POSEIDON criteria to identify participants and focus on outcome measures related to live birth and perinatal performance to more accurately assess the effectiveness and safety. of the delayed start antagonist protocol.	Very Low
Di M, Wang X, Wu J, Yang H. Ovarian stimulation protocols for poor ovarian responders: a network meta-analysis of randomized controlled trials. Arch Gynecol Obstet. 2023 19 Jun;307(6):1713–26.	Meta-Analysis	This network meta-analysis included 15 trials on 2173 participants with poor ovarian response.	The PubMed, EMBASE, and Chinese National Knowledge Infrastructure (CNKI) databases were searched for trials on with and without OCP pretreatment before stimulation with gonadotropins.	Delayed start GnRH antagonist was the best regimen in terms of clinical pregnancy rate per initiating cycle (74.04% probability of being the optimal), low risk of cycle cancellation (75.30%), number of oocytes retrieved (68.67%), number of metaphase II (MII) oocytes (97.98%) and endometrial thickness on triggering day (81.97%), while for E2 level on triggering day, microdose GnRH agonist (99.25%) was the most preferred. Regarding number of embryos obtained and number of transferred embryos, no statistical significances were found	Delayed start GnRH antagonist and microdose GnRH agonist were the two superior regimens in the treatment of poor ovarian response, providing favorable clinical outcomes. Future investigation is needed to confirm and enrich our findings.	moderate

	between different ovarian stimulation protocols.

4.8. Does Antioxidant Pre-Treatment Improve Efficacy and Safety of Ovarian Stimulation in Patients with Poor Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Jahromi BN, Sadeghi S, Alipour S, Parsanezhad ME, Alamdarloo SM. Effect of Melatonin on 15 the Outcome of Assisted Reproductive Technique Cycles in Women with Diminished Ovarian 16 Reserve: A Double-Blinded Randomized Clinical Trial. Iran J Med Sci. 2017 Jan;42(1):73–8	Randomized Controlled Trial	80 women with DOR DOR was defined as the presence of 2 of the following 3 criteria: 1) anti-Müllerian hormone ≤1, 2) follicle-stimulating hormone ≥10, and 3) bilateral antral follicle count ≤6.	The women received 3 mg/d melatonin or a placebo since the fifth day of one cycle prior to gonadotropin stimulation and continued the treatment up to the time of ovum pickup.	The serum estradiol level on the triggering day was significantly higher in the case group (P=0.005). The mean number of MII oocytes was higher in the case group, but the difference did not reach statistical significance. Number of the patients who had mature MII oocytes (P=0.014), top-quality embryos with grade 1 (P=0.049), and embryos with grades 1 and 2 (P=0.014) was higher among the women who received melatonin. However, the other ART outcomes were not different between the groups.	The serum estradiol level was higher and more women with DOR had good-quality oocytes and embryos after receiving melatonin; however, no other outcome was different between the case and control groups.	Low

4.9. Does Alternative Medicine-Based Therapy Improve Efficacy and Patient Related Outcomes in Patients with Poor Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Lin G, Liu X, Cong C, Chen S, Xu L. Clinical efficacy of acupuncture for diminished ovarian reserve: a 32 systematic review and meta-analysis of randomized controlled trials. Front Endocrinol. 2023 Aug 33 2;14:1136121.	Meta-Analysis	A total of 13 RCTs involving 787 patients were included in this meta-analysis.	Evaluate the clinical efficacy of acupuncture for the treatment of diminished ovarian reserve (DOR)	The review of available evidence revealed acupuncture produced a significant efficacy in decreasing follicle-stimulating hormone (FSH) levels (SMD = -1.07, 95%CI [-1.79, -0.36], p = 0.003), FSH/LH ratio (MD = -0.31, 95%CI [-0.54, -0.09], p = 0.006) and increasing anti-Müllerian hormone (AMH) levels (SMD = 0.25, 95%CI [-0.00, 0.49], p = 0.05), along with AFC (MD = 1.87, 95%CI [0.96, 2.79], p < 0.0001) compared to controls. Compared with electro-acupuncture treatment, manual acupuncture was superior in reducing FSH levels, FSH/LH ratio, and increasing AMH levels	Acupuncture may have significant clinical potential for patients with DOR in terms of improving sex hormones level and increasing AFC, although the evidence is drawn with high heterogeneity. This finding suggests that more rigorous trials conducted in diverse regions worldwide are necessary to identify the efficacy of acupuncture for patients diagnosed with DOR.	Low

				and AFC ($p < 0.05$). A notable association was also seen when acupuncture was combined with traditional Chinese medicine therapy for improving FSH levels, FSH/LH ratio, and AFC ($p < 0.05$). Besides, a high dose of acupuncture (≥10 acupoints) was more conducive to ameliorating FSH levels, FSH/LH ratio, and AFC ($p < 0.05$) than a low dose of acupuncture (<10 acupoints). Substantial heterogeneity existed among studies.		

4.10. Do Lifestyle Based Therapies Improve Efficacy and Patient Related Outcomes in Patients with Poor Response?

No evidece

5. Ovarian Stimulation Protocols

5.1 Is GnRH-antagonist Protocol Superior to GnRH-agonist Protocols in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Pamentzelopoulou M, Stavros S, Mavrogianni D, Kalantzis C, Loutradis D, Drakakis P. Meta analysis of GnRH-antagonists versus GnRH-agonists in poor responder protocols. Arch Gynecol Obstet. 2021 Aug;304(2):547–57.	Meta-Analysis	9 studies were matched comparing ovarian stimulation protocols in IVF/ ICSI cycles with GnRH-antagonists and GnRH-agonists in poor responders	compare GnRH-antagonist versus GnRH-agonist protocols in poor responders	GnRH-agonists were shown to correlate with fewer cancelled IVF/ICSI cycles ($p = 0.044$, OR = 1.268 > 1, 95% CI 1.007, 1.598), a larger number of embryos transferred ($p = 0.008$, SMD = - 0.230, 95% CI - 0.400, - 0.0599), and more clinical pregnancies ($p = 0.018$, OR = 0.748 < 1, 95% CI 0.588, 0.952). However, GnRH-antagonists resulted in a significantly shorter duration of ovarian stimulation ($p =$	Based on the present meta-analysis, agonist protocols could be suggested as a first-choice approach, in terms of effectiveness. Due to the high studies' heterogeneity, results should be considered with caution. Accordingly, larger cohort studies and meta-analyses like the present one will enhance the robustness of the emerging results to identify the ideal protocol for poor	Low

				0.007, SMD = - 0.426. 95% CI - 0.736, - 0.115). The number of oocytes and mature oocytes retrieved in both protocols did not differ statistically (p = 0.216, SMD = - 0.130, 95% CI - 0.337, 0.0763 and p = 0.807, SMD = - 0.0203, 95% CI - 0.183, 0.142, respectively). Moreover, a high heterogeneity among studies was observed regarding duration of ovarian stimulation (I2 = 90.6%), number of oocytes (I2 = 82.83%)/mature oocytes retrieved (I2 = 70.39%), and embryos transferred (I2 = 72.83%).	responders.	
Lambalk CB, Banga FR, Huirne JA, Toftager M, Pinborg A, Homburg R, et al., GnRH antagonist versus long agonist protocols in IVF: a systematic review and meta-analysis accounting for patient type. Hum Reprod Update. 2017 Sep 1;23(5):560–79	Meta-analysis	Included 50 studies. Of these, 34 studies reported on general IVF patients, 10 studies reported on PCOS patients, and 6 studies reported on poor responders.	Compare GnRH antagonist protocols versus standard long agonist protocols in couples undergoing IVF or ICSI, while accounting for various patient populations and treatment schedules.	In general IVF patients, ongoing pregnancy rate was significantly lower in the antagonist group compared with the agonist group (RR 0.89, 95% CI 0.82-0.96). In women with PCOS and in women with poor ovarian response, there was no evidence of a difference in ongoing pregnancy between the antagonist and agonist groups (RR 0.97, 95% CI 0.84-1.11 and RR 0.87, 95% CI 0.65-1.17, respectively). Subgroup analyses for various antagonist treatment schedules compared to the long protocol GnRH agonist showed a significantly lower ongoing pregnancy rate when the oral hormonal programming pill (OHP) pretreatment was combined with a flexible protocol (RR 0.74, 95% CI 0.59-0.91) while without OHP, the RR was 0.84, 95% CI 0.71-1.0. Subgroup analysis for the	In a general IVF population, GnRH antagonists are associated with lower ongoing pregnancy rates when compared to long protocol agonists, but also with lower OHSS rates. Within this population, antagonist treatment prevents one case of OHSS in 40 patients but results in one less ongoing pregnancy out of every 28 women treated. Thus, standard use of the long GnRH agonist treatment is still the approach of choice for prevention of premature luteinization. In couples with PCOS and poor responders, GnRH antagonists do not seem to compromise ongoing pregnancy rates and are associated with less OHSS and therefore could be considered as standard treatment.	Low

				fixed antagonist schedule demonstrated no evidence of a significant difference with or without OHP (RR 0.94, 95% CI 0.79-1.12 and RR 0.94, 95% CI 0.83-1.05, respectively). Antagonists resulted in significantly lower OHSS rates both in the general IVF patients and in women with PCOS (RR 0.63, 95% CI 0.50-0.81 and RR 0.53, 95% CI 0.30-0.95, respectively). No data on OHSS was available from trials in poor responders.		
Xiao J, Chang S, Chen S. The effectiveness of gonadotropin-releasing hormone antagonist in poor ovarian responders undergoing in vitro fertilization: a systematic review and meta-analysis. Fertility and Sterility 2013; 100(6): 1594-1601.e9.	Systematic Review/Meta-analysis	A total of 12 published studies (1,332 cases) were included.	GnRH antagonist group versus the long-protocol GnRH agonist group GnRH antagonist group versus the short-protocol GnRH agonist group	Both the stimulation period (mean difference [MD], 0.43; 95% confidence interval [CI], 0.68 to 0.17) and the gonadotropin dosage (MD, 5.41; 95% CI, 7.51 to 3.31) were statistically significantly lower in the GnRH antagonist protocol than in the long GnRH agonist protocol. Both the endometrial thickness (MD 0.45; 95% CI, 0.76 to 0.13) and oestrogen (E2) level on the day of hCG administration (MD, 1,299.15; 95% CI, 1,716.34 to 881.95) were statistically significantly lower in the GnRH antagonist protocol than the GnRH agonist protocol. Fewer oocytes were retrieved in the GnRH antagonist protocol than the long GnRH agonist protocol (MD, 0.34; 95% CI, 0.54 to 0.13) or the short GnRH agonist protocol (MD, 0.54; 95% CI, 0.9, 8 to 0.10). The cycle cancellation and clinical pregnancy rates were not statistically significantly different between the two groups.	Compared with GnRH agonist protocols, the GnRH antagonist protocol is associated with fewer oocytes retrieved, lower E2 levels, and thinner endometrium, whereas the clinical pregnancy and cycle cancellation rates are similar.	Low

Prapas Y, Petousis S, Dagklis T, Panagiotidis Y, Papatheodorou A, Assunta I, Prapas N. GnRH antagonist versus long GnRH agonist protocol in poor IVF responders: a randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2013 Jan;166(1):43-6.	Randomized Controlled Trial	Women characterised as poor responders after having 0–4 oocytes retrieved at a previous IVF cycle.Overall 364 women fulfilled the inclusion criteria and were allocated to the two groups: finally, 330 participated in the trial. Of these, 162 were treated with the long GnRH agonist protocol (group I), and 168 with the fixed GnRH antagonist protocol (group II).	Long GnRH agonist protocol (group I) or a GnRH antagonist protocol (group II).	Numbers of embryos transferred, and implantation rates were similar between the two groups (P = NS). The overall cancellation rate was higher in the antagonist group compared to the agonist group, but the difference was not significant (22.15% vs. 15.2%, P = NS). Although clinical pregnancy rates per transfer cycle were not different between the two groups (42.3% vs. 33.1%, P = NS), the clinical pregnancy rate per cycle initiated was significantly higher in the agonist compared to the antagonist group (35.8% vs. 25.6%, P = 0.03).	Although long GnRH agonist and fixed GnRH antagonist protocols seem to have comparable pregnancy rates per transfer in poor responders undergoing IVF, the higher cancellation rate observed in the antagonist group suggests the long GnRH agonist protocol as the first choice for ovarian stimulation in these patients.	Moderate
Sunkara SK, Coomarasamy A, Faris R, Braude P, Khalaf Y. Long gonadotropin-releasing hormone agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. Fertil Steril. 2014 Jan;101(1):147–53.	Randomized Controlled Trial	One hundred eleven women who were poor responders were randomized to the long GnRH agonist, short agonist, and antagonist regimens	Randomized to the long GnRH agonist, short agonist, and antagonist regimens.	The primary outcome was the number of oocytes retrieved. Number of oocytes retrieved was significantly higher with long GnRH agonist compared with the short agonist regimen (4.42 ± 3.06 vs. 2.71 ± 1.60), while there was no significant difference between long agonist and antagonist regimens (4.42 ± 3.06 vs. 3.30 ± 2.91). Duration of stimulation and total gonadotropin dose were significantly higher with long agonist compared with short agonist and antagonist regimens. The ongoing pregnancy rate was 8.1% with long and short agonist regimens and 16.2% with the antagonist regimen.	Long GnRH agonist and antagonist regimens offer a suitable choice for poor responders, whereas the short agonist regimen may be less effective because of fewer eggs retrieved.	Moderate
Bavarsadkarimi M, Omidi S, Shahmoradi F, Heidar Z, Mirzaei S. Comparison of two ovarian stimulation protocols among women with poor response: A randomized clinical trial. Eur J Transl Myol. 2022	Randomized Controlled Trial	Poor responders were defined as having at least two of the following three characteristics, according to the	**The short GnRH agonist and antagonist regimens.** GnRH agonist (Buserelin, CinnaFact®) was started on day 1 of the cycle after the ultrasound scan to confirm	The **number of oocytes retrieved** was higher with the gonadotrophin-releasing hormone (GnRH) antagonist regimen compared to the short agonist regimen (3.10	In terms of lower cycles cancelation and higher chemical pregnancy, the short GnRH agonist regimen is an appropriate choice for poor responders.	Moderate

Jul 6;32(3):10634		Bologna criteria: i) Advanced maternal age (≥40 years) ii) Previous POR (≤3 oocytes with a conventional stimulation protocol); and iii) Abnormal ovarian reserve test (Follicle Count ≤7 follicles or AMH ≤1.2 ng/mL corr. 7.85 pmol/L). Patients were eligible to participate if they met two of the three criteria listed above. Participants were women with previous poor ovarian response undergoing in vitro fertilization. (IVF). One hundred and ninety-two women were randomized to the short GnRH agonist and antagonist regimens.	quiescence of the ovaries. Buserelin (CinnaFact®) was administered at a dose of 100 (IU), followed by follitropin alfa (Cinnal-F) injections and hMG (PD Homog) administration at a dose of 300 to 375 IU/day, began on the second day of the cycle, with the dose fluctuating based on ovarian response. From day 1 to day 5 of the cycle, the dose of Buserelin injected was 100 IU, 50 IU, 30 IU, 10 IU, and 5 IU, respectively. Both buserelin and gonadotropin injections were continued until hCG (Ovitrel, Merck, Italy) was administered; at this stage, at least two follicles of 16 to 18 mm or a few follicles of 14 to 16 mm were obtained. For the GnRH antagonist regimen, gonadotropin injections were started at the same dose after an ultrasound scan on day 2 of the cycle to confirm quiescence of the ovaries. When the lead follicle reached a diameter of 12 mm, the GnRH antagonist cetrorelix (Cetrotide; Merck - Serono) was given at a dose of 0.25 mg daily.	2.70 vs 2.992.60), but there was no significant difference. The **duration of stimulation and total gonadotropin dose** were higher with short agonist regimens compared to antagonist regimens, with the latter being statistically significant (p<0.001). The **chemical pregnancy rate** was 8.33% with the short agonist regimen and 7.29% with the antagonist regimen, with no statistically significant difference (p=0.79).		
Schimberni M, Ciardo F, Schimberni M, Giallonardo A, De Pratti V, Sbracia M. Short gonadotropin-releasing hormone agonist versus flexible antagonist versus clomiphene citrate regimens in poor responders undergoing in vitro fertilization: a randomized controlled trial. Eur Rev Med Pharmacol Sci. 2016 Oct;20(20):4354-4361.	Randomized Controlled Trial	Two hundred and fifty patients, poor responders in a previous IVF cycle at least 3 months before at the center and undergoing a new IVF attempt, were enrolled in the study.	We divided the patients into three groups: group A, 68 women treated with clomiphene citrate and FSH plus antagonist; Group B, 71 patients treated with FSH plus antagonist; Group C, 75 patients treated with FSH plus GnRH agonist.	The GnRH agonist protocol showed a significantly higher pregnancy rate (29.3% vs 5.9% vs 14.1%, respectively) than the clomiphene and the GnRH antagonist protocol, number of mature oocytes collected, oestradiol levels and endometrial thickness. The cost of medications for each baby born was lower for the GnRH agonist protocol	This study demonstrates that the short GnRH agonist protocol should be the first choice in poor responders; instead, clomiphene citrate should be avoided due to its extremely low success rate and high costs.	Very Low

				than for the others; the implantation rate was significantly lower in the clomiphene group (4.8%) than in the GnRH antagonist group (9.3%) and the GnRH agonist groups (19.2%). No significant differences emerged for total FSH administered, days of stimulation, numbers of oocytes retrieved, and embryos transferred.		

5.2 Is Mild Ovarian Stimulation Protocol Superior to Conventional Protocols (GnRH-antagonist or long GnRH Agonist Protocol) in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Montoya-Botero P, Drakopoulos P, González-Foruria I, Polyzos NP. Fresh and cumulative live birth rates in mild versus conventional stimulation for IVF cycles in poor ovarian responders: a systematic review and meta-analysis. Hum Reprod Open. 2021 Feb 14;2021(1):hoaa066.	Systematic Review/Meta-analysis	15 RCTs were included in the meta-analysis. Liu et al., 2020: 97 vs. 94 Van Tilborg et al., 2017: 120 vs. 113 Ragini et al., 2012: 148 vs 156 Lee et al., 2011: 26 vs 27 Yu et al., 2018: 52 vs 54 Ashrafi et al., 2005: 34 vs 52 Karimzadeh et al., 2011: 79 vs. 80 Mohsen et al., 2013: 30 vs. 30 Revelli et al., 2014: 309 vs. 331 Pilehvari et al., 2016: 42 vs. 35 Bastu et al., 2016: 33 vs 31 Goswami et al., 2004: 13 vs 25	Liu et al, 2020: 97 vs 94 (**Let + GN + Antag vs. Agonist)** Van Tilborg et al., 2017: 120 vs 113 (**Low dose GN + Antag vs Antag or Agonist)** Ragini et al., 2012 148 vs 156(**CC + GN + Antag vs Agonist)** Lee et al., 2011: 26 vs 27 (**Let + GN + Antag vs Antag)** Yu et al., 2018: 52 vs 54 (**Let + GN + Antag vs. Agonist)** Ashrafi et al., 2005: 34 vs 52 (**CC + GN + Antag vs Agonist)** Karimzadeh et al., 2011: 79 vs. 80 **CC + GN + Antag vs Agonist** Mohsen et al., 2013: 30 vs 30 (**CC + GN + Antag vs. Agonist)** Revelli et al., 2014: 309 vs. 331 (**CC + GN + Antag vs**	**CLBR and FLBR** were comparable between mild versus conventional stimulation (RR 1.15; 95% CI: 0.73 1.81; I 2 ¼ 0%, n ¼ 424, moderate certainty and RR 1.01; 95% CI: 0.97 1.04; I2 ¼ 0%, n ¼ 1001, low certainty, respectively). No difference was observed either when utilizing oral compounds (i.e., letrozole and clomiphene) or lower doses. Similarly, **ongoing pregnancy rate (OPR)** and **clinical pregnancy rate (CPR)** were equivalent when comparing the two groups (RR 1.01; 95% CI: 0.98 1.05; I2 ¼ 0%, n ¼ 1480, low certainty, and RR 1.00; 95% CI: 0.97 1.03; I2 ¼ 0%, n ¼ 2355, low certainty, respectively). A significantly **lower oocyte yield** (mean differences (MD) -0.80; 95% CI: -1.28, -0.32; I2 ¼ 83%, n ¼ 2516, very low certainty) and	Despite the limitations described above, this meta-analysis provides robust evidence to suggest that in POR women with very poor response prognosis, MOS should be considered as a treatment option given that it results in comparable FLBRs and CLBRs with COS. However, a milder approach is associated with a lower number of oocytes retrieved and a higher cancellation rate. Future research should focus on whether COS may be of benefit in better prognosis women.	High

		Youssef et al., 2017: 195 vs 199	**Agonist)** Pilehvari et al., 2016: 42 vs 35 (**CC + GN + Antag vs Antag)** Bastu et al., 2016: 33 vs 31 (**Letrazole + GN + Antag vs Antag)** Goswami et al., 2004: 13 vs 25 (**Let + GN + Antag vs Agonist)** Youssef et al., 2017: 195 vs 199 (**Low dose GN + Antag vs Antag or Agonist)**	higher **rate of cycle cancellation** (RR 1.48; 95% CI: 1.08 2.02; I2 ¼ 62%, n ¼ 2588, low certainty) was observed in the MOS group.		
Bechtejew TN, Nadai MN, Nastri CO, Martins WP. Clomiphene citrate and letrozole to reduce follicle-stimulating hormone consumption during ovarian stimulation: systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2017 Sep;50(3):315-323.	Systematic Review/Meta-analysis	Total = 1551; CC alone = 145 vs 146, CC+FSH=79 vs 80, CC+FSH+ant=436 vs 419, LTZ+FSH=39 vs 52, LTZ+FSH+ant=63 vs 92	1. OS with only clomiphene citrate (CC), CC with a reduced dose of exogenous FSH and CC with a reduced dose of exogenous FSH and gonadotropin-releasing hormone agonist (ant) in late follicular phase vs standard OS in women with an expected poor ovarian response, 2. OS with only letrozole (LTZ), LTZ with a reduced dose of exogenous FSH, and LTZ with a reduced dose of FSH and gonadotropin-releasing hormone agonist (ant) in late follicular phase vs standard OS in women with expected poor ovarian response.	1. CC in women with expected POR: No significant difference in **Live Birth,** RR 0.9 (95% CI 0.6–1.2), **Clinical pregnancy**, RR 1.0 (95% CI, 0.8–1.4), **Miscarriage rate,** RR 1.3 (95% CI, 0.7–2.3), **Consideration reduction in FSH consumption,** MD −18 (95% CI, −21 to −15). For other outcomes, including cycle cancellation, RR 2.14 (95% CI, 1.0–4.8), Oocytes retrieved, MD 0.1 (95% CI, -1.1 to 1.3), very imprecise estimates/ very low quality of evidence, preventing conclusions from being drawn 2. LTZ in women with expected POR: No significant differences in number of oocytes retrieved, MD -0.4 (95% CI, -0.9 to 0.1), considerable reduction in FSH consumption MD −35.2 (95% CI, −47.3 to −23.0). For other outcomes, including Live Birth, RR 2.6 (95% CI 0.6–12.2), Clinical pregnancy, RR 1.0 (95% CI, 0.6–1.7), Miscarriage rate, RR 0.1 (95% CI, 0.0–2.2), Cycle cancellation, RR 1.4(95% CI, 0.7–3.0), very imprecise estimates/ very low quality of evidence, preventing conclusions from being drawn	The current evidence suggests that using CC reduces FSH consumption without changing pregnancy rates (clinical pregnancy and live birth), even considering the reduction in the number of oocytes retrieved. Regarding the use of LTZ in women with expected POR, evidence also showed a reduction in the number of FSH ampoules, without a relevant impact on the mean number of oocytes retrieved. When treating women with normal ovarian response, the use of CC or LTZ for OS should be considered because they both reduce the risk of OHSS. The available evidence should be interpreted with caution, however, since CC and LTZ can be used in several separate ways to reduce FSH consumption. Therefore, it is likely that the available evidence does not apply to all the available protocols. More trials evaluating all the clinically relevant outcomes are needed to increase the confidence in the observed estimates. Research evaluating the effect on miscarriage, cycle cancellation, and multiple pregnancies would add important data to the body	High

					of evidence. Future studies should also evaluate other interesting outcomes, such as quality of life and satisfaction with the treatment, total cost per live birth (including eventual OHSS treatment and considering both fresh and cryopreserved embryo transfers), and frequency of congenital anomalies.	
Youssef MA, van Wely M, Mochtar M, Fouda UM, Eldaly A, El Abidin EZ, Elhalwagy A, Mageed Abdallah AA, Zaki SS, Abdel Ghafar MS, Mohesen MN, van der Veen F. Low dosing of gonadotropins in vitro fertilization cycles for women with poor ovarian reserve: systematic review and meta-analysis. Fertil Steril. 2018 Feb;109(2):289-301.	Systematic Review/Meta-analysis	5 studies (Low dose vs high dose) N=717, 9 studies (Gonadotropins with oral compounds vs high dose gonadotropins) N=1387	1.Bastu et al 2016- Ovarian stimulation: Low dose150 IU hMG and 150 IU recombinant FSH. Low dose – II:75 IU hMG and 75 IU recombinant FSH and 5 mg/d letrozole. Conventional: 225 IU hMG and 225 IU recombinant FSH. 2.Youssef et al 2017- Ovarian stimulation: Low dose:150 IU/d recombinant FSH. Conventional dose: 450 IU of hMG. 3.Berkkanoglu & Ozgur 2010- Ovarian stimulation: Low dose 300 IUor 450 IU recombinant FSH. Conventional dose: 600 IU recombinant FSH. 4.Kim et al 2009- Ovarian stimulation: Low dose: 150 IU/d recombinant FSH Conventional dose: 225 IU of recombinant FSH. 5.Klinkert et al 2005 - Ovarian stimulation: Low dose: 150 IU/d recombinant FSH, adjusted to 300 IU/d in case E2 <200 pg/mL. Conventional dose: 300 IU of recombinant FSH. 6.Revelli et al 2014- Ovarian stimulation:	1. ongoing pregnancy rate (low dose vs. high dose)- Risk ratio 0.98(0.62,1.57) 2. ongoing pregnancy rate (gonadotropins plus oral compounds v. gonadotropins)- Risk ratio -0.01(-0.06,0.03) 3. Clinical Pregnancy Rate (low dose vs. high dose)- Risk ratio 1.00(0.57,1.51) 4. Clinical pregnancy rate (gonadotropins plus oral compounds vs. gonadotropins)- Risk ratio 1.00(0.78, 1,28) 5. live birth rate (low dose vs. high dose) - Risk ratio 1.11(0.30,4.12)	low doses of gonadotropins or gonadotropins combined with oral compounds could be alternative treatment options in women with poor ovarian reserve undergoing ovarian stimulation for IVF. Whether the low doses of gonadotropins or gonadotropins combined with oral compounds are to be preferred is unknown, as they have never been compared head-to-head. A health economic analysis to test the hypothesis that ovarian stimulation with low dosing is more cost-effective than high doses of gonadotropins is needed.	Very Low

	gonadotropins/oral compounds: (CC 100 mg (cd 2-5) and 150 IU/day (cd 5).Conventional dose: 300 IU/d hMG (cd 3), after 1 week increased to 450 IU. 7. Karimzade et al 2011- Ovarian stimulation: gonadotropins/oral compounds CC 100 mg/d (cd 3-7) and 225–300 IU/d of hMG/FSH (cd 5) Conventional dose: 225–300 IU/day. 8.Mohsen & el Din, 2013- Ovarian stimulation: gonadotropins/oral compounds (CC 100 mg/d (cd 2–6) and hMG 225 IU/d (cd 7).Conventional dose: hMG 300 IU/d. 9. Mohsen et al 2013- Ovarian stimulation: gonadotropins/oral compounds letrozole 2.5 mg/d (cd 2-6) and hMG 150 IU/d. Conventional dose:hMG 300 IU/d. 10. Lee et al 2011- Ovarian stimulation: gonadotropins/oral compounds: letrozole 2.5 mg (cd 2-6) and recombinant FSH 225 IU/d (cd 7) Conventional dose: hMG 225 IU/d. 11.Fouda & Sayed 2011- Ovarian stimulation: gonadotropins/oral compounds: 2.5 mg/d and FSH 300 IU/d (cd 3). Conventional dose: letrozole 5.0 mg (cd 1-5) 2.5 mg/d (cd 5-8) and recombinant FSH 300 IU/d (cd 5)

			12. Goswami et al., 2004- Ovarian stimulation: gonadotropins/oral compounds: letrozole 2.5 mg/d (cd 3–7) and recombinant FSH 75 IU/d (cd 3 and 8). Conventional dose: recombinant FSH (300–450 IU/d). 13. Huang et al., 2015- Ovarian stimulation: gonadotropins/oral compounds: letrozole (cd 3 to 7) and recombinant FSH (<150 IU/d) (cd 4, 6 and 8 onward). Conventional dose: 300 IU/d recombinant FSH (cd 1-5) adjusted from cd 6 onward.		

5.3 Is GnRH-agonist flare protocol superior to long GnRH-agonist protocols in patients with poor ovarian response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Sunkara SK, Tuthill J, Khairy M, El-Toukhy T, Coomarasamy A, Khalaf Y, Braude P. Pituitary suppression regimens in poor responders undergoing IVF treatment: a systematic review and meta-analysis. Reprod Biomed Online. 2007 Nov;15(5):539-46.	Systematic Review/Meta-analysis	A total of 680 women considered as poor responders undergoing IVF/ICSI treatment were included in nine randomized controlled trials. The quality of these studies was variable: for example, only three of the studies had unambiguous evidence of allocation concealment.	Long agonist Short agonist antagonist	Meta-analyses of the results of the studies did not show a consistent benefit for any one pituitary suppression regimen over the other regimens in improving outcome measures. Long agonist vs. short agonist- higher number of oocytes in long agonist short agonist vs antagonist long agonist vs. antagonist- higher number of oocytes in antagonists	Because of these inconsistent findings, a well-designed, adequately powered, multicentre three arm trial comparing the GnRH agonist long regimen versus the GnRH agonist short regimen versus the GnRH antagonist regimen is needed.	Moderate
Weissman A, Farhi J, Royburt M, Nahum H, Glezerman M, Levran D. Prospective evaluation of two stimulation protocols for low responders who were undergoing in vitro	Randomized Controlled Trial	Sixty low responders who were recruited based on results in previous cycles.	Modified flare protocol in which a high dose of GnRH agonist was administered for the first 4 days, followed by a standard agonist dose, or a modified long protocol in which a standard agonist dose	Twenty-nine cycles were performed with the modified flare protocol and 31 were performed with the modified long protocol. Significantly more oocytes were obtained with the modified long protocol than the modified flare protocol (4.42 +/- 2.6	These preliminary results substantiate the poor prognosis and outcome for low responders undergoing IVF. A modified long "mini dose" protocol is superior to a	Moderate

fertilization-embryo transfer. Fertil Steril. 2003 Apr;79(4):886–92.			was used until pituitary down-regulation, after which the agonist dose was halved during stimulation.	vs. 3.07 +/- 2.15). The number and quality of embryos available for transfer was similar in both groups. One clinical pregnancy (3.4%) was achieved with the modified flare protocol, and 7 pregnancies (22.5%) were achieved using the modified long protocol.	modified mega-dose flare protocol in terms of oocyte yield and cycle outcome.	
Sunkara SK, Coomarasamy A, Faris R, Braude P, Khalaf Y. Long gonadotropin-releasing hormone 20 agonist versus short agonist versus antagonist regimens in poor responders undergoing in vitro. 21 fertilization: a randomized controlled trial. Fertil Steril. 2014 Jan;101(1):147–53.	Randomized Controlled Trial	One hundred eleven women who were poor responders were randomized to the long GnRH agonist, short agonist, and antagonist regimens	Randomized to the long GnRH agonist, short agonist, and antagonist regimens.	The primary outcome was the number of oocytes retrieved. Number of oocytes retrieved was significantly higher with long GnRH agonist compared with the short agonist regimen (4.42 ± 3.06 vs. 2.71 ± 1.60), while there was no significant difference between long agonist and antagonist regimens (4.42 ± 3.06 vs. 3.30 ± 2.91). Duration of stimulation and total gonadotropin dose were significantly higher with long agonist compared with short agonist and antagonist regimens. The ongoing pregnancy rate was 8.1% with long and short agonist regimens and 16.2% with the antagonist regimen.	Long GnRH agonist and antagonist regimens offer a suitable choice for poor responders, whereas the short agonist regimen may be less effective because of fewer eggs retrieved.	Moderate
Chatillon-Boissier K, Genod A, Denis-Belicard E, Felloni B, Chene G, Seffert P, et al., [Prospective randomised study of long versus short agonist protocol with poor responder patients during in vitro fertilization]. Gynecol Obstet Fertil. 2012 Nov;40(11):652–7.	Randomized Controlled Trial	44 patients randomized; 39 cycles were taken into account. Poor responder patients (age between 38 and 42 years and FSH at day 3 more than 9.5 IU/L; and/or antral follicles count lesser or equal to 6; and/or failure of previous stimulation). The primary endpoint is based on the number of oocytes retrieved at the end of an IVF cycle.	Long agonist half-dose protocol versus short agonist protocol without pretreatment	Out of the 44 patients randomized, 39 cycles were taken into account (20 in the long protocol, 19 in the short one). At the end of the stimulation (FSH-r 300 to 450 UI/d), the number of follicles recruited appears higher in the long protocol but the difference is 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 tendency is observed for all the following criteria: the number of retrieved oocytes (6.74±2.73 vs. 6.38±4.26), the total number of embryos (3.16±2.03 vs. 2.25±2.11), the 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, but the long half-dose is better.	Low

5.4 Is DUOSTIM superior to Antagonist/Mild Stimulation or Two Conventional (BISTIM) in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Sfakianoudis K, Pantos K, Grigoriadis S et al. What is the true place of a double stimulation and double oocyte retrieval in the same cycle for patients diagnosed with poor ovarian reserve? A systematic review including a meta-analytical approach. J Assist Reprod Genet. 2020 Jan;37(1):181-204.	Systematic Review/Meta-analysis	Regarding the sample size of this systematic review, a total of 1026 and 988 patients were enrolled in the FPS group and LPS group, respectively. In the FPS group, the number of patients enrolled ranged from 38 to 353, and in the LPS group, the number of patients enrolled ranged from 30 to 366. 4/9 studies in poor responders **Zhang et al. 2017 153 FPS and 153 LPS** **Jin et al. 2018 72 FPS and 76 LPS** **Zhang et al. 2018 61 FPS and 61 LPS** **Madani et al., 2019 121 FPS and 121 LPS**	Four studies included participants characterized as POR patients according to the Bologna criteria. In the other five, different inclusion criteria were employed. 1. In the prospective study of Kuang et al., patients had to meet at least two out of the following five criteria: advanced maternal age defined as over 40 years of age; a history of ovarian surgery; previous IVF attempts using conventional COS protocols that resulted to less than three oo-cytes; antral follicle count (AFC) of less than five on menstru-al cycle days 2–3; and basal serum FSH levels between 10 and19 IU/L. 2. In the prospective study of Ubaldi et al., patients included had been submitted to preimplantation genetic diagnosis for aneuploidy testing (PGD-A) and had presented with a medical history including: anti-Müllerian hormone (AMH) levels of less than 1.5 ng/mL, AFC of less than six follicles, and/or less than five oocytes retrieved in previous IVF attempts. 3. In the retrospective study of Liu et al., all enrolled patients were 38 years or older, were presenting with normal menstruation, and had at least one follicle 6–11 mm in diameter observed during oocyte retrieval following FPS. 4. In the retrospective study of Rashtian et al., patients had to meet the following inclusion criteria: basal serum FSH levels >	Comparison of FPS/LPS 1. **Days of stimulation** - FPS/LPS - Number studied 254/241 Mean difference 0.38 (-1.18, 0.42) 2. **Cycle cancelation rate** - FPS/LPS - Number studied 346/333 OR 1.27 (0.36, 4.48) 3. **Number of oocytes retrieved -** FPS/LPS - Number studied Mean difference - 335/318 0.52(-1.10, 0.05) 4. **Comparison of mean difference of MII oocytes. FPS/LPS** - Number studied 274/257 mean difference - 0.49 (-1.82.0.88) 5. **Comparison of MII oocyte rate FPS/LPS -** Number studied 784/1108 RR 0.84(0.33, 1.26 6. **Fertilization rate FPS/LPS** - Number studied 518/734 OR 1.08 (0.82,1.42) 7. C**linical pregnancy rate FPS/LPS -** Number studied 77/82 OR o.46(0.22,0.99) 8. **Live birth/ongoing pregnancy rate FPS/LPS** - Number studied 27/29 OR 0.52(0.10, 2.29) 9.M**iscarriage/early pregnancy loss rate FPS/LPS -** Number studied OR 0.53(0.10,2.90) Comparison of Duo stim vs Con Stim 1. **Number of oocytes retrieved DS/CS** - 0/0 Not estimated 2. **Comparison of mean difference of MII oocytes.**	DuoStim favors an enhanced clinical outcome regarding the total number of yielded oocytes, mature oocytes, and available embryos, along with the quality of obtained embryos. Sourced data indicate that LPS is not correlated with a higher aneuploidy rate. This option may present promising for the time-sensitive nature of POR patients' management, by enabling a higher oocyte yield during a single menstrual cycle.	Low

			15 IU/m on menstrual cycle day 3; total AFC of less than eight; and at least one failed IVF attempt following conventional COS. 5. In the prospective study of Vaiarelli et al., patients had to meet at least two out of the following four criteria: advanced maternal age defined as over 35 years of age; AMH levels of less than 1.5 ng/mL; AFC of less than six follicles; previous IVF attempts yielding less than five metaphase II (MII) oocytes.	DS/CS - 0/0 Not estimated 3. **Comparison of MII oocyte rate DS/CS Number studied** 257/716 OR 0.96(0.28,3.27) 4. **Fertilization rate DS/CS** Number studied 458/831 OR 0.92(0.66, 1.27) 5. **Clinical pregnancy rate** DS/CS Number studied 95/150 OR 0.74(0.23,2.41) 6. **Live birth/ongoing pregnancy rate** DS/CS Number studied 95/150 OR 0.80(0.28, 0.23) 7. **Miscarriage/early pregnancy loss** rate DS/CS Number studied 26/48 OR 0.76 (0.13,4.40)		
Massin N, Abdennebi I, Porcu-Buisson G, Chevalier N, Descat E, Piétin-Vialle C, Goro S, Brussieux M, Pinto M, Pasquier M, Bry-Gauillard H. The BISTIM study: a randomized controlled trial comparing dual ovarian stimulation (duostim) with two conventional ovarian stimulations in poor ovarian responders undergoing IVF. Hum Reprod. 2023 May 2;38(5):927-937.	Randomized Controlled Trial	Eighty-eight women with POR, defined using adjusted Bologna criteria (antral follicle count 5 and/or anti-Mullerian hormone 1.2 ng/ml) were randomized, 44 in the **duostim group** and 44 in the **conventional (control) group (Antag)**.	Dual ovarian stimulation (duostim) with HMG 300 IU/day with flexible antagonist protocol was used for ovarian stimulation, except in luteal phase stimulation of the duostim group. In the duostim group, oocytes were pooled and inseminated after the second retrieval, with a freeze-all protocol.	The mean (SD) **cumulative number of oocytes** retrieved from two ovarian stimulations was not statistically different between the control and duostim groups, respectively, 12 (3.4) and 5.0 (3.4) [mean difference (MD) [95% CI] 0.4 [-1.1; 1.9], P = 0.56]. The **mean cumulative numbers of mature oocytes and total embryos obtained** were not significantly different between groups. The **total number of embryos transferred** by patient 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** comparing Cycle 1 versus Cycle 2, both in control and duostim groups. The	Based on the number of total and mature oocytes retrieved in women with poor ovarian response (POR), there is no benefit of duostim versus two consecutive antagonist cycles.	Moderate

				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 live birth rate** was not statistically different, comparing controls versus the duostim group, 34.1% versus 17.9%, respectively (P = 0.08). The time to transfer resulting in an ongoing pregnancy did not differ in controls 1.7 (1.5) months versus the duostim group, 3.0 (1.6) (P =0.08). **No serious adverse events were reported.**		
Ubaldi FM, Capalbo A, Vaiarelli A, Cimadomo D, Colamaria S, Alviggi C, et al., Follicular versus luteal phase ovarian stimulation during the same menstrual cycle (DuoStim) in a reduced ovarian reserve population results in a similar euploid blastocyst formation rate: new insight in ovarian reserve exploitation. Fertil Steril. 2016 Jun;105(6):1488-1495.e1.	Prospective paired noninferiority observational study	Forty-three reduced ovarian reserve patients undergoing a PGD-A.	Compare the euploid blastocyst formation rates obtained after follicular phase (FP) versus luteal phase (LP) stimulation performed in the same menstrual cycle in a preimplantation genetic diagnosis for aneuploidy testing (PGD-A)	Patients with an antimüllerian hormone level of <1.5 ng/mL, antral follicle count of <6 follicles, and/or <5 oocytes retrieved in a previous cycle were included. No statistically significant differences were found in the number of retrieved COCs (5.1 ± 3.4 vs. 5.7 ± 3.3), MII oocytes (3.4 ± 1.9 vs. 4.1 ± 2.5), or biopsied blastocysts per stimulated cycle (1.2 ± 1.2 vs. 1.4 ± 1.7) from FP versus LP stimulation, respectively. No differences were observed in the euploid blastocyst rate calculated either per biopsied blastocyst (46.9% vs. 44.8%) or injected MII oocyte (16.2% vs. 15.0%).	Stimulation with an identical protocol in the FP and LP of the same menstrual cycle resulted in a similar number of blastocysts in patients with reduced ovarian response. The LP stimulation statistically significantly contributed to the final transferable blastocyst yield, thus increasing the number of patients undergoing transfer per menstrual cycle.	Low
Kuang Y, Chen Q, Hong Q, Lyu Q, Ai A, Fu Y, Shoham Z. Double stimulations during the follicular and luteal phases of poor responders in IVF/ICSI programmes (Shanghai protocol). Reprod Biomed Online. 2014 Dec;29(6):684-91	Others	In a pilot study, the efficacy of double stimulations during the follicular and luteal phases in women with poor ovarian response was explored (defined according to the Bologna criteria). **Thirty-eight women** began with **mild ovarian stimulation.** After the first oocyte retrieval, **human**	**Double stimulation (Shanghai Protocol)** Stage one of treatment protocol patients were screened by transvaginal ultrasound and serum FSH testing on day 3 of their menstrual cycle. Clomiphene citrate (Fertilan; Codal-Synto Ltd., France) 25 mg/day co treatment and letrozole (Jiangsu Hengrui	First vs second stimulation Stimulation duration (days) 10.2 ± 2.4 10.8 ± 3.1 NS **Human menopausal gonadotrophin dose (IU)** 326.4 ± 248.9 1802.5 ± 712.7 <0.001 **Number of follicles >10 mm on trigger day** 1.9 ± 0.9 4.3 ± 2.8 <0.001 **Number of follicles >14 mm on**	Double stimulation during the follicular and luteal phases in the same menstrual cycle provided more opportunities to retrieve oocytes in poor responders, with the resulting embryos having similar development potential. Double stimulation and	Low

	menopausal gonadotrophin and letrozole were administrated to stimulate follicle development, and oocyte retrieval was carried out a second time when dominant follicles had matured.	Medicine Co., China) 2.5 mg/day were given from cycle day 3 onwards. Letrozole was only given for 4 days, and clomiphene citrate was continuously used before the trigger day. Patients started to inject human menopausal gonadotrophin (HMG) 150 IU (Anhui Fengyuan Pharmaceutical Co., China) every other day beginning on cycle day 6. Follicular monitoring started on cycle day 10 and was carried out every 2–4 days using a transvaginal ultrasound examination to record the number of developing follicles and serum FSH, LH, oestradiol and progesterone concentrations. When one or two dominant follicles reached 18 mm in diameter, the final stage of oocyte maturation was induced with triptorelin (Decapeptyl; Ferring GmbH, Germany) 100 g, followed by ibuprofen 0.6 g (Ibuprofen Sustained Release Capsules; Tianjin Glaxo Smith Kline Pharmaceuticals, China), which was used on the triggering day and the next day, for preventing possible follicle rupture before oocyte retrieval (Kadoch et al., 2008). Transvaginal ultrasound-guided oocyte retrieval was conducted 32–36 h after GnRH agonist administration. All follicles of less than 10 mm were not retrieved and left for the second-stage stimulation in the luteal phase. Fertilization of the aspirated oocytes was carried out in vitro, by either conventional insemination or ICSI, depending on semen parameters. Embryos were examined for the number and regularity of blastomeres and the degree of embryonic	**trigger da**y 1.5 ± 0.6 3.5 ± 2.0 <0.001 **Number of oocytes retrieved** 1.7 ± 1.0 3.5 ± 3.2 0.001 **Number of metaphase II (metaphase II) oocytes** 1.4 ± 1.0 2.7 ± 2.7 0.008 **Number of immature oocytes** 0.2 ± 0.5 0.8 ± 1.0 0.011 **Number of fertilized oocytes** 1.0 ± 1.0 2.1 ± 2.5 0.019 **Number of cleaved embryos** 1.0 ± 1.0 2.0 ± 2.4 0.045 Number of top-quality embryos 0.7 ± 1.0 1.2 ± 1.5 NS Number of cryopreserved embryos 0.9 ± 1.0 1.3 ± 1.4 NS **Oocyte retrieval rate per follicle n** (%) 62/78 (79.5) 105/183 (57.4) <0.001 Mature oocyte rate n (%) 53/62 (85.5) 82/105 (78.1) NS Fertilization rate n (%) 37/53 (69.8) 62/82 (75.6) NS Cleavage rate n (%) 37/37 (100) 59/62 (95.2) NS Cancellation rate n (%) 20/38 (52.6) 13/30 (43.3) NS	subsequent cryopreserved embryo transfer is a promising approach both for patients with POR, especially for the cases that repeat edly did not have oocytes retrieved or viable embryos using conventional IVF regimens, and for cancer patients needing emergency fertility preservation.

	fragmentation, and graded according to Cummins's criteria (Cummins et al., 1986). All highest-quality embryos (including grade 1 and grade 2, eight-cell blastomere embryos) were cryopreserved on the third day after oocyte retrieval. The non-top-quality embryos were placed in extended culture until the blastocyst stage. During this stage, on day 5 or day 6, only good morphology blastocysts were cryopreserved. Both cleavage-stage embryos and blastocysts were cryopreserved by vitrification. In brief, the cryotop carrier system (Kitazato Biopharma Co Ltd, Japan) was used for vitrification and 15% (v/v) ethylene glycol, 15% (v/v) Dimethylsulphoxide and 0.5 M sucrose as the cryoprotectant. For warming, 1 M, 0.5 M, and 0 M sucrose solutions were used for cryoprotectants dilution step by step. All vitrification and warming steps were carried out at room temperature except the first warming step at 37°C. Stage two of treatment protocol: ovarian stimulation and oocyte retrieval Transvaginal ultrasound examination was carried out after oocyte retrieval to determine whether to continue the second ovarian stimulation. The criterion for continued stimulation was the presence of at least two antral follicles 2–8 mm in diameter. A total of 225 IU HMG and letrozole 2.5 mg were administered daily from the day of, or the day after, oocyte retrieval. The initial second stage follicular monitoring was conducted 5–7 days later, and then every 2–4 days, using a transvaginal ultrasound examination to record	

	the number of developing follicles, and serum FSH, LH, oestradil and progesterone concentrations. Letrozole administration was stopped when the dominant follicles reached diameters of 12 mm, given that large follicles have redundant LH and FSH receptors, and good response to exogenous hormone stimulations. Daily administration of medroxyprogesterone acetate 10 mg was added beginning on stimulation day 12 for cases in which post-ovulation follicle size was smaller than 14 mm in diameter and stimulation needed to continue for several more days. This was done to postpone menstruation and avoid oocyte retrieval during menstruation, to prevent the risk of infection from the procedure. When three dominant follicles reached diameters of 18 mm or one mature dominant follicle exceeded 20 mm, the final stage of oocyte maturation was induced again with triptorelin 100 g by injection. Again, ibuprofen 0.6 g was used on the day of oocyte maturation triggering and the day after. Transvaginal ultrasound-guided oocyte retrieval was conducted 36–38 h after GnRH agonist administration. All oocytes collected were treated as in study stage one. Endometrial preparation and cryopreserved embryo transfer Embryo and endometrium synchronization in cryopreserved embryo transfer cycles in this study was according to the method described earlier (Kuang et al., 2013). In brief, for natural cryopreserved embryo transfer cycles, follicular growth was monitored by measuring	

	serum hormone levels and by ultrasound beginning on cycle day 10. When the diameter of the dominant follicle exceeded 16 mm and endometrial thick ness was more than 8 mm, with oestradiol greater than 150 pg/ml, one of two procedures was carried out, depend ing on the LH and progesterone value. If LH was less than 20 IU/l and progesterone was less than 1.0 ng/ml, HCG 10,000 IU was administrated at night (21:00) to trigger ovulation, and the transfer of the 3-day-old embryos was arranged for 5 days later. If the LH value was more than 20 IU/l or the progesterone value was more than 1.0 ng/ml, HCG 10,000 IU was injected the same afternoon and the transfer of the 3-day-old embryos was con ducted 4 days later. The transfer of blastocysts was arranged for the sixth or seventh day, depending on serum hormones and ultrasound results. Duphaston (Abbott Biologicals B.V., America) 40 mg/day was used for luteal support beginning on the third day after HCG injection. For cases with irregular menstrual cycles, letrozole was used and, if necessary, HMG, to stimulate mono-follicular growth. The common method used was letrozole 2.5–5 mg administered from cycle day 3 to 7, and then follicle growth was monitored beginning on day 10. At times, treatment included a low dose of HMG (75 IU/day) to stimulate follicular and endometrial-lining growth. Administration of HCG 10,000 IU and the timing of cryopreserved embryo transfer were determined according to the	

			above criteria. For patients with thin endometria during either natural cycles or stimulation cycles, hormone replacement treatment was recommended for endometrial preparation, specifically, oral ethinyl oestradiol (Shanghai Xinyi Pharmaceutical Co., China) 25 g three times a day from cycle day 3 onwards. Once the endometrial lining was greater than 8 mm thick, the following medications were started: two yellow femoston tablets twice a day (Solvay Pharmaceuticals B.V., France) (each tablet contains 2 mg oestradiol and 10 mg dydrogesterone) and vaginal progesterone soft capsules 200 mg twice a day (Laboratoires Besins International). The timing of warming and transfer was determined on the third day after femoston administration. The maximum number of transferred embryos was two per patient. When pregnancy was diagnosed by a positive beta-HCG test, the progesterone supplementation was continued until 10 weeks of gestation.			
Vaiarelli A, Cimadomo D, Conforti A, Schimberni M, Giuliani M, D'Alessandro P, Colamaria S, Alviggi C, Rienzi L, Ubaldi FM. Luteal phase after conventional stimulation in the same ovarian cycle might improve the management of poor responder patients fulfilling the Bologna criteria: a case series. Fertil Steril. 2020 Jan;113(1):121-130	Others	A total of 100 out of 297 patients fulfilling the Bologna criteria chose to undergo DuoStim. The FPS and LPS with the same antagonist protocol and agonist trigger, intracytoplasmic sperm injection with ejaculated sperm, preimplantation genetic testing for aneuploidies, and vitrified-warmed euploid single blastocyst transfer was performed.	Follicular phase stimulation was started on Day 2 of the menstrual cycle with a fixed dose of recombinant follicle stimulation hormone and recombinant luteinizing hormone (300 IU/d of Gonal-F, Merck KGaA or Puregon, MSD plus 150 IU/d of Luveris, Merck KGaA) for 4 days. Follicular growth was monitored on Day 5 and then every 2–3 days. The gonadotrophin-releasing hormone antagonist (Cetrorelix, Cetrotide, Merck KGaA; Ganirelix, or galutran, MSD) was administered daily after the identification of a leading follicle with a diameter	Patients (100) underwent FPS (maternal age, 42.1 1.4 y; previous in vitro fertilization cycles with =<3 collected oocytes,0.7 +/- 0.9; antral follicle count, 3.8 +/- 1.2 follicles; and antimullerian hormone, 0.56 +/- 0.3 ng/mL). Ninety-one patients completed DuoStim. All patients were included in the analysis. More **oocytes were obtained** after LPS with similar **developmental and chromosomal competence** as paired FPS-derived ones. The **CLBR per ITT** increased from 7% after FPS to 15% after	In conclusion, this study does not support that DuoStim is superior to two conventional COS protocols in terms of CLBR per ITT. The mean number of euploid blastocysts obtained and the clinical outcomes after each ovarian stimulation (FPS-only, LPS-only, or conventional COS) are similar. However, DuoStim strategy lessens the patient drop-out rate, which is highly likely after a failed attempt with conventional	Low

			R13–14 mm and until the day of ovulation trigger. When at least one follicle had reached 17–18 mm in diameter, final maturation of oocytes was triggered with a single subcutaneous bolus of buserelin at the dose of 0.5 mL (Suprefact 5.5 mL; Hoechst Marion Roussel) to reduce the time of luteolysis.	DuoStim. Conversely, the **CLBR per ITT** among the 197 patients that chose a conventional controlled ovarian stimulation strategy was 8%, as only 17 patients who were not pregnant returned for a second stimulation after the first attempt (drop-out rate, 81%).	COS. On the other hand, LPS provides these patients with a higher chance to obtain and transfer an euploid blastocyst in the same ovarian cycle.	

5.5 Is Luteal Phase Stimulation superior to Follicular Phase Stimulation in patients with poor ovarian response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Lu BJ, Lin CJ, Lin BZ et al. ART outcomes following ovarian stimulation in the luteal phase:a systematic review and meta-analysis. J Assist Reprod Genet. 2021 Aug;38(8):1927-1938.	Systematic Review/Meta-analysis	LPS 1295 FPS 3138 7 studies in poor responders **Li et al. 2015 China Retrospective 33 vs. 98 (LPS vs. FPS)** **Wei et al. 2016 China Retrospective 50 vs. 158 (LPS vs. FPS)** **Wu et al. 2017 China Retrospective 113 vs. 224 (LPS vs. FPS)** **Lin et al. 2018 Taiwan Prospective cohort 30 vs. 30 (LPS vs. FPS)** **Jin et al. 2018 China Retrospective cohort 52 vs. 132 (LPS vs. FPS)** **Zhang et al. 2018 China Retrospective 154 vs. 231 (LPS vs. FPS)** **Llacer et al. 2020 Spain RCT 27 vs. 30 (LPS vs. FPS)**	LPS versus FPS	The regimen employed can be categorized into two groups, but there is currently no evidence to support one over the other. After excluding the largest study, the clinical **pregnancy rate** and **live birth rate** were similar after FPS and LPS. There were significantly more **stimulation days and total gonadotropins used** in the LPS group. After subgroup analysis, it was observed that poor responders received significantly more cumulus oocyte complexes (+0.64) in the LPS group. LPS vs. FPS **Stimulation days:** MD 1.62 (1.13 to 2.11) **Total dose of gonadotrophins:** MD 576 (329.6 to 822.69) **Total Number of cumulus oocytes retrived:** MD 0.49 (0.10 to 0.88) **Viable embryos for transfer:** MD 0.45 (0.06 to 0.84) **Clinical pregnancy rate per transfer:** OR 1.05 (0.77 to 1.43) **Live birth per transfer:** OR 0.98	Our review of current evidence showed that there were borderline significant trends towards higher CPR and LBR for patients in the LPS group. However, after excluding the largest study, both CPR and LBR were similar between the two groups. For normal and poor responders, LPS required longer stimulation and higher total dosages of gonadotropins. Only poor responders received more COCs in the LPS group. As a result, there is currently insufficient evidence to support the universal use of LPS and there are no standard protocols for LPS. The evidence level of this study was based on prospective and retrospective studies, and more well-designed studies are necessary in the future.	Very Low

				(0.64 to 1.52)		
Li Y, Yang W, Chen X, Li L, Zhang Q, Yang D. Comparison between follicular stimulation and luteal stimulation protocols with clomiphene and HMG in women with poor ovarian response. Gynecol Endocrinol. 2016;32(1):74-7	Cohort Study	(IVF). A total of 131 women were diagnosed as poor responders. Thirty-three women started ovarian stimulation in early-luteal phase and 98 women started in early follicular phase with 100 mg/d clomiphene citrate and 75–150 IU/d HMG.	**Follicular stimulation VS luteal stimulation protocols** Ovarian stimulation was initiated with 100 mg/d clomiphene citrate for 5 days and 75–150 IU/d hMG until hCG day.In the control group, ovarian stimulation was initiated on day 3 of menstruation with the same protocol, but when the size of dominant follicle reached to 13–14 mm GnRH antagonist (Cetrotide) was administered with 0.25 mg/d until hCG day. In both groups, when the size of the dominant follicle was 17 mm, a trigger of 10,000 IU hCG (Lizhu) was administered.	There were more **oocytes retrieved** (2.8 ± 2.0 versus 2.0 ± 1.2, p50.05), more **available embryos** (1.8 ± 1.4 versus 1.3 ± 1.1, p50.05) and **top-quality embryos** (0.9 ± 0.9 versus 0.4 ± 0.6, p50.05), and **reduced cycle cancellation rate** (12.1% versus 30.6%, p<0.05) in luteal group than in follicular group. The **clinical pregnancy** (17.7%, 20.0% and 41.2%) and **live-birth rates** (10.78%, 20.0% and 29.4%) after transferring embryos obtained from luteal, follicular, and mixed stages were comparable (p>0.05).	In a conclusion, for poor responders, early luteal-phase stimulation comparing with mild follicular stimulation showed reduced cycle cancellation rate, more matured oocytes and top-quality embryos, and acceptable pregnancy outcome. It should be an available protocol for poor responders.	Low

5.6 Is modified natural cycle protocol superior to GnRH antagonist protocol in patients with poor ovarian response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality

Chung-Hoon K, So-Ra K, Yong-Pil C, Sung-Hoon K, Hee-Dong C, Byung-Moon K. Minimal stimulation using gonadotropin-releasing hormone (GnRH) antagonist and recombinant human follicle-stimulating hormone versus GnRH antagonist multiple-dose protocol in low responders undergoing in vitro fertilization/intracytoplasmic sperm injection . Fertil Steril 2009;92:2082–4.	Randomized Controlled Trials	The study population consisted of 90 low responders who had undergone 90 IVF/ICSI cycles. A low responder was defined as a patient who failed to produce three or fewer follicles with a mean diameter of at least 16 mm with the result that three or fewer oocytes were retrieved despite the use of a high gonadotropin dose (>2500 IU) in previous failed IVF/ICSI cycles.	Patients were randomly allocated into the minimal stimulation group (n = 45) or the GnRH antagonist MDP group (n = 45)	Minimal Stimulation vs. GnRH antagonist MDP: No. of ET cycles (%) 37/45 (82.2%) versus 42/45 (93.3%), NS Cancellation rate, % 17.8 (8/45) versus 6.7 (3/45) NS No. of oocytes retrieved (range): 1.5 ± 0.9 (0–3) versus 3.1 ± 1.6 (0–7) p value <.001 Clinical PR/cycle initiated (% 13.3 (6/45) versus 17.8 (8/45 NS Clinical PR/cycle completed (%)16.2 (6/37) versus 19.0 (8/42), NS Live birth rate/ET, % 13.5 (5/37) versus 16.7 (7/42) NS	In conclusion, the present study suggests that the minimal stimulation protocol in natural cycles provides similar pregnancy rates to GnRH antagonist MDP with fewer doses and days of rhFSH and thus can be a patient-friendly and cost-effective alternative in low responders.	Moderate
Elizur SE, Aslan D, Shulman A, Weisz B, Bider D, Dor J. Modified natural cycle using GnRH antagonist can be an optional treatment in poor responders undergoing IVF. J Assist Reprod Genet. 2005 Feb;22(2):75-9. doi: 10.1007/s10815-005-1496-2. PMID: 15844732; PMCID: PMC3455473.	Cohort Study	540 cycles of 433 suitable patients who were divided by treatment protocol into modified natural, antagonist, and long agonist groups. There were 52 modified natural cycles with GnRH antagonist supplementation, 200 stimulated cycles with GnRH antagonist, and 288 long GnRH agonist cycles.	GnRH antagonist protocol, GnRH long agonist protocol and modified natural cycle protocol	Mean number of oocytes retrieved in the modified natural group was significantly lower than in the stimulated antagonist and long agonist groups (1.4 +/- 0.5 vs. 2.3 +/- 1.1 and 2.5 +/- 1.1, $p < 0.05$). Implantation and pregnancy rates were 10% and 14.3%, 6.75% and 10.2%, and 7.4% and 10.6%. Cycle outcome and cycle properties were similar.	Modified natural IVF cycle with GnRH antagonist supplementation is a feasible alternative to ovarian stimulation protocols in poor responders.	Low

Lainas TG, Sfontouris IA, Venetis CA, Lainas GT, Zorzovilis IZ, Tarlatzis BC, Kolibianakis EM. Live birth rates after modified natural cycle compared with high-dose FSH stimulation using GnRH antagonists in poor responders. Hum Reprod. 2015 Oct;30(10):2321-30. doi: 10.1093/humrep/dev198. Epub 2015 Aug 25. PMID: 26307091.	Cohort Study	Irrespective of their age, poor responder patients should have a diminished ovarian reserve as shown by low antral follicle count (≤5) and increased basal FSH (>12 IU/l), and one or more previous failed IVF cycles in which ≤3 oocytes were retrieved using a high gonadotrophin dose.	161 MNCs (106 women in the MNC group) and 164 HDFSH (high dose FSH) antagonist cycles (136 women in the HDFSH group) performed between January 2008 and December 2013 at Eugonia Assisted Reproduction Unit.	The probability of live birth was significantly higher in the MNC when compared with the HDFSH group (OR: 4.01, 95% CI: 1.14-14.09), after adjusting for basal FSH, female age and cause of infertility, variables which were shown to be associated with the probability of live birth in univariable analysis. MNCs were characterized by significantly lower total gonadotrophin dose (490.0 ± 35.2 IU versus 2826.1 ± 93.4 IU, P < 0.001), lower estradiol concentrations (237.5 ± 12.3 pg/ml versus 487.3 ± 29.8 pg/ml, P < 0.001), fewer follicles present on the day of hCG (1.9 ± 0.1 versus 3.2 ± 0.2, P < 0.001), fewer oocytes retrieved (1.1 ± 0.01 versus 2.4 ± 0.1, P < 0.001), fewer oocytes fertilized (0.7 ± 0.1 versus 1.4 ± 0.1, P < 0.001), fewer embryos transferred (0.7 ± 0.1 versus 1.4 ± 0.1, P < 0.001), fewer good-quality embryos available (0.5 ± 0.1 versus 0.8 ± 0.1, P < 0.001) and fewer good-quality embryos transferred (0.5 ± 0.05 versus 0.8 ± 0.1, P < 0.001) compared with the HDFSH group. However, the proportion of cycles with at least one good-quality embryo transferred per started cycle was similar between the two groups compared (62.5, 95% CI: 52.7-72.3 versus 62.7, 95% CI: 53.0-72.5, respectively).	Both MNC and HDFSH antagonist protocols offer very low chances of live birth in poor responder patients who fulfill the Bologna criteria. However, MNC-IVF is a more patient-friendly approach, with a higher probability of live birth compared with the HDFSH antagonist protocol. In this respect, the current data might be of help in counseling such patients, who do not wish to undergo oocyte donation, prior to abandoning treatment altogether and/or proceeding to adoption.	Low

Drakopoulos P, Romito A, Errázuriz J, Santos-Ribeiro S, Popovic-Todorovic B, Racca A, Tournaye H, De Vos M, Blockeel C. Modified natural cycle IVF versus conventional stimulation in advanced-age Bologna poor responders. Reprod Biomed Online. 2019 Oct;39(4):698-703. doi: 10.1016/j.rbmo.2019.05.009. Epub 2019 May 16. PMID: 31383604.	Cohort Study	Patients with poor ovarian response (POR) attending a tertiary referral university hospital from 1 January 2011 to 1 March 2017. All women who fulfilled the Bologna criteria for POR and aged ≥40 years who underwent their first intracytoplasmic sperm injection (ICSI) cycle in the study centre were included.	476 advanced-age Bologna poor responder patients were included in the study: 189 in the MNC-IVF group and 287 in the HDOS group.	OPR per patient were significantly lower in the MNC-IVF group (5/189, 2.6%) compared with the HDOS group (29/287, 10.1%) (P = 0.002). However, after adjustment for relevant confounders (number of oocytes and presence of at least one top-quality embryo), the multivariate logistic regression analysis showed that the type of treatment strategy (HDOS versus MNC-IVF) was not significantly associated with OPR (odds ratio 2.56, 95% confidence interval 0.9-7.6).	In advanced-age Bologna poor responders, MNC-IVF, which is a more patient-friendly approach, could be a reasonable alternative in this difficult-to-treat group of women.	Low
Kedem A, Tsur A, Haas J, Yerushalmi GM, Hourvitz A, Machtinger R, Orvieto R. Is the modified natural in vitro fertilization cycle justified in patients with "genuine" poor response to controlled ovarian hyperstimulation? Fertil Steril. 2014 Jun;101(6):1624-8. doi: 10.1016/j.fertnstert.2014.02.036. Epub 2014 Mar 26. PMID: 24680364.	Cohort Study	One hundred eleven patients with POR, defined according to the Bologna criteria, who underwent a subsequent MNC-IVF within 3 months of the previous failed conventional IVF/ICSI cycle.	Modified natural cycle IVF protocol with GnRH antagonist (GnRH-a) supplementation. Gonadotropin-releasing versus previous cycle	MNC vs. Previous cycle Average total dose of gonadotropins used (ampules)14.0 ± 6.0 versus 55.0 ± 23.0 p-value:<.001 peak E2 level on the day of hCG administration (341 ± 290 vs. 557 pmol/L ± 483; P<.002) were significantly lower in the MNC-IVF cycle compared with the previous conventional IVF/ICSI cycles, the number of cycles resulting with no oocyte at oocyte pick-up (15 vs. 7; P<.001) was significantly higher The authors did not observe any pregnancies among patients undergoing the 58 MNC-IVF cycles.	Modified natural cycle-IVF is of no benefit for genuine poor ovarian responders and the option of egg donation should be seriously considered for this population.	Very Low

5.7 Is Progesterone Primed Ovarian Stimulation Protocol Superior to GnRH Antagonist Protocol in Patients with Poor Ovarian Response?

Article citation	Type of	Patient	Intervention	Effect Size	Conclusion	Quality

Study						
Cai R, Zheng B, Lin Q, Deng J, Zeng X, Lin W, Shi D. A meta-analysis of the efficacy of progestin-primed ovarian stimulation with medroxyprogesterone acetate in ovulation induction in poor ovarian responders. J Gynecol Obstet Hum Reprod. 2021 Sep;50(7):102049.	Systematic Review/Meta-analysis	NA	1. PPOS vs Chinese minimal stimulation IVF 2. PPOS vs Antagonist protocol 3. PPOS vs ultra-short GnRH a protocol	**Number of mature eggs**: patients receiving PPOS had a higher number of mature eggs compared to those receiving other protocols (MD = 0.3, 95% CI: 0.04–0.56, *P*=0.02). **Number of available embryos:** patients receiving PPOS produced more available embryos compared to those receiving other protocols (MD = 0.23, 95% CI: 0.12–0.33, *P* < 0.0001). **Number of high-quality embryos:** patients receiving PPOS produced more optimal embryos compared to those receiving other protocols (MD = 0.21, 95% CI: 0.12–0.29, *P* < 0.00001). **Cumulative pregnancy rate:** patients receiving PPOS had a higher cumulative rate of pregnancies compared to those receiving other protocols [32.46 % (N 1297) vs 27.26 % (N 1137)] (OR = 1.30, 95 % CI: 1.08–1.58, *P*=0.006). **Serum luteinizing hormone on the day of HCG injection:** was lower in patients receiving PPOS compared to those receiving other protocols (MD = 1.47, 95 % CI: 2.77 to 0.16, *P*=0.03).	PPOS has obvious advantages in many clinical indicators. Progesterone is taken orally, which is easy for patients to accept, and is less costly than other medications used in IVF; therefore, it may be a promising ovulation induction program for patients with poor ovarian response.	Very Low

				Cycle cancellation rate: that patients receiving PPOS had fewer cycle cancellations compared to those receiving other protocols [23.57 % (N 2291) vs 27.34 % (N 2034)] (OR = 0.73, 95% CI: 0.56–0.95, *P* =0.02).		
Chen Q, Chai W, Wang Y, Cai R, Zhang S, Lu X, Zeng X, Sun L, Kuang Y. Progestin vs. Gonadotropin-Releasing Hormone Antagonist for the Prevention of Premature Luteinizing Hormone Surges in Poor Responders Undergoing In vitro Fertilization Treatment: A Randomized Controlled Trial. Front Endocrinol (Lausanne). 2019 Nov 22;10:796	Randomized Controlled Trial	A total of 340 women were randomly assigned to GnRH antagonist group or PPOS group, with 170 participants in each group. **Inclusion**: infertility women with age ≥22 and ≤42 years old, spontaneous menstrual cycle (21–35 days) and had at least one of the following indications for IVF or ICSI: tubal factor, male factor, diminished ovarian reserve, endometriosis or unexplained factors. The participants were diagnosed with poor responders according to the Bologna criteria. **Exclusion:** clinically significant systemic diseases such as renal failure and systemic lupus erythematosus, premature ovarian insufficiency, with known müllerian duct anomalies and with any contraindications to ovarian stimulation treatments. The women who had previous unsuccessful IVF attempts up to 5 times and were unable to comply with the study procedures were excluded.	**Flexible GnRH antagonist protocol:** human menopausal gonadotropin (hMG) 150–225 IU daily was administered from menstrual cycle day 3, follicle monitoring done 5 days later. When the dominant follicles reached the diameter about 14 mm, GnRH antagonist 0.125–0.25 mg daily was administered up to the trigger day. For the cases with low/normal BMI (<25.0 kg/m2) and low LH levels before GnRH antagonist administration (<2.0 mIU/ml), antagonist 0.125 mg daily was administered, and for the cases with higher BMI (≥25.0 kg/m2) or LH levels ≥2.0 mIU/ml, antagonist 0.25 mg was used daily up to the trigger day. hMG dose adjusted according to ovarian response. When the dominant follicles reached the diameter of 18 mm, the final stage of oocyte maturation was induced with triptorelin 100 μg S.C and human chorionic gonadotropin (hCG) 5,000 IU intramuscular injection. The oocyte retrieval was performed 36 h later. **PPOS Protocol:** hMG 150–225 IU and medroxyprogesterone acetate (MPA) 10 mg started daily from cycle day 3, follicles monitored 5 days later and the dose of hMG was adjusted according to ovarian response. MPA dose was consistent up to the trigger day.	Incidence of **premature LH rise** (LH>10 mIU/ml) during ovarian stimulation was higher in GnRH antagonist group vs PPOS (7.1 va 0.6%, *P*<0.05); incidence of premature LH surge in PPOS group was lower than in antagonist group (0 vs. 5.88%, *P*<0.05). In PPOS group, average **numbers of oocytes and viable embryo**s were comparable to those in GnRH antagonist group (3.7±2.6 vs 3.4±2.4; 1.6±1.7 vs 1.4±1.3, *P*>0.05), the **live birth rate** was similar between the 2 groups (21.8 vs 18.2%, RR 1.25 (95% CI 0.73, 2.13) *P*>0.05).	PPOS had a more robust control for preventing premature LH surge than GnRH antagonist in poor responders, but PPOS in combination with freeze-all did not significantly increase the probability of pregnancy than GnRH antagonist protocol for poor responders. PPOS showed similar efficacy of collecting competent oocytes and embryos as GnRH antagonist in poor responders. PPOS in combination with freeze-all did not significantly increase the probability of pregnancy than GnRH antagonist protocol for poor responders. The two treatment strategies need further analysis using a large sample well-designed trial to compare the live birth outcome and health economic significance.	Moderate

		When the dominant follicles reached the diameter of 18 mm, the final stage of oocyte maturation was induced with triptorelin 100 µg S.C and hCG 5,000 IU intramuscular injection. The oocyte retrieval was performed 36h later.

6. Type of Stimulation Drug

6.1 What is the Safety and Efficacy of Recombinant FSH versus Urinary Gonadotropins in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Ye H, Huang G, Pei L, Zeng P, Luo X. Outcome of in vitro fertilization following stimulation with highly purified hMG or recombinant FSH in downregulated women of advanced reproductive age: a prospective, randomized, and controlled trial. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2012 Jul;28(7):540–4.	Randomized Controlled Trial	127 consecutive normogonadotropic infertile women ≥ 35 years old undergoing their first in vitro fertilization/intracytoplasmic sperm injection cycles received ovarian stimulation with HP-hMG (n = 63) or with rFSH (n = 64) in a long gonadotropin-releasing hormone agonist protocol.	Highly purified human menopausal gonadotropin (HP-hMG) versus recombinant follicle-stimulating hormone (rFSH) on ovarian response and pregnancy outcome in downregulated women of advanced reproductive age.	More leading (≥ 18 mm) follicles and oocytes were obtained in rFSH group ($p = 0.008$ and $p < 0.001$, respectively). The proportion of top-quality embryo from oocyte retrieval and live birth rate per started cycle trended towards improvement with HP-hMG (OR 1.3, 95% CI 0.9-1.8; OR 1.9, 95% CI 0.9-3.9; respectively), although they were not significant difference between two groups. At end of stimulation, higher serum progesterone level was found in rFSH group ($p < 0.001$).	Following downregulated women of advanced reproductive age, superiority of HP-hMG over rFSH in live birth rate could not be concluded from this study, but noninferiority was established. Pharmacodynamic differences in follicular development, oocyte/embryo quality and endocrine response exist between HP-hMG and rFSH, which may be relevant to treatment outcome.	Moderate
De Placido G, Mollo A, Alviggi C, Strina I, Varricchio MT, Ranieri A, et al. Rescue of IVF cycles by HMG in pituitary downregulated normogonadotrophic young women characterized by a poor initial response to recombinant FSH. Hum	Randomized Controlled Trial	43 patients with normoovulatory normogonadotrophic patients showing an initial suboptimal response to a standardized long protocol therapy with recombinant FSH (rFSH) (300 IU/day).	Group A, 150 IU rFSH was substituted by 150 IU HMG after day 8 of stimulation. The stimulation protocol of Group B involved a simple increase of the daily rFSH dose to 375 IU after day 8. A total of 40 BMI and age	The mean Group A serum concentration of oestradiol on the day of HCG administration and average number of oocytes retrieved were significantly higher than Group B ($P < 0.001$) and equivalent to Group C. A total of 10 pregnancies (50%) in	The data suggest that LH supplementation improves the ovarian outcome in patients characterized by an inadequate initial response to rFSH therapy in a long protocol.	Moderate

Reprod Oxf Engl. 2001 Sep;16(9):1875–9.			matched patients with an optimal ovarian response formed the control group (Group C).	Group A, 8 (34.8%) in Group B and 19 (47.5%) in the control group were achieved.		
Ferraretti AP, Gianaroli L, Magli MC, D'angelo A, Farfalli V, Montanaro N. Exogenous luteinizing hormone in controlled ovarian hyperstimulation for assisted reproduction techniques. Fertil Steril. 2004 Dec;82(6):1521–6.	Randomized Controlled Trial	130 women showing a hyporesponsiveness to FSH under GnRH agonist down-regulation were randomized into three groups	Group A (n = 54) received an increased dosage of FSH; group B (n = 54) was administered recombinant LH in addition to the increased dose of FSH; group C (n = 22) was given additional FSH and LH using hMG as a combined drug. Fifty-four age-matched women with no need to increase the FSH dose were included as a control group (D).	In group B, the pregnancy and implantation rates were statistically higher when compared with groups A and C and did not differ from the control group for normal response. The live birth rate was similar in groups B and D but was half as high in groups A and C.	Hyporesponsiveness to FSH could be related to iatrogenic LH deficiency that, in turn, could affect oocyte competence. Addition of a small amount of recombinant LH can rescue oocyte competence to produce viable embryos.	Moderate
Toporcerová S, Hredzák R, Ostró A, Zdilová V, Potoceková D. [Influence of exogenous supplementation with luteinizing hormone during controlled ovarian hyperstimulation on the results of IVF cycle]. Ceska Gynekol. 2005 May;70(3):187–91.	Randomized Controlled Trial	68 in vitro fertilization cycles in normogonadotrophic women undergoing assisted reproduction with GnRH agonist down-regulation and recombinant FSH controlled ovarian stimulation were included.	The cycles were randomized into three groups. The first group was stimulated with pure recombinant FSH. In the second group the exogenous LH activity in the form of human menotrophin was added. And in the third group the human recombinant LH was added.	Better outcomes of assisted reproduction were detected in both groups with exogenous LH activity. But these results, except the dosage of FSH, were not statistically significant. The increase of pregnancy rate by more than one fifth in these both groups can be considered as clinically relevant.	It cannot be positively proved at the base of our results that exogenous LH activity in cycles with low residual LH level can improve outcomes of assisted reproduction. It could be appropriate in the future to select women that can profit from exogenous LH activity according to other parameters not only to the LH serum level.	Low
Raga F, Bonilla-Musoles F, Casañ EM, Bonilla F. Recombinant follicle stimulating hormone stimulation in poor responders with normal basal concentrations of follicle stimulating hormone and oestradiol: improved reproductive outcome. Hum Reprod Oxf Engl. 1999 Jun;14(6):1431–4.	Randomized Controlled Trial	30 young infertile patients who exhibited a poor response in two previous consecutive cycles, despite having normal basal follicle stimulating hormone (FSH) and oestradiol concentrations	Recombinant (rFSH) versus urinary (uFSH)	An evaluation of the total dose used (3800 IU versus 4600 IU, $P < 0.05$) and duration of treatment (10.2 days versus 13.2 days, $P < 0.05$) showed a significantly shorter treatment period as well as a significantly lower total dose of FSH required to induce ovulation successfully in the group of patients treated with rFSH. Significantly more oocytes (7.2 versus 5. 6, $P < 0.05$) as well as mature oocytes (5.9 versus 3.2, $P < 0.01$) were retrieved after rFSH treatment. In addition, significantly more good quality embryos were obtained (3.4	It is concluded that rFSH is more effective than uFSH in inducing multifollicular development and achieving pregnancy in young low responders.	Low

				versus 1.8, P < 0.05) in the group of patients treated with rFSH and, as a result, higher pregnancy (33 versus 7%, P < 0.01) and implantation (16 versus 3%, P < 0.01) rates were achieved in these patients.		
Berker B, Şükür YE, Özdemir EÜ, Özmen B, Sönmezer M, Atabekoğlu CS, Aytaç R. Human Menopausal Gonadotropin Commenced on Early Follicular Period Increases Live Birth Rates in POSEIDON Group 3 and 4 Poor Responders. Reprod Sci. 2021 Feb;28(2):488-494.	Cohort Study	The aim of this study was to assess the effects of hMG, and its commencement time on the outcome of assisted reproductive technology (ART) cycles of POSEIDON group 3 and 4 poor responders. Data of **558 POSEIDON group 3 and 4 poor responders** who underwent ART treatment following a GnRH antagonist cycle at a university-based infertility clinic between January 2014 and December 2019 were reviewed. hMG was commenced at the **early follicular phase or mid-follicular phase** in the study groups.	Ovarian stimulation was carried out with **recombinant FSH** (Gonal-F; Merck-Serono, Geneva, Switzerland) beginning from the second day of the menstrual cycle with a starting dose of 225–300 IU/day. Dose adjustment was performed individually according to ovarian response, as assessed by estradiol levels and ultrasound. The maximum dose of rFSH was 450 IU/day. The GnRH antagonist cetrorelix 0.25 mg/day (Cetrotide; Merck-Serono, Geneva, Switzerland) was initiated in a flexible manner when a follicle with a mean diameter of14 mm was present at ultrasound and/or serum LH levels reached > 10 IU/L and continued throughout ovarian stimulation. In the first study group, daily **75–150 IU hMG menotropin** (Menogon, Ferring, Kiel, Germany; or Menopur, Ferring, Kiel, Germany) was initiated on cycle day 2. In the second study group, daily 75–150 IU hMG menotropin was initiated at the mid-follicular phase following initiation of the GnRH antagonist.	The **mean duration of stimulation** was significantly shorter in the early follicular hMG group than in the mid-follicular hMG group (11.9 ± 3.6 days vs. 12.8 ± 4 days, respectively; P = 0.027). The **total dose of rFSH** showed significant differences between all groups (1124 ± 1218 IU vs.1559 ± 1416 IU vs. 2847 ± 1164 IU, respectively; P < 0.001). The **clinical pregnancy rates** showed a significant difference between the groups when compared per oocyte retrieval procedure (21.9% vs. 13.8% vs. 11.9%, respectively; P = 0.015). The **LBRs per started cycle**, per oocyte retrieval procedure, and per embryo transfer were significantly higher in the early follicular hMG group than those in the mid-follicular hMG and control groups (P = 0.043, P =0.008, and P = 0.035, respectively)	The addition of hMG to controlled ovarian stimulation of POSEIDON group 3 and 4 poor responders significantly increases the LBRs when initiated together with rFSH at the beginning of the cycle. However, the results obtained from the study should be interpreted with caution considering its limitations. Appropriately sized RCTs assessing effects of hMG and its time of initiation, and in comparison with rLH are needed to get clear conclusions.	Low
Yenigul NN, Ozelçi R, Baser E,	Cohort Study	The women younger than	Patients in Group-1	Total number of retrieved	We observed no beneficial effect	Very Low

Dilbaz S, Aldemir O, Dilbaz B, et al. The value of LH supplementation in young women with diminished ovarian reserve treated with GnRH Antagonist Protocol for ovarian hyperstimulation in ICSI-cycles. Ginekol Pol. 2022 Jan 24		35 years of age who were diagnosed as diminished ovarian reserve and underwent standard GnRH antagonist protocol were included.	underwent controlled ovarian stimulation with rFSH alone and Group-2 with rFSH in combination with hp-hMG. Patients in both groups were divided into three subgroups according to their antral follicle count at Day 3: < 4 (a), 4-6 (b), and 7-10 (c). Demographic features and IVF outcomes of the patients were extracted.	oocytes was higher in Group-1 than Group-2 (6.5 ± 2.1 vs 5.5 ± 2.3, respectively, p < 0.001). However, there were no significant differences between the two groups in terms of clinical pregnancy rate, implantation rate, miscarriage rate and live birth rate. Although the main study outcome parameters did not show significant difference between Group-1a and Group-2a, the number of mature oocytes (5 ± 2.8 vs 1.8 ± 1.2, respectively, p = 0.006) was higher in Group-1a.	of LH supplementation during IVF for the treatment of women under 35 years old with diminished ovarian reserve in the first treatment cycle when compared with rFSH only in the antagonist protocols.	
Drakopoulos P, Di Guardo F, Boudry L, Mackens S, De Vos M, Verheyen G, et al. Does the dose or type of gonadotropins affect the reproductive outcomes of poor responders undergoing modified natural cycle IVF (MNC-IVF)? Eur J Obstet Gynecol Reprod Biol. 2022 Nov;278:95–9.	Retrospective cohort study	In total 484 patients undergoing 1398 cycles were included. All predicted poor responders (Poseidon groups 3 and 4) who underwent MNC-IVF in our center were included.	Dose or type of gonadotropin	The daily dose of gonadotropins was either < 75 IU/d [11/1398 (0.8 %)] or 75 to < 100 IU/d [1303/1398 (93.2 %)] or ≥ 100 to 150 IU/d [84/1398 (6 %)]. Patients were stimulated with rFSH [251/1398 (18 %)], uFSH [45/1398 (3.2 %)] or hp-hMG [1102/1398 (78.8 %)]. Clinical pregnancy rate was 119/1398 (8.5 %). Live birth was achieved in 80/1398 (5.7 %) of cycles. There was no significant difference in rates of pregnancy and live birth across different types and doses of gonadotropins. The GEE multivariate regression analysis, adjusting for relevant confounders, showed that the type of treatment strategy (rFSH/uFSH/hp-hMG) and the daily dose of gonadotropins were not associated with live birth rates (LBR) (p value 0.08 and 0.8, respectively).	The type and daily dose of gonadotropins do not affect the reproductive outcome of poor responders undergoing MNC-IVF.	Very Low

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

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Lensen SF, Wilkinson J, Leijdekkers JA, La Marca A, Mol BWJ, Marjoribanks J, Torrance H, Broekmans FJ. Individualised gonadotropin dose selection using markers of ovarian reserve for women undergoing in vitro fertilisation plus intracytoplasmic sperm injection (IVF/ICSI). Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD012693. DOI: 10.1002/14651858.CD012693.pub2. Accessed 05 May 2024.	Metaanalysis	5 Studies in low responders indicated 300/400 IU vs 150 IU: 300 IU vs 150 IU (Klinkert 2005) 450 IU vs 150 IU (Van Tilborg 2017) 400/450 IU vs 300 IU: 400 IU vs 300 IU (Harrison 2001) 450 IU vs 300 IU (Bastu 2016) 600 IU vs 450 IU: (Lefebrve 2015)		High dose Gonadotrophin vs, Low dose Gonadotrophin Poor response to stimulation: OR 0.52, (95% CI 0.32-0.84), 2 studies Live birth or ongoing pregnancy per woman randomised a. 300/450IU vs. 150IU: OR 0.71 (0.32-1.58), 2 studies b. 400/450 vs. 300IU: OR 0.77 (0.19-3.19), 1 study c. 600 vs. 450IU: OR 1.33 (0.71-2.52), 1 study Live birth or ongoing pregnancy. a. 300/450IU vs. 150IU: OR 0.71 (0.32-1.58), 2 studies b. 400/450 vs. 300IU: OR 0.77 (0.19-3.19), 1 study c. 600 vs. 450IU: OR 1.33 (0.71-2.52), 1 study Cumulative live birth: 1 cycle (fresh + frozen)- 300/450IU vs. 150IU: OR 0.78 (0.35-1.73), 1 study Cumulative live birth: 18 months- 300/450IU vs. 150IU: OR 0.78 (0.46-1.32), 1 study Clinical pregnancy- 300/450IU vs. 150IU: OR 0.50 (0.25-1.00), 2 studies	Current evidence does not provide a clear justification for adjusting the standard dose of 150 IU in the case of poor or normal responders, especially as increased dose is generally associated with greater total FSH dose and therefore greater cost. However, a decreased dose in predicted high responders may reduce OHSS.	High
Lefebvre J, Antaki R, Kadoch IJ, Dean NL, Sylvestre C, Bissonnette F, Benoit J, Ménard S, Lapensée L. 450 IU versus 600 IU gonadotropin for controlled ovarian stimulation in poor responders: a randomized controlled trial. Fertil Steril. 2015 Dec;104(6):1419-25. doi: 0.1016/j.fertnstert.2015.08.014. Epub 2015 Sep 8. PMID: 26361207.	Randomized Controlled Trial	Women considered to be at risk of poor ovarian response: aged <41 years with basal FSH >10 IU/L, antimüllerian hormone <1 ng/mL, antral follicle count ≤ 8, or a previous IVF cycle with ≥ 300 IU/d gonadotropin that resulted in a cancellation, <8 follicles, or <5 oocytes.	A total of 356 patients underwent a microdose GnRH agonist flare-up IVF/intracytoplasmic sperm injection protocol with a fixed daily dose of either 450 IU FSH (n = 176) or 600 IU FSH (n = 180) equally divided between Menopur and Bravelle.	The two groups were similar in terms of age, ovarian reserve, cause of infertility, duration of stimulation, and cycle cancellation rate. There were no significant differences in the number of metaphase II oocytes retrieved (4 [range 0-6] vs. 4 [range 2-7]), fertilization rate (62.4% vs. 57.0%), biochemical pregnancy rate (20.5% vs. 22.9%), clinical pregnancy rate (16.4% vs. 18.3%), and implantation rate (29.8% vs. 30.4%) between the 450 IU and 600 IU groups, respectively.	Gonadotropin of 600 IU/d does not improve outcome of IVF cycles compared with 450 IU/d in women at risk of poor ovarian response.	Modrate

van Tilborg TC, Torrance HL, Oudshoorn SC, Eijkemans MJC, Koks CAM, Verhoeve HR, Nap AW, Scheffer GJ, Manger AP, Schoot BC, Sluijmer AV, Verhoeff A, Groen H, Laven JSE, Mol BWJ, Broekmans FJM; OPTIMIST study group. Individualized versus standard FSH dosing in women starting IVF/ICSI: an RCT. Part 1: The predicted poor responder. Hum Reprod. 2017 Dec 1;32(12):2496-2505. doi: 10.1093/humrep/dex318. PMID: 29121326.	Randomized Controlled Trial	RCT in women with an AFC < 11 (Dutch Trial Register NTR2657). In total, 511 women were randomized, 234 with an AFC ≤ 7 and 277 with an AFC 8-10.	Women with an AFC ≤ 7 were randomized to an FSH dose of 450 IU/day or 150 IU/day, and women with an AFC 8-10 were randomized to 225 IU or 150 IU/day. In the standard group, dose adjustment was allowed in subsequent cycles based on pre-specified criteria.	The cumulative live birth rate for increased versus standard dosing was 42.4% (106/250) versus 44.8% (117/261), respectively [relative risk (RR): 0.95 (95%CI, 0.78-1.15), P = 0.58]. As an increased dose strategy was more expensive [delta costs/woman: €1099 (95%CI, 562-1591)], standard FSH dosing was the dominant strategy in our economic analysis.	An increased dose in women scheduled for IVF/ICSI with a predicted poor response (AFC < 11) does not improve live birth rates and is more expensive	Modrate
Liu X, Wen W, Wang T, Tian L, Li N, Sun T, Wang T, Zhou H, Zhang N, Qu P, Mol BW, Li W, Shi J. Increased versus standard gonadotrophin dosing in predicted poor responders of IVF: an open label randomized controlled trial. Hum Reprod. 2022 Jul 30;37(8):1806-1815. doi: 10.1093/humrep/deac113. PMID: 35595197.	Randomized Controlled Trial	661 women <43 years of age with AFC <10 referred for their first IVF cycle were randomized for increased or standard FSH dosing.	In participants allocated to increased FSH dosing, women with AFC 1-6 started with 300 IU/day, while women with AFC 7-9 started with 225 IU/day. In participants allocated to the standard care, women started with 150 IU/day. Increased dosing (n = 328) or standard dosing (n = 333).	The primary outcome cumulative live birth occurred in 162/328 (49.4%) women in the increased group versus 141/333 (42.3%) women in the standard group [risk ratio (RR) 1.17 (95% CI, 0.99-1.38), risk difference 0.07 (95% CI, -0.005, 0.15), P = 0.070]. The live birth rate after the first embryo transfer in the increased versus standard group was 125/328 (38.1%) versus 117/333 (35.1%), respectively [RR 1.08 (95% CI, 0.83-1.33), P = 0.428]. Cumulative clinical pregnancy rates were 59.1% versus 57.1% [RR 1.04 (95% CI, 0.91-1.18), P = 0.586] with miscarriage rates of 9.8% versus 14.4% [RR 0.68 (95% CI, 0.44-1.03), P = 0.069] in the increased versus standard group, respectively. Other secondary outcomes, including biochemical pregnancy, ongoing pregnancy, multiple pregnancy, and ectopic pregnancy, were not significantly different between the two groups both from the first and cumulative embryo transfer.	In women with predicted poor response, the study did not find evidence that increased FSH dosing improves live birth rates. A standard dose of 150 IU/day is recommended at the start of IVF in these women to reduce potential adverse effects and costs.	Modrate

Liu X, Wang D, Wen W, Wang T, Tian L, Li N, Sun T, Wang T, Zhou H, Qu P, Liu S, Mol BW, Li W, Shi J. Effect of increased gonadotropin dosing on maternal and neonatal outcomes in predicted poor responders undergoing IVF: follow-up of a randomized trial. Eur J Obstet Gynecol Reprod Biol. 2023 Jun;285:123-129. doi: 10.1016/j.ejogrb.2023.04.007. Epub 2023 Apr 14. PMID: 37105131.	Randomized Controlled Trial	A follow-up study of an open-labelled randomized controlled trial comparing increased (225 or 300 IU/d) versus standard (150 IU/d) dose gonadotrophins on cumulative live birth rates. 661 women <43 years of age with AFC <10 referred for their first IVF cycle were randomized for increased or standard FSH dosing.	In participants allocated to increased FSH dosing, women with AFC 1-6 started with 300 IU/day, while women with AFC 7-9 started with 225 IU/day. In participants allocated to the standard care, women started with 150 IU/day. Increased dosing (n = 328) or standard dosing (n = 333).	There was a trend of increased risk of gestational diabetes mellitus in the increased gonadotrophin dose group compared with the standard group in both cumulative live birth pregnancies (14.8% vs. 7.8%, relative risk (RR) 1.90, 95% confidence interval (CI) 0.96-3.74, P = 0.06) and live birth pregnancies in the first transfer (15.2% vs. 7.7%, RR 1.98, 95 %CI 0.93-4.19, P = 0.08), without reaching statistical significance. The occurrence of gestational diabetes mellitus was significantly higher in the increased gonadotrophin dose group (24/149, 16.1% vs. 8/128, 6.3%; risk ratio (RR) 2.58, 95 %CI 1.19 to 5.54, P = 0.02) in singleton pregnancies. In women with first embryo transfer cycle, maternal hypothyroidism occurred also more frequent in the increased gonadotrophin dose group than the standard group (16.0% vs. 6.8%, RR 2.34, 95 %CI:1.07-5.11, P = 0.03).	In women with predicted poor ovarian response, increased dosing of gonadotropin may result in an increased risk of gestational diabetes mellitus and maternal hypothyroidism.	Modrate

van Tilborg TC, Oudshoorn SC, Eijkemans MJC, Mochtar MH, van Golde RJT, Hoek A, Kuchenbecker WKH, Fleischer K, de Bruin JP, Groen H, van Wely M, Lambalk CB, Laven JSE, Mol BWJ, Broekmans FJM, Torrance HL; OPTIMIST study group. Individualized FSH dosing based on ovarian reserve testing in women starting IVF/ICSI: a multicentre trial and cost-effectiveness analysis. Hum Reprod. 2017 Dec 1;32(12):2485-2495. doi: 10.1093/humrep/dex321. PMID: 29121350.	Cohort Study	Based on the AFC, women entered one of the two RCTs (RCT1: AFC < 11; RCT2: AFC > 15) or the cohort (AFC 11-15). The primary outcome was ongoing pregnancy achieved within 18 months after randomization resulting in a live birth (delivery of at least one live foetus after 24 weeks of gestation). Data from the cohort with weight 0.5 were combined with both RCTs to conduct a strategy analysis.	Between May 2011 and May 2014, we performed a multicentre prospective cohort study with two embedded RCTs in women scheduled for IVF/ICSI. Based on the AFC, women entered one of the two RCTs (RCT1: AFC < 11; RCT2: AFC > 15) or the cohort (AFC 11-15). The primary outcome was ongoing pregnancy achieved within 18 months after randomization resulting in a live birth (delivery of at least one live foetus after 24 weeks of gestation). Data from the cohort with weight 0.5 were combined with both RCTs to conduct a strategy analysis. Potential half-integer numbers were rounded up.	The study included 1515 women, of whom 483 (31.9%) entered the cohort, 511 (33.7%) RCT1 and 521 (34.4%) RCT2. Live births occurred in 420/747 (56.3%) women in the individualized strategy and 447/769 (58.2%) women in the standard strategy (risk difference -0.019 (95% CI, -0.06 to 0.02), P = 0.39; a total of 1516 women due to rounding up the half integer numbers). The individualized strategy was more expensive (delta costs/woman = €275 (95% CI, 40 to 499)). Individualized dosing reduced the occurrence of mild and moderate ovarian hyperstimulation syndrome (OHSS) and subsequently the costs for management of these OHSS categories (costs saved/woman were €35). The analysis based on AMH as a tool for dose individualization suggested comparable results.	Individualized FSH dosing for the IVF/ICSI population should not be pursued as it does not improve live birth rates and it increases costs. Women scheduled for IVF/ICSI with a regular menstrual cycle are therefore recommended a standard FSH starting dose of 150 IU per day.	Low
Dilbaz S, Demir B, Cinar O, Dede S, Aydin S, Beydilli G, Goktolga U. Does 75 IU difference improve the cycle performance in poor responders? Comparison of daily 375 versus 450 IU gonadotrophin doses. Gynecol Endocrinol. 2011 Dec;27(12):1001-6. doi: 10.3109/09513590.2011.569784. Epub 2011 Apr 18. PMID: 21500998.	Cohort Study	A total of 91 poor responder patients who were treated with the microdose flare-up protocol were enrolled in this study.	Group 1 (n = 40) was stimulated with 375 IU/day gonadotrophin. Group 2 (n = 51) was stimulated with 450 IU/day gonadotrophin.	Baseline characteristics are similar between the two groups. Higher number of oocyte cumulus complexes and lower total gonadotrophin requirement were noted in Group 1 compared with Group 2. Number of metaphase II oocytes and implantation rates were similar between the groups. A trend toward higher clinical pregnancy and live birth rate was observed in Group 1 but these results did not reach statistical significance.	Total gonadotrophin costs are lower using the 375 IU/day gonadotrophin compared to the 450 IU/day in poor responders. Additional 75 IU/day does not give any improvement neither	Low

				embryology nor pregnancy outcomes.		

6.3 What is the Safety and Efficacy of Recombinant LH + Recombinant FSH versus Recombinant FSH Monotherapy in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Alviggi C, Conforti A, Esteves SC, Andersen CY, Bosch E, Bühler K, et al., Recombinant luteinizing hormone supplementation in assisted reproductive technology: a systematic review. Fertil Steril. 2018 Apr;109(4):644–64	Systematic Review	Six populations were investigated: 1) women with a hyporesponse to recombinant human FSH (r-hFSH) monotherapy; 2) women at an advanced reproductive age; 3) women cotreated with the use of a GnRH antagonist; 4) women with profoundly suppressed LH levels after the administration of GnRH agonists; 5) normoresponder women to prevent ovarian hyperstimulation syndrome; and 6) women with a "poor response" to ovarian stimulation, including those who met the European Society for Human Reproduction and Embryology Bologna criteria.	Role of recombinant human LH (r-hLH) supplementation in ovarian stimulation	Recombinant hLH supplementation appears to be beneficial in two subgroups of patients: 1) women with adequate prestimulation ovarian reserve parameters and an unexpected hyporesponse to r-hFSH monotherapy; and 2) women 36-39 years of age. Indeed, there is no evidence that r-hLH is beneficial in young (<35 y) normoresponders cotreated with the use of a GnRH antagonist. The use of r-hLH supplementation in women with suppressed endogenous LH levels caused by GnRH analogues and in poor responders remains controversial, whereas the use of r-hLH supplementation to prevent the development	Recombinant hLH can be proposed for hyporesponders and women 36-39 years of age.	Low

				of ovarian hyperstimulation syndrome warrants further investigation.		
Lehert P, Kolibianakis EM, Venetis CA, Schertz J, Saunders H, Arriagada P, et al., Recombinant human follicle-stimulating hormone (r-hFSH) plus recombinant luteinizing hormone versus r-hFSH alone for ovarian stimulation during assisted reproductive technology: systematic review and meta-analysis. Reprod Biol Endocrinol RBE. 2014 Feb 20;12:17.	Meta-Analysis	40 RCTs (6443 patients) were included in the analysis. Data on the number of oocytes retrieved were reported in 41 studies and imputed in two studies. Total 43 studies (r-hFSH plus r-hLH, n=3113; r-hFSH, n=3228)	Benefit of adding recombinant human luteinizing hormone (r-hLH) to recombinant human follicle-stimulating hormone (r-hFSH) during ovarian stimulation	Overall, no significant difference in the number of oocytes retrieved was found between the r-hFSH plus r-hLH and r-hFSH groups (weighted mean difference -0.03; 95% confidence interval [CI] -0.41 to 0.34). However, in poor responders, significantly more oocytes were retrieved with r-hFSH plus r-hLH versus r-hFSH alone (n=1077; weighted mean difference +0.75 oocytes; 95% CI 0.14-1.36). Significantly higher clinical pregnancy rates were observed with r-hFSH plus r-hLH versus r-hFSH alone in the overall population analysed in this review (risk ratio [RR] 1.09; 95% CI 1.01-1.18) and in poor responders (n=1179; RR 1.30; 95% CI 1.01-1.67; ITT population); the observed difference was more pronounced in poor responders.	These data suggest that there is a relative increase in the clinical pregnancy rates of 9% in the overall population and 30% in poor responders. In conclusion, this meta-analysis suggests that the addition of r-hLH to r-hFSH may be beneficial for women with POR.	Low
Humaidan P, Chin W, Rogoff D, D'Hooghe T, Longobardi S, Hubbard J, et al., Efficacy and safety of follitropin alfa/lutropin alfa in ART: a randomized controlled trial in poor ovarian responders. Hum Reprod Oxf Engl. 2017 Mar 1;32(3):544–	Randomized Controlled Trial	939 Women classified as having POR, based on criteria incorporating the ESHRE Bologna criteria, were down-regulated with a long GnRH agonist protocol and following successful down-regulation were randomized (1:1) to COS with r-hFSH/r-hLH or r-	r-hFSH/r-hLH versus r-hFSH alone. The primary efficacy endpoint was the number of oocytes retrieved following COS.	Of 949 subjects achieving down-regulation, 939 were randomized to r-hFSH/r-hLH (n = 477) or r-hFSH (n = 462) and received treatment. Efficacy assessment: In the intention-to-treat (ITT) population, the mean (SD) number of oocytes	In the population of women with POR investigated in this study, although the number of oocytes retrieved was similar following stimulation with either a fixed-ratio combination of r-hFSH/r-hLH or r-hFSH monotherapy, post hoc analyses showed that	Moderate

55.	hFSH alone.	retrieved (primary endpoint) was 3.3 (2.71) in the r-hFSH/r-hLH group compared with 3.6 (2.82) in the r-hFSH group (between-group difference not statistically significant). The observed difference between treatment groups (r-hFSH/r-hLH and r-hFSH, respectively) for efficacy outcomes decreased over the course of pregnancy (biochemical pregnancy rate: 17.3% versus 23.9%; clinical pregnancy rate: 14.1% versus 16.8%; ongoing pregnancy rate: 11.0% versus 12.4%; and live birth rate: 10.6% versus 11.7%). An interaction (identified post hoc) between baseline characteristics related to POR and treatment effect was noted for live birth, with r-hFSH/r-hLH associated with a higher live birth rate for patients with moderate or severe POR, whereas r-hFSH was associated with a higher live birth rate for those with mild POR. A post hoc logistic regression analysis indicated that the incidence of total pregnancy outcome failure was lower in the r-hFSH/r-hLH group (6.7%) compared with the r-hFSH group (12.4%) with an odds ratio of 0.52 (95% CI	there was a lower rate of total pregnancy outcome failure in patients receiving r-hFSH/r-hLH, in addition to a higher live birth rate in patients with moderate and severe POR. These findings are clinically relevant and require additional investigation. The benefit:risk balance of treatment with either r-hFSH/r-hLH or r-hFSH remains positive.

				0.33, 0.82; P = 0.005). Safety assessment: The overall proportion of patients with treatment-emergent adverse events (TEAEs) occurring during or after r-hFSH/r-hLH or r-hFSH use (stimulation or post-stimulation phase) was 19.9% and 26.8%, respectively. There was no consistent pattern of TEAEs associated with either treatment.		
Behre HM, Howles CM, Longobardi S, PERSIST Study Investigators. Randomized trial comparing luteinizing hormone supplementation timing strategies in older women undergoing ovarian stimulation. Reprod Biomed Online. 2015 Sep;31(3):339–46.	Randomized Controlled Trial	Women aged 36-40 years undergoing ovarian stimulation were randomized	Recombinant human FSH (rhFSH) plus recombinant human luteinizing hormone (rhLH) from stimulation day 1 (group A; n = 103), or rhFSH alone (days 1-5) followed by rhFSH plus rhLH from day 6 (group B; n = 99)	The primary objective was equivalence in number of oocytes retrieved per patient. The mean (±SD) number of oocytes retrieved was 9.7 (±6.9) in group A and 10.9 (±6.5) in group B; the estimated difference between groups (-1.28 oocytes [95% confidence interval: -3.15 to 0.59]) did not reach the predefined limit of equivalence (±3 oocytes). The study's primary objective was therefore not met. In both groups, a mean (±SD) of 1.9 (±0.6) embryos were transferred per patient. Implantation rates were 24.7% in group A and 13.3% in group B. Clinical pregnancy rates per started cycle and per embryo transfer were 31.6% and 34.4% in Group A, 17.2% and 18.9% in Group B. Ovarian hyperstimulation syndrome was reported	The potential benefit of initiating LH supplementation earlier during ovarian stimulation in older women is of interest, warranting further exploration.	Moderate

				in four (group A) and five (group B) patients.		
Revelli A, Chiado' A, Guidetti D, Bongioanni F, Rovei V, Gennarelli G. Outcome of in vitro fertilization in patients with proven poor ovarian responsiveness after early vs. mid-follicular LH exposure: a prospective, randomized, controlled study. J Assist Reprod Genet. 2012 14 Sep;29(9):869–75	Randomized Controlled Trial	Five hundred-thirty women with poor ovarian responsiveness during the first IVF cycle, undergoing their second IVF attempt.	In a GnRH-analogue long protocol, ovarian stimulation with recombinant FSH (300 IU/day) plus randomly assigned addition of recombinant LH (150 IU/day) from day 1 (early LH exposure; n = 264) or from day 7 (late LH exposure; n = 266).	Apart from the totally administered LH dose, which was significantly higher in the group receiving it from day 1, all parameters related to IVF outcome were non significantly different in the two groups.	Adding LH to FSH from day 1 or from day 7 of ovarian stimulation in a GnRH-agonist long protocol exerts comparable effects on IVF outcome in poor responders.	Low

6.4 What is the Safety and Efficacy of Long-Acting Recombinant FSH (Corifollitropin Alpha) versus Recombinant FSH or hMG in Patients with Poor Ovarian Response?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Cozzolino M, Vitagliano A, Cecchino GN, Ambrosini G, Garcia-Velasco JA. Corifollitropin alfa for ovarian stimulation in in vitro fertilization: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2019 Apr;111(4):722-733.	Systematic Review/Meta-analysis	Eight randomized controlled trials were included; 2,345 women were assigned to the intervention group and 1,995 to the control group. The analysis of 4,340 IVF cycles **Devroey et al. 2004**, 99 Patients **The Corifollitropin Alfa Dose-finding Study Group 2008,** 315 patients **Devroey et al. 2009,** 1509 Patients **Kolibianakis et al. 2015**, 79 patients with POR **Drakopoulos et al. 2017,** 152 patients with poor response	Randomized controlled trials (RCTs) of infertile women undergoing a single IVF/ICSI cycle with either corifollitropin alfa or a conventional ovarian stimulation protocol based on daily injections. Stimulation regimen. Two of the studies were corifollitropin alfa dose finding (12, 14), but all other studies used 150 mg of corifollitropin alfa starting on menstrual cycle day 2 or 3, except for one study that used 100 mg (13). One week later, from stimulation day 8 onward, treatment was continued with a fixed daily dose of rFSH varying from 150 to 450 IU. Drakopoulos et al. was the single study to use	**LBR** RR 0.92[0.80,1.05], heterogeneity i2=23%, P=0.21 **CPR** RR 0.96[0.88,1.05], heterogeneity i2=0%,P=0.33 **Total Number of oocytes** RR 0.89 [0.13,1.64], heterogeneity i2=69%,P=0.02 **M2 Oocytes** RR 1.13 [0.33,1.92], heterogeneity i2=82%,P=0.006 **Embryos** RR 0.55 [0.14,0.96], heterogeneity i2=45%,P=0.008 **Overall OHSS** RR 1.15 [0.83,1.57], heterogeneity i2=0%,P=0.40 **Moderate/Severe OHSS** RR 1.17 [0.54,2.56], heterogeneity i2=48%,P=0.69 **EPR** RR 0.72 [0.39,1.34], heterogeneity i2=0%,P=0.29	Randomized controlled trials (RCTs) of infertile women undergoing a single IVF/ICSI cycle with either corifollitropin alfa or a conventional ovarian stimulation protocol based on daily injections. Stimulation regimen. Two of the studies were corifollitropin alfa dose finding (12, 14), but all other studies used 150 mg of corifollitropin alfa starting on menstrual cycle day 2 or 3, except for one study that used 100 mg (13). One week later, from stimulation day 8 onward, treatment was continued with a fixed daily dose of rFSH varying from 150 to 450 IU. Drakopoulos et al. was the single study to use 300 IU of	Very Low

			300 IU of highly purified hMG starting on stimulation day 8(11). In the control group, the rFSH dose ranged from 150 to 450 IU. Pituitary block was performed with GnRH antagonist (0.25 mg daily). In most studies, ovulation induction was triggered with 5,000–10,000 IU of urinary hCG when at least one follicle was R17–20 mm in mean diameter. However, two RCTs used 250 mg of recombinant hCG to trigger ovulation. Ovarian puncture was performed 34–36 hours after hCG and followed with conventional IVF or ICSI.A maximum of three embryos were transferred between days 2 and 5 after oocyte retrieval and luteal phase support carried out with vaginal or IMP.		highly purified hMG starting on stimulation day 8(11). In the control group, the rFSH dose ranged from 150 to 450 IU. Pituitary block was performed with GnRH antagonist (0.25 mg daily). In most studies, ovulation induction was triggered with 5,000–10,000 IU of urinary hCG when at least one follicle was R17–20 mm in mean diameter. However, two RCTs used 250 mg of recombinant hCG to trigger ovulation. Ovarian puncture was performed 34–36 hours after hCG and followed with conventional IVF or ICSI.A maximum of three embryos were transferred between days 2 and 5 after oocyte retrieval and luteal phase support carried out with vaginal or IMP.	
Kolibianakis EM, Venetis CA, Bosdou JK, Zepiridis L, Chatzimeletiou K, Makedos A, et al., Corifollitropin alfa compared with follitropin beta in poor responders undergoing ICSI: a 6 randomized controlled trial. Hum Reprod Oxf Engl. 2015 Feb;30(2):432–40.	Randomized Controlled Trial	Seventy-nine women with previous poor ovarian response undergoing ICSI treatment were enrolled in this open label, non-inferiority, randomized clinical trial (RCT).	On Day 2 of the menstrual cycle, patients were administered either a single s.c dose of 150 μg corifollitropin alfa (n = 40) or a fixed daily dose of 450 IU of follitropin beta (n = 39). In the corifollitropin alfa group, 450 IU of follitropin beta were administered from Day 8 of stimulation until the day of human chorionic gonadotrophin (hCG) administration, if necessary. To inhibit premature luteinizing hormone surge, the gonadotrophin releasing hormone antagonist ganirelix was used. Triggering of final oocyte maturation was performed using 250 μg of recombinant hCG, when at least two follicles reached 17	The number of COCs retrieved was not statistically different between the corifollitropin alfa and the follitropin beta groups [Median 3 versus 2, 95% CI 2-4, 2-3, respectively, P = 0.26]. The 95% CI of the difference between medians in the number of oocytes retrieved was -1 to +1. A multivariable analysis adjusting for all the potential baseline differences confirmed this finding. No significant difference was observed regarding the probability of live birth between the corifollitropin alfa and the follitropin beta group (live birth per patient reaching oocyte retrieval: 7.9 versus 2.6%, respectively, difference +5.3%, 95% CI: -6.8 to +18.3).	Corifollitropin alfa simplifies IVF treatment because it is administered in a GnRH antagonist protocol and replaces seven daily FSH injections with one of a long acting FSH without compromising the outcome. It could reduce the burden of treatment for poor responders, and this deserves further investigation.	Moderate

			mm in mean diameter.			
Boostanfar R, Shapiro B, Levy M, Rosenwaks Z, Witjes H, Stegmann BJ, et al., Large, comparative, randomized double-blind trial confirming noninferiority of pregnancy rates for corifollitropin alfa compared with recombinant follicle-stimulating hormone in a gonadotropin-releasing hormone antagonist controlled ovarian stimulation protocol in older patients undergoing in vitro fertilization. Fertil Steril. 2015 Jul;104(1):94-103.e1.	Randomized Controlled Trial	A total of 1,390 women aged 35-42 years. (Older patients) Multicenter recruitment	A single injection of 150 µg of corifollitropin alfa or daily 300 IU of recombinant FSH for the first 7 days then daily recombinant FSH until three follicles reach ≥17 mm in size. Ganirelix was started on stimulation day 5 up to and including the day of recombinant hCG administration. If available, two good quality embryos were transferred on day 3.	Vital PRs per started cycle were 23.9% in the corifollitropin alfa group and 26.9% in the recombinant FSH group, with an estimated difference (95% confidence interval) of -3.0% (-7.4 to 1.4). The mean (SD) number of recovered oocytes per started cycle was 10.7 (7.2) and 10.3 (6.8) in the corifollitropin alfa and the recombinant FSH groups, respectively, with an estimated difference of 0.5 (-0.2 to 1.2). The live birth rates per started cycle were 21.3% in the corifollitropin alfa group and 23.4% in the recombinant FSH group, with an estimated difference (95% confidence interval) -2.3% (-6.5 to 1.9). The incidence of serious adverse events was 0.4% versus 2.7% in the corifollitropin alfa and recombinant FSH groups, respectively, and of ovarian hyperstimulation syndrome (OHSS; all grades) was 1.7% in both groups.	Treatment with corifollitropin alfa was proven noninferior to daily recombinant FSH with respect to vital PRs, number of oocytes retrieved, and live birth rates, and was well tolerated.	Moderate
Fauser BCJM, Alper MM, Ledger W, Schoolcraft WB, Zandvliet A, Mannaerts BMJL, et al., Pharmacokinetics and follicular dynamics of corifollitropin alfa versus recombinant FSH during 34 ovarian stimulation for IVF. Reprod Biomed Online. 2010 Nov;21(5):593–601.	Randomized Controlled Trial	1509 patients undergoing IVF	150µg corifollitropin alfa versus daily 200IU rFSH	Serum levels of FSH immunoreactivity were analysed (pharmacokinetic analysis), together with the number and size of growing follicles and serum inhibin B and oestradiol concentrations as biomarkers of the ovarian response (pharmacodynamic analysis). Serum FSH immunoreactivity levels were higher up to stimulation day 5 for corifollitropin alfa compared with the daily rFSH regimen but were similar from day 8 onwards, when patients started rFSH if the criteria for human chorionic gonadotrophin were not yet	It is concluded that the pharmacokinetics of corifollitropin alfa and rFSH are quite different but their induced pharmacodynamic effects at the dosages used are similar.	Low

				reached. Corifollitropin alfa treatment resulted in a similar growth rate of follicles though a slightly higher number of follicles were recruited compared with daily rFSH.		
Drakopoulos P, Vuong TNL, Ho NAV, Vaiarelli A, Ho MT, Blockeel C, Camus M, Lam AT, van de Vijver A, Humaidan P, Tournaye H, Polyzos NP. Corifollitropin alfa followed by highly purified HMG versus recombinant FSH in young poor ovarian responders: a multicentre randomized controlled clinical trial. Hum Reprod. 2017 Nov 1;32(11):2225-2233.	Randomized Controlled Trial	The study included 152 patients younger than 40 years old, fulfilling the Bologna criteria for poor ovarian response, from one tertiary referral centre in Europe (Universitair Ziekenhuis Brussel, Brussels, Belgium) and one tertiary referral centre in Asia (IVFMD, My Duc Hospital, Ho Chi Minh City, Vietnam). Patients underwent ovarian stimulation for ICSI from March 2013 to May 2016.	In conclusion, treatment of poor ovarian responders remains difficult for clinicians, as at the end of the day none of the available treatment options seem to be of benefit for this group of patients. These randomized trial adds further to the available evidence by demonstrating that the administration of corifollitropin alfa followed by hp-HMG does not increase pregnancy rates as compared with rFSH in a GnRH antagonist protocol. However, it results in a significantly higher number of supernumerary embryos. On the other hand, the baseline characteristics of poor responders may play a significant role in their clinical prognosis. Oocyte quality remains the biggest challenge for reproductive science with sparse evidence being published in recent years, mainly because the factors responsible for cellular health and competence are poorly understood and investigated.	Overall, 152 poor ovarian responders defined by the 'Bologna' criteria were included in the study. Using an intention-to treat analysis, the **ongoing pregnancy rates** 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 and clinical pregnancy rates**, **live birth rates** and the **number of oocytes** retrieved were also comparable between the two groups. Nevertheless, more patients in the corifollitropin alfa group **had cryopreserved embryos** compared to the rFSH group [22 (28.6%) versus 10 (14.3%), OR = 2.4 (1.01–5.5)]. Incidentally, Asian patients had significantly **lower cancellation rates** compared to European poor responders [2/64 (3.1%) versus 17/83 (20.4%), OR = 0.12 (0.03–0.5)]. This discrepancy could be explained by the fact that Asian women were better prognosis patients than European patients, with significantly lower FSH [9.8 (5.3) versus 11.5 (5.4), P = 0.017] and significantly higher AMH [1.1 (0.9) versus 0.4 (0.3), p-value <0.001]	In conclusion, treatment of poor ovarian responders remains difficult for clinicians, as at the end of the day none of the available treatment options seem to be of benefit for this group of patients. These randomized trial adds further to the available evidence by demonstrating that the administration of corifollitropin alfa followed by hp-HMG does not increase pregnancy rates as compared with rFSH in a GnRH antagonist protocol. However, it results in a significantly higher number of supernumerary embryos. On the other hand, the baseline characteristics of poor responders may play a significant role in their clinical prognosis.	Moderate
Nl V, Dt P, Ht P, Hn G, Gb H, Ttl N, et al., Corifollitropin alfa vs	Randomized Controlled	A total of 400 patients were included, 200 in	Participants aged 35-42 years with a body weight ≥50 kg	Patients in the corifollitropin alfa and follitropin beta groups were	This study adds to the body of evidence supporting the	Low

recombinant FSH for controlled. ovarian stimulation in women aged 35-42 years with a body weight ≥50 kg: a randomized. controlled trial. Hum Reprod Open [Internet]. 2017 Nov 28 [cited 2024 Feb 17];2017(3).	Trial	each treatment group. The primary outcome measure was the number of oocytes retrieved.	who were undergoing an IVF cycle were randomized to undergo COS with a single dose of corifollitropin alfa 150 µg on Day 2 or 3 of the menstrual cycle, or follitropin beta 300 IU/day for 7 days starting on Day 2 or 3 of the menstrual cycle. All underwent ICSI according to standard institutional protocols.	well matched at baseline (mean age 37.5 ± 1.9 vs 37.7 ± 2.0 years, mean body weight 53.7 ± 5.4 vs 52.5 ± 4.8 kg). There was no significant difference between the corifollitropin alfa and follitropin beta groups in the number of oocytes retrieved (11.4 ± 5.9 vs 10.8 ± 5.8; P = 0.338). The ongoing pregnancy rate (31.5 vs 32.0%; P = 0.99) and live birth rate (30.5 vs 32.0%; P = 0.83) (both per initiated cycle at 12 months after randomization) were also similar in the two treatment groups. Complication rates were low and similar in the corifollitropin alfa and follitropin beta groups, and there were no significant between-group differences in obstetric outcomes.	equivalence of corifollitropin alfa and follitropin beta for COS in a variety of patients undergoing IVF and/or ICSI. The ability to provide COS with corifollitropin alfa has the potential to reduce the burden of treatment for patients.	
Selman H, Rinaldi L. Effectiveness of corifollitropin alfa used for ovarian stimulation of poor responder patients. Int J Womens Health. 2016 Oct 17;8:609-615.	Randomized Controlled Trial	2 of the following criteria 1) advanced women's age (.40 years) 2) few numbers of retrieved oocytes (,3 oocytes) following previous ovarian stimulation; and 3) abnormal ovarian reserve test (antral follicle count ,5–7 or anti-Mullerian hormone ,0.5–1.1 ng/mL).	**group A (study group)** (n=42) received clomiphene citrate (150 MG) and corifollitropin alfa (150 UGM) for the first 7 days of stimulation followed by recombinant follicle stimulating hormone (rFSH=225IU) in a antagonist protocol **group B (control group)** (n=43) received clomiphene citrate (150 MG) and a daily injection of rFSH (225 IU) in a antagonist protocol	Similar cancellation rate , stimulation outcomes and serum E2 levels. Comparable embryological results number of retrieved oocytes (3±0.8 and 2.7±0.7, respectively) the number of mature oocytes (25±0.8 and 2.4±0.8, respectively) and the number of cleaving transferred (1.8±0.6 and 1.7±0.7, respectively). Higher, though not statistically significant, difference in favour of group A compared to B in terms of pregnancy rate per embryo transfer (21.6% in group A and 17.9% in group B), pregnancy rate per cycle (19% in group A and 16.3% in group B), implantation rate (14.7 in group A and 13.4 in group B), and delivery rate per transfer	Ovarian stimulation with corifollitropin alfa appears to be as efficacious and efficient as daily injection rFSH regimen to treat patients with poor ovarian response.	Moderate

				(13.5 in group A and 10.3 in group B). Ongoing pregnancy rate and miscarriage rate were also similar between the two groups.		
Taronger R, Martínez-Cuenca S, Ferreros I, Rubio JM, Fernández-Colom PJ, MartínezTriguero ML, et al., Ovarian stimulation with corifollitropin alfa followed by hp-hMG compared to hp-hMG in patients at risk of poor ovarian response undergoing ICSI: A randomized controlled trial. Eur J Obstet Gynecol Reprod Biol. 2018 Dec;231:192–7.	Randomized Controlled Trial	234 patients, under 40 years of age and at risk of poor ovarian response	First protocol was a single injection of 150 µg corifollitropin alfa 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 until the criteria for hCG administration are met.	The ongoing pregnancy rate, live birth rate (15.2 vs 20.2) (P = 0.33), and the cumulative live birth rate (15.2 vs 22.0) (P = 0.19) per started cycle did not show significant differences between the corifollitropin alfa and hp-hMG groups, and the difference estimated between treatments was -5% [95% CI: (-15.1, 5.0)].	It was not possible to probe non-inferiority of the protocol with corifollitropin alfa followed by hp-hMG compared to hp-hMG in patients at risk of poor ovarian response undergoing ICSI.	Low
Ob'edkova KV, Kogan IY, Muller VC, Tapilskaya NI, Krikhely IO, Dzhemlikhanova LK, et al., IVF protocol efficacy in women with expected suboptimal response depending on ovary stimulation mode. Gynecol Endocrinol Off J Int Soc Gynecol Endocrinol. 2021;37(sup1):44–8.	Randomized Controlled Trial	51 IVF cycle in women with ovary suboptimal response The suboptimal response prognostic analysis was performed basing on ≤9 oocyte cumulus complexes obtained in previous IVF programs, the presence of no less than 5-9 antral follicles in both oocytes and amount of anti-Mullerian Hormone ≥0,8 ng/mL.	In Group I (n = 25), the stimulation was performed by recombinant corifollitropin alfa combined with highly purified urinary gonadotropin, while in Group II (n = 26) it was made by means of recombinant follitropin/lutropin alfa within the protocol of applying gonadotropin-releasing hormone antagonists.	The total gonadotropin dose in Group II patients was authentically lower compared to Group I (p<,01). No statistical difference between the two studied groups was detected concerning the number of obtained oocytes, 2pn zygote, good-quality transferred embryos and clinical pregnancy rate (p>.05). Embryo cryopreservation was performed only for group-II patients.	Corifollitropin alfa administration combined with highly purified menotropin in IVF cycles for suboptimal responders is quite effective, however, this strategy has no preference over other stimulation modes. The strategy of using recombinant follitropin/lutropin alfa can be promotive to IVF outcomes for suboptimal responders by means of embryo banking.	Moderate

7. Adjuvant Therapies: Do adjuvant therapies enhance efficacy or safety of ovarian stimulation in poor responders?

7.1 Is the addition of Growth Hormone as an Adjuvant superior to no Adjuvant in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Sood A, Mohiyiddeen G, Ahmad G, Fitzgerald C, Watson A, Mohiyiddeen L. Growth hormone for in vitro fertilisation (IVF). Cochrane Database Syst Rev. 2021 Nov 22;11(11):CD000099	Systematic Review/Meta-analysis	14 RCTs (1272 women) studied GH in poor responders. The evidence was low to very low certainty, the main limitations being risk of bias, imprecision, and heterogeneity. Dakhly 2018 Safdarian 2019 Tesarik 2005 Mohammad 2019 Norman 2019 Owen 1991 Suikkari 1996 (1) Zhuang 1994 Choe 2017 Lee 2019 Bergh 1994 Hazout 2003 (1) Hazout 2003 (2) Kucuk 2008	1.Bergh 1994- GH 0.1 IU/kg daily subcutaneous. Recombinant GH used 2. Choe 2017- sustained-release HGH (Eutropin Plus 20 mg, LG life sciences, Seoul, Korea) three times before and during COS (mid-luteal, late luteal, and menstrual cycle day 2). 3. Dakhly 2017-adjuvant rGH 2.5 mg (7.5 IU) GH SC from day 21 of previous cycle along with GnRHa, until the day of HCG. 4. Dor 1995- GH (18 IU on alternate days, total dose 72 IU). Recombinant GH used 5. Hazout 2003- 4 IU or 8 IU subcutaneous. Recombinant GH used 6. Kucuck 2008-GH 12 IU subcutaneous from day 21 of preceding cycle along with GnRHa, until the day of HCG. Recombinant GH used 7. Lee 2019-Recombinant GH (Saizen; Merck Serono) at a dosage of 4 IU, 4 IU, and 2 IU for three successive days, along with the ovulation induction. The total GH dosage was 10 IU for each patient in the GH (+) group. 8. Mohammad 2019- GH group - received GH 4 IU per day from day 2 of cycle until 1 day before egg collection. Recombinant GH used	**Primary outcome:** LBR-odds ratio (OR **1.77, 95% CI 1.17 to 2.70;** I2 = 0%; 8 trials poor responders, 737 participants; very low-certainty evidence **Secondary outcomes:** 1. **CPR-** OR **1.85, 95% CI 1.35 to 2.53**; I2 = 15%; 11 trials, 1033 participants 2.**OCR-** OR **5.67, 95% CI 1.54 to 20.83**; I2 = 0; 2 trials, 148 participants 3.Mean OR: (mean difference (MD) -0.02, 95% CI -0.79 to 0.74; I2 = 0%; 2 trials, 80 normo responders; MD 1.40, 95% CI 1.16 to 1.64; I2 = 87%; 12 trials,1153 poor responder 4. ET rate- (OR **2.32, 95% CI 1.08 to 4.96**; I2 = 25%; 4 trials, 214 participants; 5. Gn usage-(MD **-1088.19, 95% CI -1203.20 to -973.18**; I2 = 91%; 8 trials, 685 participants	Use of adjuvant GH in IVF treatment protocols slightly increases the number of oocytes retrieved and pregnancy rates in 'poor responders' but has uncertain effects on live birth rates. However, it slightly increases the number of oocytes retrieved and pregnancy rates in poor responders, while there is an uncertain effect on live birth rates in this group. The results, however, need to be interpreted with caution, as the included trials were small and few, with significant bias and imprecision. Also, the dose and regimen of GH used in trials was variable. Therefore, further research is necessary to fully define the role of GH as adjuvant therapy in IVF.	High

	9. Norman 2019- GH (Recombinant GH- Saizen 8 mg, Merck, Australia), in a syringe of 24 IU with a daily administered dose of 12 IU. Placebo control- identical syringe provided by Merck but containing 0.3% metacresol in water. 10. Owen 1991-GH 24 IU intramuscular (IM), days 1, 3, 5, 7, 9, and 11 of hMG treatment, during long Gn-RHa protocol, vs placebo given IM on same cycle days as active treatment groups. Recombinant GH used 11. Safdarian 2019- The patients in all groups received gonadotropin (Gonal-f 300 to 450 IU/day, subcutaneously, based on age, AFC, and the level of AMH) plus GnRH antagonist (Cetrotide, 0.25mg/day, subcutaneously, after production of 14mm follicles until HCG injection) from the third day of their cycle. In addition to common regimens, group A received recombinant GH (Somatropin, 2.5mg/day, subcutaneously from the eighth day of the cycle until the injection of HCG) and group C received placebo (normal saline, 0.1mg/ day, subcutaneously) from the eighth day of the cycle until the injection of HCG). 12. Sulkari 2019-Intervention: six women received 12 IU GH and 10 women received 4 IU GH daily SC from day three of spontaneous menstrual cycle. Recombinant GH used. Study Protocol: A boost "flare-up" protocol was used for ovarian stimulation. On day two of spontaneous menstrual cycle leuprolide acetate was administered SC 0.75mg in the morning. On day three gonadotrophin Metrodin was started at 300IU SC for four days	

	then adjusted according to serum E2 and follicular growth. Dose of human chorionic gonadotropin 5000 IU IM given when the largest follicle(s) reached a diameter of 18 to 20mm.previous poor response in < two assisted cycles. 13. Tapanainen 1992-Intervention: Recombinant GH 24 IU IM beginning on cycle day four, then every 2 days until human chorionic gonadotropin, vs sterile saline IM on same cycle days. Treatment Protocol: Short GnRHa protocol used for ovulation induction, 300 cg BA 3 times daily on cycle days 1-4. Three ampoules of hMG given IM on day 4 and then 150-223 IU daily until human chorionic gonadotropin injection. 5000 IU human chorionic gonadotropin given. Clinical Pregnancy Diagnosis: USS at six weeks gestation 14. Tesarik 2005- Recombinant GH 8IU Subcutaneous treatment Protocol: Long. Dose of human chorionic gonadotropin:25mg when at least 1 follicle measured > 18mm in diameter. 15. Younis 1992- recombinant GH 12 IU SC on days 1, 3, 5, and 7 of hMG treatment vs Mannitol 30 mg SC on same cycle days. Treatment protocol: All women received GnRHa/hMG 0.5mg/day from day 21 of previous cycle ovulation induction protocol. 16. Zhuang 1994-Intervention: recombinant GH 12 IU IM on alternate days. • Treatment protocol: GnRH-a (Buserelin nasal spray) from day 21 of previous menstrual cycle today of human chorionic gonadotropin injection (do not know dose of GnRH-a)2 IU hMG given on alternate days for 12 days (at same time as GH). Dose of human	

			chorionic gonadotropin: 10000 IU.			
Elkalyoubi M, Schindler L, Zaheer H. Effect of growth hormone cotreatment in sub-fertile women ≥ 40 years: A Meta-analysis. Reprod Fertil. 2023 Feb 1;4(1):e220107.	Systematic Review/Meta-analysis	**Tesarik et al. (2005)** - RCT 100 women aged 41 to 44 years. Couples with azoospermia and women with basal FSH > 14 IU/mL or those with basal inhibin B of <30 pg/ mL **Kaene et al** (2015)Retrospective 163 women aged ≥40 years who had failed at least 1 IVF (a subgroup of the total 400 women). Only the first cycle was considered in the analysis. Excluded were freezing all cycles, canceled cycles, failed fertilization, failed oocyte retrieval, pregnancy with ectopic and blight ovum, **Ho et al. (2017)** January 2005 to December 2009 Retrospective 134 women aged ≥40 years old. No exclusion criteria **Lan et al. (2019)** January 2009 to March 2014 Retrospective ≥ 40 years old with a history of poor ovarian response or poor ovarian reserve (POSEIDON group 4) who underwent their first IVF cycles in their center were included. Women with a history of intrauterine synechiae, congenital Mullerian duct anomaly, hydrosalpinx, endometrial fluid, sub-mucosal myoma, and incidentally found endometrial lesions during ovarian stimulation were excluded. 15 women (9 with and 6 without GH supplementation), were excluded. **Lee et al. (2019)** January 2010 to October 2012. Combined RCT and retrospective the study was divided into two parts. The first part was RCT and was included in this meta-analysis. The inclusion criteria included women classified as poor responders according to the definition of the Bologna criteria. Only the first IVF cycle with the	Tesarik et al : Daily s.c. injection of 8 IU of GH started on day 7 of stimulation until the day of ovulation trigger. The control group received only the solvent. All were non donor cycles. Kaene et al : Some women received GH (Saizen) injections starting in the previous menstrual cycle (from day 2 or 3) and included 6 injections over 6 weeks leading up to the day of oocyte retrieval. Approximately 54 IU were administered for 33–37 days (1.5 IU per day). Others received 1 IU of GH injection (Sci-Tropin) per day for 45 days up to the day of oocyte retrieval. Ho et al : daily injections of GH from day 3 coincide with the start of the gonadotrophin injection and up to the day of triggering. Fresh embryo transfer with at least two blastocysts of the best quality. Lan et al : 8 IU of daily injections of GH starting on the day that the leading follicle had reached 14 mm in diameter until the day of triggering. Lee at el :A total of 10 IU of GH were administered, divided into 4, 4, and 2 IU of GH daily injections for 3 consecutive days along with induction of ovulation. chan et al : In the antagonist group (approximately 75%) of the patients, 3 IU daily injections of GH (Jintropin AQ) were started from the day of the start of the gonadotropin injection until the day of the hCG (about 10 days). In the agonist group (about 25) of the patients, 2 IU of daily injections of GH (Jintropin AQ) were started after the pituitary down-regulation was confirmed and until the day of hCG	There was a statistically significant increase in **clinical pregnancy per embryo transfer** (OR: 2.2; (95% CI): 1.34–3.61; I2=31%) (Fig. 2). **After excluding four non-RCTs (Ho et al. 2017, Keane et al. 2017, Lan et al. 2019, Chen et al. 2022), the clinical pregnancy rate was still significantly higher in GH (+) with (OR: 4.48; (95% CI): 1.58–12.64; I2=0%)** while excluding studies with a high risk of bias (Ho et al. 2017, Lee et al. 2019, Chen et al. 2022) OR of 2.27; (95% CI: 1.52–4.66; I2=0%) was still statistically significant. LBR : A pooled analysis of three studies (Fig. 3) showed a significantly higher **live birth rate** (OR: 4.12; 95% CI: 1.82–9.32; I2=0%).The pooled calculated ARD of four studies (GH (+) 28/196 and GH (−) 9/223) was 0.08; 95% CI: 0.01–0.16; I2 = 50% . Based on that, if the chance of clinical pregnancy is 4% (9/223) with GH (−), it would be between 5% and 20% with GH (+). The NNT is 9.75 (1/((28/196) − (9/223)). This meta-analysis did not show a statistically significant difference in the number of mature	This meta-analysis showed a significant improvement in clinical pregnancy and live birth rates with the use of GH cotreatment in a subgroup of women of AMA, but due to the unclear dosage and regimen of GH, it is difficult to confidently recommend its routine use. Further studies should consider the optimal dose and duration of GH injection and its safety.	High

	fresh transfer was managed by the same clinician. **Chen et al. (2022)** June 2018 to December 2019 Retrospective Couples with unexplained poor embryonic development after previous IVF (i.e., no top-quality embryos graded 1 or 2). Inclusion criteria were BMI between 18 and 25 kg/m2, tubal infertility, regular menstrual cycle, normal uterine morphology, and no residual frozen embryo. The exclusion criteria were preimplantation genetic testing cycle (PGT), endometriosis, polycystic ovary syndrome, medical comorbidities, azoospermia, and the insemination method changed in the second IVF **Dakhly et al. (2018)** April 2015 to November 2017 Open-label RCT Women who met the Bologna criteria. The authors excluded women > 45 years old, basal FSH > 20 IU/mL, or husbands with azoospermia or severe teratozoospermia.	Dakhly et al :GH cotreatment 2.5 mg s.c. injection (equivalent to 7.5 IU) (Norditropin pen, Novo Nordisk, Denmark) from day 21 of the previous cycle to the day of hCG.	and retrieved oocytes between GH (+) and GH (−). The OR of the average number of retrieved oocytes was 0.14; 95% CI: −0.75 to 1.03; I2= 81%. The total of participants in the 5 included studies (Tesarik et al. 2005, Ho et al. 2017, Dakhly et al. 2018, Lan et al. 2019, Chen et al. 2022) was 749. The total number of participants in the 4 studies (Tesarik et al. 2005, Ho et al. 2017, Dakhly et al. 2018, Chen et al. 2022) that reported an average number of mature oocytes was 492. The OR was 0.87; 95% CI: −1.8 to 0.06; I2= 83%		

7.2 Is the addition of Testosterone as an Adjuvant superior to no Adjuvant in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Katsika ET, Bosdou JK, Goulis DG, Grimbizis GF, Kolibianakis EM. Higher live birth rate following transdermal testosterone pretreatment in poor responders: a systematic review and meta-analysis. Reprod Biomed Online. 2023 Jan;46(1):81-91.	Systematic Review/Meta-analysis	434 versus 308 Massin et al. (2006), 53 Kim et al. (2011), 110 Kim et al. (2014), 120 Bosdou et al. (2016), 50 Doan et al. (2017), 110 Al-Jeborry (2019), 132 Hoang et al. (2021), 159 Subirá et al. (2021), 63	Pretreatment with transdermal testosterone gel was performed in all studies, with a daily dose ranging from 10 to 12.5 mg/day. The duration of testosterone pretreatment ranged from 10 to 56 days	Primary outcome: The **probability of pregnancy** was significantly increased in women pretreated with transdermal testosterone compared with those who were not, regarding both live birth (RR 2.07, 95% CI 1.09–3.92; Risk Difference 10%, 95% CI 2–17; fixed effects model I2 0%, four studies, 333 women) and clinical	In conclusion, based on the currently available evidence, testosterone pretreatment increases clinical pregnancy and live birth rates in poor responders undergoing ovarian stimulation for IVF.	Low

			pregnancy (RR 2.25, 95% CI 1.54–3.30; RD 11%, 95% CI 4–18%; fixed effects model I2 0%, eight studies, 797 women) Secondary outcomes: **Duration of ovarian stimulation :** Significantly fewer days in pre-treated with testosterone women.(WMD –0.81, 95% CI –1.46 to –0.16, random effects model I2 92%, seven studies, 744 women). **Total dose of gonadotrophin** for ovarian stimulation: A significantly **total lower dose of gonadotrophin** was required for ovarian stimulation in testosterone pre-treatment group.(WMD –368.8 IU, 95% CI –612.4 to –125.2 IU, random effects model I2 87%,eight studies, 797 women). Endometrial thickness on the day of trigger of final oocyte maturation: Significantly **thicker endometrium** in those who received transdermal testosterone. (WMD 0.83 mm, 95% CI 0.13–1.53 mm, random effects model I2 77.6%, five studies, 561 women). **Cancellation rate** due to poor ovarian response: Significantly lower cancellation rate in the pre-treatment group. (RR 0.37, 95% CI 0.20–0.71, fixed effects model I2 0%, six studies, 681 women). **COC retrieved:** Significantly more COC was retrieved in the pre-treatment group.	

				(WMD 0.88, 95% CI 0.22–1.54, random effects model I2 78.7%, eight studies, 797 women). **Oestradiol concentrations on the day of triggering** final oocyte maturation: No significant difference. (WMD –8.12 pg/ml, 95% CI –118.2 to 101.96 pg/ml, fixed effects model I2 0%, four studies, 394 women). **Number of follicles ≥17 mm on the day of triggering** final oocyte maturation: No significant difference. (WMD 0.82, 95% CI –0.11 to 1.74, random effects model I2 85.7%, five studies, 386 women). **Miscarriage:** A significant difference in the probability of miscarriage was present between women pretreated with transdermal testosterone and those who were not (RR 1.12, 95% CI 0.30–4.22, fixed effects model I2 0%, three studies, 202 women).		
Noventa M, Vitagliano A, Andrisani A, Blaganje M, Viganò P, Papaelo E, et al., Testosterone therapy for women with poor ovarian response undergoing IVF: a meta-analysis of randomized controlled trials. J Assist Reprod Genet. 2019 Apr;36(4):673–83.	Meta-Analysis	8 RCTs were included in the analysis	Summarize evidence on the effectiveness of testosterone supplementation for poor ovarian responders (POR) on IVF outcomes.	Women receiving testosterone showed higher LBR (RR 2.29, 95% CI 1.31-4.01, p = 0.004), CPR (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 MR (p = ns). Sensitivity and subgroup analysis did not provide statistical changes to the pooled results.	Testosterone therapy seems promising to improve the success at IVF in POR patients. Further RCTs with rigorous methodology and inclusion criteria are still mandatory.	Moderate
Nagels HE, Rishworth JR,	Systematic	Of the 17 studies, 828	The dosage varied: one study	When DHEA was compared	In women identified as poor	High

Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2015 Nov 26;(11): CD009749.	Review/Meta-analysis	women were in the intervention group and 785 in the control group. Artini 2012- Poor responders Bologna criteria Divita 2003 Kara 2014 Kim 2010 Kim 2011 Marzal 2014 Massin 2006 Moawad 2012 Yeung 2014 Jindal 2014	used a daily oral dose of 40 mg of micronized DHEA sulfate (DHEAS) as co-treatment with GnRHa (commenced in the mid-luteal phase of the previous cycle) (Divita 2003), while most used a daily oral dose of 75 mg DHEA as a pre- and then co-treatment with a long gonadotropin-releasing hormone agonist (GnRHa) protocol (Artini 2012; Evans 2013; Kara 2014; Moawad 2012; Tartagni 2015a; Tartagni 2015b; Wiser 2010; Yeung 2013a; Yeung 2014; Zhang 2014). Wiser 2010 included two IVF cycles. Jindal 2014 used a 75 mg dose of DHEA in a combination of GnRHa and antagonist cycles. Testosterone (five studies): • One study compared transdermal testosterone with placebo gel (Massin 2006). • Three studies compared transdermal testosterone with no treatment (Fábregues 2009; Kim 2010; Kim 2011). • One study compared transdermal testosterone with estradiol and with estradiol plus oral contraceptive pill (Marzal 2014). Again, the dosage and length of treatment varied: 2.5 mg per day pre-treatment (20 µg/kg) for five days (Fábregues 2009); 10 mg per day pre-treatment for 15 to 20 days (Massin 2006); 12.5 mg per day pre-treatment for 14, 21 or 28 days (Kim 2010); 12.5 mg per day pre-treatment for 21 days (Kim	with placebo or no treatment, pre-treatment with DHEA was associated with higher **rates of live birth or ongoing pregnancy** (OR 1.88, 95% CI 1.30 to 2.71; eight RCTs, N = 878, I2 statistic = 27%, moderate quality evidence). This suggests that in women with a 12% chance of live birth/ongoing pregnancy with placebo or no treatment, the live birth/ongoing pregnancy rate in women using DHEA will be between 15% and 26%. **However, in a sensitivity analysis removing trials at substantial risk of performance bias, the effect size was reduced and no longer reached significance (OR 1.50, 95% CI 0.88 to 2.56; five RCTs, N = 306, I2 statistic = 43%)**. There was no evidence of a difference in **miscarriage rates** (OR 0.58, 95% CI 0.29 to 1.17; eight RCTs, N = 950, I2 statistic = 0%, moderate quality evidence). Multiple pregnancy data were available for five trials, with one multiple pregnancy in the DHEA group of one trial (OR 3.23, 95% CI 0.13 to 81.01; five RCTs, N = 267, very low-quality evidence). When testosterone was compared with placebo or no treatment, pre-treatment with testosterone was associated with higher **live birth rates** (OR 2.60, 95% CI 1.30 to 5.20; four RCTs, N = 345, I2 statistic = 0%, moderate	responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates. The overall quality of the evidence is moderate. There is insufficient evidence to draw any conclusions about the safety of either androgen. Definitive conclusions regarding the clinical role of either androgen await evidence from further well-designed studies.

			2011); and 20 µg/kg per day for six days (Marzal 2014). Massin 2006 and Marzal 2014 utilised GnRH agonist protocols, while Kim 2010 and Kim 2011 both used a GnRH antagonist multiple-dose protocol (MDP).	evidence). This suggests that in women with an 8% chance of live birth with a placebo or no treatment, the live birth rate in women using testosterone will be between 10% and 32%. **On removal of studies at substantial risk of performance bias in a sensitivity analysis, the remaining study showed no evidence of a difference between the groups (OR 2.00, 95% CI 0.17 to 23.49; one RCT, N = 53).** There was no evidence of a difference in **miscarriage rates** (OR 2.04, 95% CI 0.58 to 7.13; four RCTs, N = 345, I2 = 0%, low-quality evidence). Multiple pregnancy data were available for three trials, with four events in the testosterone group and one in the placebo/no treatment group (OR 3.09, 95% CI 0.48 to 19.98; three RCTs, N = 292, very low-quality evidence). One study compared testosterone with oestradiol and reported no evidence of a difference in live birth rates (OR 2.06, 95% CI 0.43 to 9.87; one RCT, N = 46, very low-quality evidence) or miscarriage rates (OR 0.70, 95% CI 0.11 to 4.64; one RCT, N = 46, very low-quality evidence).		
González-Comadran M, Durán M, Solà I, Fábregues F, Carreras R, Checa MA. Effects of transdermal testosterone in poor responders undergoing IVF: systematic review and meta-analysis. Reprod Biomed Online. 2012 Nov;25(5):450-9.	Systematic Review/Meta-analysis	Inclusion criteria were heterogeneous regarding definition of poor responders. This item was defined by Fa´bregues et al. (2009) as the failure to produce more than or equal to3 follicles with a mean	Massin et al. (2006) and Kim et al. (2011) used transdermal testosterone in gel (10 mg of transdermal testosterone for 15–20 days and 12.5 mg for 21 days during pituitary desensitization, respectively), while Fa´bregues et al. (2009)	Testosterone-treated women achieved significantly higher live birth rate (risk ratio, RR, 1.91, 95% CI 1.01 to 3.63), clinical pregnancy rate (RR 2.07, 95% CI 1.13 to 3.78) and required significantly lower doses of FSH (RR	In conclusion, there is evidence from randomized controlled trials to support the use of transdermal testosterone before ovarian stimulation in women who are considered poor responders, and this treatment has been	High

		diameter >_14 mm or the collection of >_3 follicles at retrieval, whereas Kim et al.(2011) set the limit of poor response the production of _3 follicles with a mean diameter >_16 mm or the collection of >_3 follicles at retrieval. In contrast, Massin et al. (2006) defined poor response as a plasma oestradiol value below 1.200 pg/ml on HCG day and the collection of >_5 follicles at retrieval, adding as a necessary criteria for enrolment the evidence of a decreased ovarian reserve at day 3 of a spontaneous cycle, as determined with plasma hormonal values outside the normal range (FSH >12 IU/l, oestradiol >70 pg/ml and inhibin B <45 pg/ml). The protocols used were also different in different studies. Using different GnRH analogues and gonadotropins. One additional RCT Fa´bregues et al. (2009) Three trials were included (113 women in the testosterone group, 112 in the control group).	used patches of 2.5 mg per day for 5 days. Massin et al. (2006) was the only study that used an identical placebo gel in the control group, whereas the other two studies did not blind the patient assignment.	461.96, 95% CI 611.82 to 312.09). However, differences observed in clinical pregnancy per embryo transferred were not statistically significant (RR 1.72, 95% CI 0.91 to 3.26). No differences were observed regarding the number and quality of the oocytes retrieved.	shown to significantly improve live birth rates and reduce the doses of FSH required for ovarian stimulation. The exact subgroup of poor responders who would benefit from this treatment still needs to be identified. However, the result should be interpreted with caution because of the small number of trials and their clinical heterogeneity. Although trends in all parameters appear to favour testosterone supplementation, further investigations are needed to confirm these findings	
Hoang QH, Ho HS, Do HT, Nguyen TV, Nguyen HP, Le MT. Therapeutic effect of prolonged testosterone pretreatment in women with poor ovarian response: A randomized control trial. Reprod Med Biol. 2021 Jul;20(3):305–12	Randomized Controlled Trial	Infertile women with POR who underwent in vitro fertilization (IVF) were recruited and randomly classified into 4-week (n = 42) and 6-week (n = 38) TTG treatment groups and control groups (n = 42).	Therapeutic effects of transdermal testosterone gel (TTG) application at 4 and 6 weeks before controlled ovarian hyperstimulation (COH) in women with poor ovarian response (POR).	No significant differences were observed in the number of oocytes retrieved, mature oocytes and embryos between all groups. Human chorionic gonadotropin (hCG) positive, clinical, and ongoing pregnancy rates were significantly higher in the TTG pretreatment groups than in	Applying TTG in infertile women with POR may ameliorate the outcomes of IVF. The extended application of TTG to 6 weeks did not improve the response to ovarian stimulation regarding the number of retrieved oocytes nor pregnancy outcomes compared to the 4-	Modrate

				the control group, but no differences were observed between the 4- and 6-week groups.	week pretreatment.	

7.3 Is the addition of DHEA as an Adjuvant superior to no Adjuvant in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Zhang J, Jia H, Diao F, Ma X, Liu J, Cui Y. Efficacy of dehydroepiandrosterone priming in women with poor ovarian response undergoing IVF/ICSI: a meta-analysis. Front Endocrinol. 2023;14:1156280.	Meta-Analysis	A total of 32 studies were retrieved, including 14 RCTs, 11 self-controlled studies and 7 case-controlled studies.	This study aimed to investigate the efficacy of DHEA supplementation in patients with POR/DOR undergoing IVF/ICSI.	In the subgroup analysis of only RCTs, DHEA treatment significantly increased the number of antral follicle count (AFC) (weighted mean difference : WMD 1.18, 95% confidence interval(CI): 0.17 to 2.19, P=0.022), while reduced the level of bFSH (WMD -1.99, 95% CI: -2.52 to -1.46, P<0.001), the need of gonadotropin (Gn) doses (WMD -382.29, 95% CI: -644.82 to -119.76, P=0.004), the days of stimulation (WMD -0.90, 95% CI: -1.34 to -0.47, P <0.001) and miscarriage rate (relative risk : RR 0.46, 95% CI: 0.29 to 0.73, P=0.001). The higher clinical pregnancy and live birth rates were found in the analysis of non-RCTs. However, there were no significant differences in the number of retrieved oocytes, the number of transferred embryos, and the clinical pregnancy and live birth rates in the subgroup analysis of only RCTs. Moreover, meta-regression analyses showed that women with lower basal FSH had more 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 had more increase in serum AMH levels (b=-0.60, 95% CI: -1.15 to -0.06, P=0.035) after DHEA supplementation. In addition, the number of retrieved oocytes was higher in the studies on younger	DHEA treatment didn't significantly improve the live birth rate of women with DOR or POR undergoing IVF/ICSI in the subgroup analysis of only RCTs. The higher clinical pregnancy and live birth rates in those non-RCTs should be interpreted with caution because of potential bias. Further studies using more explicit criteria to subjects are needed.	Low

				women (b=-0.21, 95% CI: -0.39 to -0.03, P=0.023) and small sample sizes (b=-0.003, 95% CI: -0.006 to -0.0003, P=0.032).		
Nagels HE, Rishworth JR, Siristatidis CS, Kroon B. Androgens (dehydroepiandrosterone or testosterone) for women undergoing assisted reproduction. Cochrane Database Syst Rev. 2015 Nov 26;(11): CD009749.	Systematic Review/Meta-analysis	Of the 17 studies, 828 women were in the intervention group and 785 in the control group. Artini 2012- Poor responders Bologna criteria Divita 2003 Kara 2014 Kim 2010 Kim 2011 Marzal 2014 Massin 2006 Moawad 2012 Yeung 2014 Jindal 2014	The dosage varied: one study used a daily oral dose of 40 mg of micronized DHEA sulfate (DHEAS) as co-treatment with GnRHa (commenced in the mid-luteal phase of the previous cycle) (Divita 2003), while most used a daily oral dose of 75 mg DHEA as a pre- and then co-treatment with a long gonadotropin-releasing hormone agonist (GnRHa) protocol (Artini 2012; Evans 2013; Kara 2014; Moawad 2012; Tartagni 2015a; Tartagni 2015b; Wiser 2010; Yeung 2013a; Yeung 2014; Zhang 2014). Wiser 2010 included two IVF cycles. Jindal 2014 used a 75 mg dose of DHEA in a combination of GnRHa and antagonist cycles. Testosterone (five studies): • One study compared transdermal testosterone with placebo gel (Massin 2006). • Three studies compared transdermal testosterone with no treatment (Fábregues 2009; Kim 2010; Kim 2011). • One study compared transdermal testosterone with estradiol and with estradiol plus oral contraceptive pill (Marzal 2014). Again, the dosage and length of treatment varied: 2.5 mg per day pre-treatment (20 µg/kg) for five days (Fábregues 2009); 10 mg per day pre-treatment for 15 to 20 days (Massin 2006); 12.5 mg per day pre-treatment for 14, 21 or 28 days (Kim 2010); 12.5 mg per day pre-treatment for 21 days (Kim 2011); and 20 µg/kg per day for six days (Marzal 2014). Massin 2006 and Marzal 2014	When DHEA was compared with placebo or no treatment, pre-treatment with DHEA was associated with higher **rates of live birth or ongoing pregnancy** (OR 1.88, 95% CI 1.30 to 2.71; eight RCTs, N = 878, I2 statistic = 27%, moderate quality evidence). This suggests that in women with a 12% chance of live birth/ongoing pregnancy with placebo or no treatment, the live birth/ongoing pregnancy rate in women using DHEA will be between 15% and 26%. **However, in a sensitivity analysis removing trials at elevated risk of performance bias, the effect size was reduced and no longer reached significance (OR 1.50, 95% CI 0.88 to 2.56; five RCTs, N = 306, I2 statistic = 43%)**. There was no evidence of a difference in **miscarriage rates** (OR 0.58, 95% CI 0.29 to 1.17; eight RCTs, N = 950, I2 statistic = 0%, moderate quality evidence). Multiple pregnancy data were available for five trials, with one multiple pregnancy in the DHEA group of one trial (OR 3.23, 95% CI 0.13 to 81.01; five RCTs, N = 267, very low-quality evidence). When testosterone was compared with placebo or no treatment, pre-treatment with testosterone was associated with higher **live birth rates** (OR 2.60, 95% CI 1.30 to 5.20; four RCTs, N = 345, I2 statistic = 0%, moderate evidence). This suggests that in women with an 8% chance of live birth with a placebo or no treatment, the live birth rate in	In women identified as poor responders undergoing ART, pre-treatment with DHEA or testosterone may be associated with improved live birth rates. The overall quality of the evidence is moderate. There is insufficient evidence to draw any conclusions about the safety of either androgen. Definitive conclusions regarding the clinical role of either androgen await evidence from further well-designed studies.	High

	utilised GnRH agonist protocols, while Kim 2010 and Kim 2011 both used a GnRH antagonist multiple-dose protocol (MDP).	women using testosterone will be between 10% and 32%. **On removal of studies at elevated risk of performance bias in a sensitivity analysis, the remaining study showed no evidence of a difference between the groups (OR 2.00, 95% CI 0.17 to 23.49; one RCT, N = 53).** There was no evidence of a difference in **miscarriage rates** (OR 2.04, 95% CI 0.58 to 7.13; four RCTs, N = 345, I2 = 0%, low-quality evidence). Multiple pregnancy data were available for three trials, with four events in the testosterone group and one in the placebo/no treatment group (OR 3.09, 95% CI 0.48 to 19.98; three RCTs, N = 292, very low-quality evidence). One study compared testosterone with oestradiol and reported no evidence of a difference in live birth rates (OR 2.06, 95% CI 0.43 to 9.87; one RCT, N = 46, very low-quality evidence) or miscarriage rates (OR 0.70, 95% CI 0.11 to 4.64; one RCT, N = 46, very low-quality evidence).	

7.4 Is the addition of Co-Enzyme Q10 (CoQ10) as an Adjuvant superior to no Adjuvant in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Zhu F, Yin S, Yang B, Li S, Feng X, Wang T, et al., TEAS, DHEA, CoQ10, and GH for poor ovarian response undergoing IVF-ET: a systematic review and network meta-analysis. Reprod Biol Endocrinol RBE. 2023 Jul 18;21(1):64.	Meta-Analysis	Sixteen RCTs (2323 women) with POR defined using the Bologna criteria were included in the network meta-analysis.	Evaluate the effects of DHEA, CoQ10, GH and TEAS on pregnancy outcomes in POR patients undergoing in vitro fertilization and embryo transplantation (IVF-ET)	Compared with the control group, CoQ10 (OR 2.22, 95% CI: 1.05 to 4.71) and DHEA (OR 1.92, 95% CI: 1.16 to 3.16) had obvious advantages in improving the clinical pregnancy rate. CoQ10 was the best in improving the live birth rate (OR 2.36, 95% CI: 1.07 to 5.38). DHEA increased the embryo implantation rate (OR 2.80, 95%CI: 1.41 to 5.57) and the high-quality embryo rate (OR	Compared with COS regimen, the adjuvant use of CoQ10, DHEA and GH before IVF may have a better clinical effect on the pregnancy outcome of POR patients. TEAS needs careful consideration in improving the clinical pregnancy rate. Future large-scale RCTs with direct comparisons are needed to validate or update this conclusion.	Low

				2.01, 95% CI: 1.07 to 3.78) and number of oocytes retrieved (WMD 1.63, 95% CI: 0.34 to 2.92) showed a greater advantage, with GH in second place. Several adjuvant treatment strategies had no significant effect on reducing the cycle canceling rate compared with the control group. TEAS was the least effective of the four adjuvant treatments in most pooled results, but the overall effect was better than that of the control group.		
Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, et al., Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod Biol Endocrinol RBE. 2018 Mar 27;16(1):29.	Randomized Controlled Trial	study included 186 consecutive patients with POR stratified according to the POSEIDON classification group 3 (age < 35, poor ovarian reserve parameters). A total of 169 participants were evaluated (76 treated with CoQ10 and 93 controls); 17 women were excluded due to low compliance with CoQ10 administration.	The participants were randomized to the CoQ10 pre-treatment for 60 days preceding IVF-ICSI cycle or no pre-treatment. The number of high quality embryos was a primary outcome measure.	CoQ10 pretreatment resulted in significantly lower gonadotrophin requirements and higher peak E2 levels. Women in CoQ10 group had increased number of retrieved oocytes (4, IQR 2-5), higher fertilization rate (67.49%) and more high-quality embryos (1, IQR 0-2); $p < 0.05$. Significantly less women treated with CoQ10 had cancelled embryo transfer because of poor embryo development than controls (8.33% vs. 22.89%, $p = 0.04$) and more women from treatment group had available cryopreserved embryos (18.42% vs. 4.3%, $p = 0.012$). The clinical pregnancy and live birth rates per embryo transfer and per one complete stimulation cycle tended to be higher in CoQ10 group but did not achieve statistical significance.	Pretreatment with CoQ10 improves ovarian response to stimulation and embryological parameters in young women with poor ovarian reserve in IVF-ICSI cycles. Further work is required to determine whether there is an effect on clinical treatment endpoints.	Low
Caballero T, Fiameni F, Valcarcel A, Buzzi J. Dietary supplementation with coenzyme Q10 in poor responder patients undergoing IVF-ICSI Treatment. Fertil Steril. 2016 Sep 1;106(3):e58.		Caballero 2016 Age 38/36–40 Buenos Aires, Argentine Xu 2018 32/28–36 Beijing China	Caballero 2016 39 vs 39	CPR 1.83 (1.04 3.24) LBR 1.67 (0.66-4.25) MR 0.64 (0.08-5.05) one study Xi	This study in infertile women undergoing ART indicates that CoQ10 supplementation in-creases CPR both in total and in infertility subgroups (POR and PCOS) compared with a placebo or no-treatment. However, there is a lack of effect on LBR and MR by CoQ10 supple-mentation. Although the available data are insufficient to conclude a beneficial or detrimental effect on fertility outcomes concerning CoQ10	Low

	supplementation and ART, one could consider this as a non-pharmaceutical, inexpensive, and safe therapy to enhance infertility treatment in women of reproductive age undergoing any ART. In any case, well-designed, interventional studies, with a larger number of participants, mainly emphasizing clinical outcomes, will further elucidate these issues.

7.5 Is the addition of Glucocorticoids as an Adjuvant superior to no Adjuvant in Poor Responders?

No Evidence

8. Monitoring Stimulation Protocols

8.1 Does the Addition of Hormonal Assessment (Oestradiol/Progesterone/LH) To Ultrasound Monitoring Improve Monitoring of Efficacy And Safety In Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Kwan I, Bhattacharya S, Woolner A. Monitoring of stimulated cycles in assisted reproduction (IVF and ICSI). Cochrane Database Syst Rev. 2021 Apr 12;4(4):CD005289.	Systematic review/Meta-analysis	Subfertile couples undergoing IVF and ICSI treatment	Monitoring controlled ovarian hyperstimulation (COH) with transvaginal ultrasonography (TVUS) only.	Clinical Pregnancy Rate: The review found no significant difference in clinical pregnancy rates when monitoring with TVUS only versus combined monitoring with TVUS plus serum estradiol. The clinical pregnancy rate using TVUS only could be between 31% and 46% for women with a 36% chance of clinical pregnancy using combined monitoring. Oocytes Retrieved: There was uncertainty about the effect on the mean number of oocytes retrieved per woman between the two monitoring methods OHSS	This review update found no new randomised trials. Evidence from the six studies previously identified did not suggest that combined monitoring by TVUS and serum estradiol is more efficacious than monitoring by TVUS alone about clinical pregnancy rates and the incidence of OHSS. The number of oocytes retrieved appeared similar for both monitoring protocols. The data suggest that both these monitoring methods are safe and reliable. However, these results should be interpreted with caution because the overall quality of the evidence was low. Results were compromised by imprecision and poor reporting of study methodology. The	Very High

				Incidence: Monitoring with TVUS only versus combined monitoring showed no significant difference in the incidence of OHSS, suggesting an OHSS rate of 2% to 8% for TVUS only, compared to a 4% chance with combined monitoring. Cycle Cancellation Rate: The cycle cancellation rate was similar for both monitoring methods in the studies reported.	choice of one or the other method may depend upon the convenience of its use, and the associated costs. An economic evaluation of the costs involved with the two methods and the views of the women undergoing cycle monitoring would be welcome.	

9. Criteria for Conversion to IUI or Cycle Cancellation

9.1 Should IVF/ICSI cycles be converted to IUI or cancelled if there is Poor Response to Ovarian Stimulation?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Fujii DT, Quesnell JL, Heitmann RJ. Conversion to IUI versus continuance with IVF in low responder patients: A systematic review. Eur J Obstet Gynecol Reprod Biol. 2018 Aug;227:35–40.	Systematic review	A total of seven retrospective studies and one randomized control trial were reviewed.	Decision to proceed with oocyte retrieval, convert to intrauterine insemination (IUI), or cancel the cycle	When evaluating poor responders as a group, six studies reported higher overall clinical pregnancy rates and five studies reported overall increased live birth rates with continuance of IVF. When stratified by the number of follicles produced, continuance of IVF demonstrated higher clinical pregnancy and live birth rates with ≥ 2 follicles. When only one follicle developed there were no significant differences in clinical pregnancy or live birth rates between the two groups.	In patients undergoing IVF with ≤4 follicles, continuance with IVF may lead to higher clinical pregnancy and live birth compared to conversion to IUI except in patients with monofollicular development, although additional randomized controlled trials are needed to confirm these findings.	Very Low
Nicopoullos	Cohort Study	A total of 1,350	Group 1 (n =	Biochemical pregnancy rates of	Our data suggest that for such poor responders,	Low

JDM, Abdalla H. Poor response cycles: when should we cancel? Comparison of outcome between egg collection, intrauterine insemination conversion, and follow-up cycles after abandonment. Fertil Steril. 2011 Jan;95(1):68–71.		IVF/intracytoplasmic sperm injection cycles (7.3% of total) during 1998-2009 were found to have one or two mature follicles.	807) comprised those who proceeded to vaginal egg collection (VEC) (59.8%; outcome per egg collection), group 2 (n=248) those who converted to IUI (18.4%; outcome per insemination) and group 3 (n=259) those who abandoned the current cycle (21.9%; outcome per abandoned cycle in first subsequent cycle).	13.1%, 4.9%, and 9.7%, clinical pregnancy rates of 8.1%, 3.6%, and 7.2%, and ongoing pregnancy rates of 6.8%, 2.0%, and 5.5% were achieved in groups 1, 2, and 3, respectively. All pregnancy outcomes were significantly higher after VEC (group 1) than for those converted to IUI (group 2), and all pregnancy outcomes were higher with borderline significance in group 3 vs. group 2. There was no significant difference in outcome between groups 1 and 3.	proceeding to VEC may represent their best chance of successful outcome. Conversion to IUI offers the poorest outcome, and despite the potential for improvements in cycle protocol, abandoning and a further attempt does not improve outcome (using abandoned cycle as the denominator).	
Norian JM, Levens ED, Richter KS, Widra EA, Levy MJ. Conversion from assisted reproductive technology to intrauterine insemination in low responders: is it advantageous?. Fertil Steril. 2010;94(6):2073-2077.	Cohort Studies	Total of 269 IUI conversions and 167 ooctye retrieval procedures after a poor response to stimulation were identified among first ART attempts during the study period. Inclusion: must receive gonadotropins as part of their first planned autologous ART cycle and demonstrate 4 or less follicles measuring ≥14mm in diameter, with an E2 level <1000 pg/mL at time of hCG trigger. Patients converted from ART to IUI had	"Patients underwent standardized stimulation protocols that used a combination of purified or recombinant FSH and hMG with either leuprolide acetate or a GnRH antagonist. For patients converted to IUI: insemination occurred 36h post-hCG administration For ART patients: 1.Both agonist and antagonist	Comparison of IUI vs ART groups: **Clinical pregnancy:** 5.2% vs 25.7%, *P* < 0.0001 **Live birth:** 4.1% vs. 19.8%, *P* <.0001 **Ectopic pregnancy:** 0% vs.1.2%. *P*= 0.28 **Multiple pregnancy:** 21.4% vs. 38.9%, *P*=0.54 **Spontaneous abortion:** 21.4% vs. 23.4%, *P*=0.99 **Preterm birth:** 9.1% vs. 27.3%, *P*= 0.41 **Low birth weight:** 16.7% vs 27.9%, *P*=0.68	1.The present comparison of IUI conversion versus ART treatment in low responders to stimulation for planned ART is, to date, the largest and best-controlled examination of this issue. 2.Proceeding to oocyte retrieval in patients with four or fewer total follicles ≥14 mm resulted in a more than 3x improvement in the odds of clinical pregnancy and live birth compared with converting these cycles to IUI. 3.The improvement in live birth rates was especially significant in those who had either 3 or 4 follicles ≥14 mm. 4.When choosing a course of treatment, differences in treatment costs should be considered, which are higher for ART than IUI conversion, and the availability of insurance coverage. 5.Those with a solitary follicle had such poor results that we cannot advocate any intervention other than cancellation or timed intercourse alone (although this was not evaluated in this study). 6.Conversely, with increasing follicle numbers, significant improvements in clinical pregnancy and live birth were noted with ART. 7.Based on these results, it is warranted to proceed with oocyte retrieval rather than conversion to IUI	Low

	at least one patent fallopian tube and were inseminated with a post-wash total motile sperm count of ≥ 5 million.	protocols were used 2.oocytes were retrieved 36 hours after hCG administration when at least one follicle measured a mean diameter of 18 mm using a standard transvaginal ultrasound. 3.Conventional insemination or intracytoplasmic sperm injection were used as indicated. 4. Fresh embryo transfers were performed either cleavage stage on day 3 or in the blastocyst stage on day 5/6"		among patients with 3 or 4 follicles≥14 mm on day of hCG trigger.

10.Criteria for Triggering of Final Oocyte Maturation

10.1. What is the Preferred Drug for Triggering of Final Oocyte Maturation for Efficacy and Safety in Poor Responders Undergoing IVF/ICSI?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Sloth A, Kjølhede M, Sarmon KG, Knudsen UB. Effect of dual trigger on reproductive outcome in low responders: a systematic PRISMA review and meta-analysis. Gynecol Endocrinol. 2022;38(3):213-221	Systematic Review/Meta-analysis	The studies used different definitions of POR. Eser et al., Zhang et al. , Oliveira et al. , Maged et al., and Eftekhar et al. defined POR according	Studies used different doses and preparations of HCG and GnRH agonist **HCG:** Urinary HCG 10000 / rHCG 6500 / Ovitrelle 250 mcg **GnRH agonist:** Triptorelin 0.2 mg/ Decapeptyl 0.1mg/ Lupron 2 mg	**Dual Trigger vs. HCG Trigger** 1. **Pregnancy rate, Odds ratio**, 1.62 [1.00, 2.62] 2. **Implantation rate, Odds ratio,** 1.14	The meta-analysis of this study indicates that dual trigger as finale oocyte maturation is advantageous compared to hCG	Moderate

		to the Bologna Criteria. Chern et al. defined POR according to the POSEIDON group 4 . Finally, Lin et al.defined diminished ovarian **reserve (DOR) by** the following two criteria: 1) AFC 5, and 2) serum AMH level 1.1 ng/mL.		[0.93,1.39] 3. **Live birth rate, Odds ratio,** 2.65 [1.66, 4.24]	trigger among POR. However, large-scale, high-quality, randomized controlled trials (RCT) are required to confirm this conclusion and fully address the magnitude of this effect.	
Zhou C, Yang X, Wang Y, et al. Ovulation triggering with hCG alone, GnRH agonist alone or in combination? A randomized controlled trial in advanced-age women undergoing IVF/ICSI cycles. Hum Reprod. 2022;37(8):1795-1805.	Randomized Controlled Trial	Age, Infertility duration, Type of infertility, Etiology of infertility, Previous IVF cycles, BMI, FSH, LH, E2, AMH 510 participants conducted a single reproductive medical center from January 2019 to December 2021.	Three groups: **hCG alone** (who received 6000 IU of hCG), **GnRHa alone** (who received 0.2 mg of triptorelin) **dual trigger** (who received 0.2 mg of triptorelin plus 2000 IU of hCG) groups.	There were no significant differences in the baseline demographic characteristics among the three groups. **The dual trigger was associated with a higher retrieval rate (87.9% vs 84.1% in the hCG group, p = 0.031; 87.9% vs 83.6% in the GnRHa group**, P ¼ 0.014). However, the number of retrieved oocytes in the dual trigger group was comparable with those in the hCG group (4.08 § 2.79 vs 3.60 § 2.71, P = 0.080) and the GnRHa group (4.08 § 2.79 vs 3.81 § 3.38, P ¼ 0.101); comparable data between the groups were also found when analyzing the number of 2PN embryos and the 2PN rate. **In the dual trigger group, the numbers of good-quality embryos and viable embryos were both significantly higher than in the hCG group (1.74 § 1.90 vs**	Co-administration of GnRHa and hCG as a dual trigger is not associated with a higher number of oocytes retrieved or better pregnancy outcomes; however, compared with a single hCG trigger or single GnRHa trigger, co-administration is likely to have a positive effect on embryo development in advanced-age women.	Low

				1.19 § 1.45, P = 0.016 and 2.19 § 2.11 vs 1.56 § 1.66, P = 0.008, respectively) and the GnRHa group (1.74 § 1.90 vs 1.20 § 1.67, P = 0.003 and 2.19 § 2.11 vs 1.45 § 1.75, P = 0.001, respectively). Pregnancy outcomes after fresh embryo transfer (ET) were comparable between the groups. **The live birth rate and ongoing pregnancy rate after frozen ET in the dual trigger group were significantly higher than those in the GnRHa group (32.6% vs 14.1%, P = 0.007 and 34.8% vs 17.6%, P = 0.013, respectively), but not superior to those in the hCG group (32.6% vs 27.9%, P 1⁄4 0.537 and 34.8% vs 27.9%, P = 0.358, respectively)**.		
Haas J, Zilberberg E, Nahum R, Mor Sason A, Hourvitz A, Gat I, Orvieto R. Does double trigger (GnRH-agonist + hCG) improve outcome in poor responders undergoing IVF-ET cycle? A pilot study. Gynecol Endocrinol. 2019 Jul;35(7):628-630	Randomized Controlled Trial	33	**hCG (6500 IU) 36 h before oocyte pick-up (OPU) (hCG trigger):** 11 patients **GnRH agonist (GnRH-ag) 36 h before (OPU) and hCG (6500 IU) on the day of OPU (GnRH-ag trigger):** 10 patients **GnRH-ag and hCG (6500 IU), 40 and 34 h before OPU, respectively (double trigger):** 12 patients	**hCG-trigger vs. GnRH-ag trigger vs. Double trigger:** **No. of follicles 10-14 mm:** 2.1 ± 2.3 vs. 1.5 ± 1.3 vs. 1.7 ± 2, NS **No. of follicles >/=15mm:** 2.5 ± 1.1 vs. 2.9 ± 2.0 vs. 2.5 ± 1.4, NS **No. of oocytes retrieved:** 2 ± 2.7 vs. 3 ± 2.5 vs. 2.8 ± 2.1, NS **No. of 2PN:** 1.4 ± 1.5 vs. 2.1 ± 1.6 vs. 1.8 ± 1.4	1. There was a significant increase in the number of TQE, with a reasonable clinical pregnancy rate, compared to the conventional HCG trigger or the GnRH-ag trigger. 2. Further large prospective studies are needed to elucidate the recommendation and prior to its routine implementation.	Low

				No. of TQE (day 3): 0.3 ± 0.8 vs. 0.5 ± 0.7 vs. 1.1 ± 0.9 (P=0.02- hCG vs double) **Ongoing pregnancy:** 1/11 (9.1%) vs. 0/10 vs. 2/11 (18.2%)		
Keskin M, Ecemiş T, Atik A, Yeğen P, Kalkan E, Yücel GS. Cycle outcomes of dual trigger (GnRH agonist+hCG) versus human chorionic gonadotropin trigger alone in POSEDION group 3-4 poor responders and normo-responders: A prospective randomized study. J Gynecol Obstet Hum Reprod. 2023 Oct;52(8):102633.	Randomized Controlled Trial	Two-hundred twenty-five women participated in the study.	compare cycle outcomes of dual trigger versus human chorionic gonadotropin (hCG) trigger in NRs and POSEIDON group 3/4 (PG 3/4) PRs. PRs and NRs were divided into two subgroups: (1) study groups in both arms received dual trigger and (2) control groups received only HCG.	The number of retrieved oocytes and MII oocytes and the number of patients with excellent quality embryos were comparable between groups and live birth rates (LBR) per embryo transfer (ET) were significantly higher in the HCG group versus the dual trigger group in PG3/4 PRs (39.2% versus 19.2%; p = 0.026). NR dual trigger and HCG trigger groups were comparable in terms of patient age and LBR per ET did not significantly differ between these groups. The number of patients with good quality embryos was significantly higher in the dual trigger group versus the HCG group in NRs CONCLUSION: Dual trigger does not seem to add additional benefits in terms of live birth rates in PG3/4 PRs and NRs.	Nonetheless, considering the age difference and lack of homogenity in the number and day of embryos transferred in PG 3/4 PRs, major conclusion that can be drawn from the study is that dual trigger is not systematically useful even in poor responders since the number of mature oocytes is comparable between groups. Larger scale studies are required for additional potential implications.	Very Low
Mutlu I, Demirdag E, Cevher F, Erdem A, Erdem M. Dual trigger with the combination of gonadotropin-releasing hormone agonist and standard dose of human chorionic gonadotropin improves in vitro fertilisation outcomes in poor ovarian responders. J Obstet Gynaecol. 2022;42(5):1239-	Cohort Study (Prospective and Retrospective Study)	1283 cycles of 1010 poor responder patients according to Bologna criteria	GnRH antagonist protocol with rFSH + HMG (maximum 375 IU)Trigger: rhCG 250mcg (control group) vs rhCG 250mcg + 0.2mg triptorelin (dual trigger group)	**Mean number of retrieved oocytes** (4.5 ± 2.4 vs. 3.1 ± 2.3, p<0.001), **the mean number of mature oocytes retrieved** (3.4 ± 2.0 vs. 2.3 ± 1.9, p<.001) and	The present study results demonstrated that dual trigger with a standard dose of hCG and GnRHa could improve the clinical pregnancy and live birth rates in	Low

1244.	the mean number of fertilised oocytes (2.5 ± 1.8 vs. 1.6 ± 1.6, p<.001) **were significantly higher in the dual trigger group as compared to the standard hCG trigger group. The fertilisation and implantation rates were significantly higher in the dual trigger group than in the standard hCG group** (73.6% vs. 69.6%, p=.009 and 18.7% vs. 14.6, p=.039, respectively). The maturation rates were not different between groups (76.4% in the hCG group vs. 76.7% in the dual trigger group, p=.847). **The mean number of transferred embryos (1.75 ± 0.58 vs. 1.57 ± 0.60, p<.001), the mean number of top-quality embryos transferred (1.73 ± 0.62 vs. 1.55 ± 0.63, p<.001) and blastocyst transfer rate (8.2% vs. 3.8%, p=.007) were significantly higher in the dual trigger group than in hCG trigger group.** ET cancellation rates were higher in hCG trigger group (35% vs. 29.2%, p=.03). **Clinical pregnancy rate (CPR) per cycle (19.4% vs 13%, p=.002), live birth rate (LBR) per cycle (15.3% vs 9.7%, p=.003) and**	poor ovarian responders in GnRH antagonist ICSI cycles. These results could encourage us to use a dual trigger for improving IVF outcomes in PORs. With data accumulation, dual trigger with a combination of GnRHa and a standard dose of hCG might replace the traditional ovulation trigger with hCG in poor ovarian responders.

				CPR per ET (27.5% vs 19.9%, p=.010), LBR per ET (21.6% vs 14.9%, p=.011) were significantly higher in the dual trigger group as compared to the standard hCG trigger group.		
Tulek F, Kahraman A, Demirel LC. Dual trigger with gonadotropin releasing hormone agonist and human chorionic gonadotropin improves live birth rates in POSEIDON group 3 and 4 expected poor responders. Gynecol Endocrinol. 2022;38(9):731-735.	Cohort Study (Prospective and Retrospective Study)	A total of 1068 women who underwent dual triggering and 1931 who underwent hCG-only triggering were included in the study.	In the **study group, GnRH agonist of 0,2 mg triptorelin ace-tate(Gonapeptyl, Ferring Pharmaceuticals) and 250 mcg recom-binant human chorionic gonadotropin(Ovitrelle, Merck Serono)were administered concomitantly.** In the **control group, 250 mcg rhCG was administered.**	Cycle outcomes of dual-triggered and single-triggered expected POR patients were analyzed **Number of retrieved oocytes, M2oocytes, oocyte maturation rate, fertilization rate, obtained 2PNembryos, implantation rate, clinical pregnancy rate and live birth delivery rates were found significantly higher in dual-triggering group in comparison to single-trigger group among overall expected PORs (p<0.001, p<0.001, p<0.001, p<0.001, p< 0.001, p < 0.001, p = 0.02, p < 0.001 respectively).**	In conclusion triggering oocyte maturation with concomitantinjections of GnRH agonist and hCG in GnRH antagonist cyclesappears to improve IVF outcomes, increase quality of embryos, reduce miscarriage rates, and consequently increase live birth delivery rates in POS 3/4 poor responders.	Moderate
Ren YM, Wang YB, Fu M, Zhang QX, Shen H, Han HJ, et al., Effect of Dual Trigger In Vitro Fertilization and Intracytoplasmic Sperm Injection During the Gonadotropin-releasing Hormone-Antagonist Cycle on Final Oocyte Maturation and Cumulative Live Birth Rate in Women with Diminished Ovarian Reserve. Curr Med Sci. 2022 Oct;42(5):1066–70.	Cohort Study	This retrospective study included patients with DOR who received a GnRH-antagonist protocol during IVF and intracytoplasmic sperm injection (IVF-ICSI) cycles	Oocyte maturation was triggered by GnRH combined with hCG (n=110) or hCG alone (n=71).	The dual trigger treatment did not affect CLBR, which is an overall determinant of the success rate of assisted reproductive technology (ART). Women in the dual trigger group had significantly higher rates of fertilization than those in the hCG group (90.1% vs. 83.9%, P=0.040).	Dual trigger with GnRH agonist and hCG did not improve CLBR in patients with DOR, but did slightly improve fertilization rate, oocyte count, and embryo quality.	Low

11. Embryo Transfer

11.1. Is Elective Freeze All Transfer Beneficial for Efficacy in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Le TMC, Ong PT, Nguyen QA, Roque M. Fresh versus elective frozen embryo transfer: Cumulative live birth rates of 7,236 IVF cycles. JBRA Assist Reprod. 2022 Aug 4;26(3):450-459.	Cohort Study	A total of 7,236 IVF cycles that were followed by a fresh ET or eFET between 2013 and 2017. 10,283 ETs (n=5,639 eFET group; n=4,644 fresh group). Group 1: poor responders (1-3 oocytes); Group 2: suboptimal responders (4-9 oocytes); Group 3: normal responders (10-15 oocytes); Group 4: hyper-responders (>15 oocytes).	Fresh vs frozen embryo transfer A comparison of cumulative outcomes between the eFET (n=4,065 cycles) and the fresh ET groups (n=3,171 cycles)	**In group 1**, there were 351 IVF cycles and 387 ETs in total, and the **CLBR** was 14.3% and 17.7% (p=0.584) for the FET and fresh group, respectively. In **Group 2**, there were 2,074 IVF cycles and 2,465 ET in total, and the **CLBR** was 25.1% and 23.3% (p=0.083) in the FET and fresh group, respectively. There was a significant difference in the CLBR in Groups 3 and 4, favouring the eFET strategy. The **number needed to treat** to achieve one additional live birth was 25.9 in Group 3 and 22.3 in Group 4.	In conclusion, the implementation of the freeze-all strategy should be individualized, as although there are many potential advantages to performing a freeze-all cycle over a fresh ET, it is not ideal for all IVF patients. Based on the present data, it seems reasonable to implement this strategy to improve the CLBR per cycle in patients presenting a hyper or a normal response to COS. Indiscriminate use of the freeze-all strategy may be associated with increased costs, laboratory workflow, and time to live birth.	
Roque M, Valle M, Sampaio M, Geber S. Does freeze-all policy affect IVF outcome in poor ovarian responders? Ultrasound Obstet Gynecol. 2018 Oct;52(4):530-534.	Cohort Study	Patients undergoing IVF treatment between January 2012 and December 2016 at a single centre. 433 POR patients The mean maternal age in the freeze-all group was 39.5 ± 3.6 years and in the fresh ET group	Fresh vs frozen embryo transfer A total of 433 POR (as defined by the Bologna criteria) fulfilled the criteria and were included in the study; of these, 277 patients underwent fresh embryo transfer (ET) and 156 followed the freeze-all	**Mean number of embryos transferred (nET)** was 1.53 ± 0.6 and 1.60 ± 0.6 (p= 0.12) in the freeze-all and fresh ET groups, respectively. **Ongoing pregnancy rate** did not differ significantly between the freeze-all and fresh ET	The freeze-all strategy, compared with fresh ET, had no impact on IVF outcomes in POR patients as defined according to the Bologna criteria.	

		was 39.7 ± 3.8 years (P = 0.54).	policy.	groups (9.6% vs 10.1%, respectively; relative risk (RR), 0.95; 95% CI, 0.52–1.73), **Clinical pregnancy rate** (14.1% vs 13.7%, respectively; RR, 1.03; 95% CI, 0.63–1.67). The implantation rate was 9.6% and 9.8% (p=0.82) in the freeze-all and fresh ET groups, respectively. **Logistic regression analysis-** (including maternal age, antral follicle count, number of retrieved and mature oocytes, nET, and fresh ET vs freeze-all strategy) indicated that maternal age (p<0.001) and nET (P = 0.039) were the only independent variables associated with ongoing pregnancy rate.	Multicentre studies including large numbers of patients should be carried out to confirm the results of this study and reach conclusions about the potential benefits of the freeze-all policy for poor responders.	
Xue Y, Tong X, Zhu H, Li K, Zhang S. Freeze-all embryo strategy in poor ovarian responders undergoing ovarian stimulation for in vitro fertilization. Gynecol Endocrinol. 2018 Aug;34(8):680-683.	Cohort Study	A total of 559 poor responders who met Bologna criteria between January 2012 and December 2014 were included in this study: 256 in the fresh embryo transfer group and 303 in the freeze-all group.	Fresh and frozen embryo transfer	The poor responders treated with fresh embryo transfer and those treated with the freeze-all strategy showed similar **live birth rates per cycle** (12.1% vs. 16.2%, p ¼ .172) and **per transfer** (15.9% vs. 20.9%, p ¼ .182). Multivariate logistic regression analysis showed that **maternal age at retrieval** (odds ratio, 0.919; 95% confidence interval, 0.865–0.977; p=0.006) and **number of good quality embryos transferred** (odds ratio, 1.953; 95% confidence interval, 1.346–2.835; p<0.001) were significantly associated with the **live birth rate**.	In conclusion, freeze-all cycle is an acceptable treatment in poor ovarian responders, and it should be suggested by physicians as an alternative to cycle cancelation in case in which a fresh transfer would not be advantageous. Further studies are needed to determine whether freeze-all cycles work better in these women, to establish the role of freeze-all strategy in poor responders, and to improve its efficacy.	Moderate

12. Oocyte Retrieval and Embryology

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

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Georgiou EX, Melo P, Brown J, Granne IE. Follicular flushing during oocyte retrieval in assisted reproductive techniques. Cochrane Database Syst Rev. 2018 Apr 26;4(4):CD004634.	Meta-Analysis	Ten studies, with a total of 928 women. We included randomised controlled trials (RCTs) that compared follicular aspiration and flushing with aspiration alone in women undergoing ART using their own gametes. Primary outcomes were live birth rate and miscarriage rate per woman randomised.	Assess the safety and efficacy of follicular flushing as compared with aspiration only performed in women undergoing ART.	All included studies reported outcomes per woman randomised. We assessed no studies as being at minimal risk of bias across all domains and found that the main limitation was lack of blinding. Using the GRADE method, we determined that the quality of the evidence ranged from moderate to very low, and we identified issues arising from risk of bias, imprecision, and inconsistency.Comparing follicular flushing to aspiration alone revealed probably little or no difference in the live birth rate (OR 0.95, 95% CI 0.58 to 1.56; three RCTs; n = 303; I2 = 30%; moderate-quality evidence). This suggests that with a live birth rate of approximately 41% with aspiration alone, the equivalent live birth rate with follicular flushing is likely to lie between 29% and 52%. None of the included studies reported on the primary outcome of miscarriage rate.Data show little or no	This review suggests that follicular flushing has little or no effect on live birth rates compared with aspiration alone. None of the included trials reported on effects of follicular aspiration and flushing on the miscarriage rate. Data suggest little or no difference between follicular flushing and aspiration alone with respect to oocyte yield, total embryo number, or number of cryopreserved embryos. In addition, follicular flushing makes little or no difference in the clinical pregnancy rate. Evidence was insufficient to allow	High

				difference in oocyte yield (MD -0.28 oocytes, 95% CI -0.64 to 0.09; six RCTs; n = 708; I2 = 0%; moderate-quality evidence). Very low-quality evidence suggests that the duration of oocyte retrieval was longer in the follicular flushing group than in the aspiration only group (MD 166.01 seconds, 95% CI 141.96 to 190.06; six RCTs; n = 714; I2 = 88%). We found no evidence of a difference in the total number of embryos per woman randomised (MD -0.10 embryos, 95% CI -0.34 to 0.15; two RCTs; n = 160; I2 = 58%; low-quality evidence) and no evidence of a difference in the number of embryos cryopreserved (meta-analysis not possible). Data show little or no difference in the clinical pregnancy rate (OR 1.07, 95% CI 0.78 to 1.46; five RCTs; n = 704; I2 = 49%; moderate-quality evidence). Only two studies reported on adverse outcomes: One reported no differences in patient-reported adverse outcomes (depression, anxiety, and stress), and the other reported no differences in needle blockage, vomiting, and hypotension. No studies reported on safety.	any firm conclusions with respect to adverse events or safety.	
Neumann K, Griesinger G. Follicular flushing in patients with poor ovarian response: a systematic review and meta-analysis. Reprod Biomed Online. 2018 Apr;36(4):408-415.	Systematic Review/Meta-analysis	Effect of follicular flushing on clinical outcomes (primary outcome: mean number of cumulus-oocyte-complexes [COC]) in poor-response IVF patients). Three RCTs with a total of 210 patients could be included. **Mok-Lin et al. 2013**- RCT- 50 Patients **von Horn et al. 2017**- RCT- 80 Patients	Flushing vs. No Flushing- Double lumen vs single lumen 80% power to detect one oocyte difference	The **mean number of COC** did not increase with flushing (weighted mean difference: -0.45 COC, 95% CI -1.14 to 0.25, I2 = 70%; P = 0.21; three RCT, n = 210). **The mean number of metaphase II oocytes** and the proportion of randomized patients having at least one	In conclusion, existing evidence discourages the use of follicular flushing in poor responders.	Low

		Haydardedeoglu et al. 2017- RCT- 80 Patients		COC retrieved were no different between groups. No difference was observed between groups for the **mean number of embryos, the proportion of randomized patients achieving embryo transfer, clinical pregnancy, and live birth rates.** **Procedure duration** was significantly increased with flushing (P = 0.0006).		

12.2. Does Routine Intracytoplasmic Sperm Injection (ICSI) Improve Efficacy or Safety in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Isikoglu M, Ceviren AK, Cetin T, Avci A, Aydinuraz B, Akgul OK, Karaca M. Comparison of ICSI and conventional IVF in non-male factor patients with less than four oocytes. Arch Gynecol Obstet. 2022 Aug;306(2):493-499.	Cohort study	191 cases diagnosed with non-male factor infertility in which ≤ 3 cumulus-oocyte complexes available for fertilisation were analysed **IVF non-male factor** (Group 1, n = 77); **ICSI non-male factor** (Group 2, n =65); **ICSI male factor**-ICSI/MF n =49	ICSI vs IVF	**Fertilisation rate** per collected COC was significantly higher in group 1 compared to the other two groups (85.68%, 72.58%, 73.33% respectively, p=0.004) Both techniques yielded similar **implantation rates** (20.42%, 28.49%, 23.33% respectively, p=0.407) and **live birth rates** (26.8%, 30.6%, 31.1%, respectively, p=0.643).	In the presence of normal semen parameters, a low egg number is not an indication to perform ICSI. The choice of fertilisation method should be based primarily on semen quality, in combination with the patient's previous history regardless of the ovarian reserve.	Low
Supramaniam PR, Granne I, Ohuma EO, Lim LN, McVeigh E, Venkatakrishnan R, Becker CM, Mittal M. ICSI does not improve reproductive outcomes in autologous ovarian response cycles with non-male factor subfertility. Hum Reprod. 2020 Mar 27;35(3):583-594.	Cohort study	272,433 (47.8%) IVF cycles and 297 172 (52.2%) ICSI cycles. **Of these, the POR cohort represented 62 641** stimulated fresh cycles (11.0%): 33 436 (53.4%) IVF cycles and 29 205 (46.6%) ICSI cycles.	ICSI vs IVF	ICSI did not confer any benefit in improving the **LB outcome** when compared to conventional IVF per treatment cycle (PTC) when adjusted for female age, number of previous ART treatment cycles, number of	This is the largest study to date which evaluates the impact of the method of fertilisation in the POR patient and compares this to all	Low

	previous live births through ART, oocyte yield, stage of the transfer, method of fertilisation and number of embryos transferred in the POR cohort (adjusted odds ratio [OR] 1.03, 99.5% confidence interval [CI] 0.96-1.11, p=0.261) The **mean fertilisation rate** was statistically lower for IVF treatment cycles (64.7%) when compared to ICSI treatment cycles (67.2%) in the POR cohort (mean difference -2.5%, 99.5% CI -3.3 to -1.6, p<0.001). **Results in 1-3 oocyte yield group: ICSI vs. IVF** **Live birth rate:** 12.4% vs. 12.2% **Clinical pregnancy rate:** 14.7% vs. 14.8% Adjusted odds ratio- Clinical pregnancy-1.04 (0.97–1.12) Adjusted odds ratio- Live birth- 1.03 (0.96–1.11)	autologous ovarian response categories. The results demonstrate that ICSI does not confer any benefit in improving reproductive outcomes in the absence of male factor subfertility, with no improvement seen in the clinical pregnancy or LB outcomes following a fresh treatment cycle.

12.3. Does Routine Pre-implantation Genetic Testing for Aneuploidies (PGT-A) Improve Efficacy in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Fouks Y, Penzias A, Neuhausser W, Vaughan D, Sakkas D. A diagnosis of diminished ovarian reserve does not impact embryo aneuploidy or live birth rates compared to patients with normal ovarian reserve. Fertil Steril. 2022;118(3):504-512.	Cohort Study (Prospective and Retrospective Study)	Autologous frozen embryo transfer cycles from December 2014 to June 2020 were reviewed. Demographic and clinical factors that impact outcomes were used for propensity score matching (PSM) in a ratio of 2:1 and 4:1 for preimplantation genetic testing for aneuploidy pre-cycle DOR and POR after stimulation, respectively.383 women diagnosed with DOR were	NA	Aneuploid rates did not differ significantly between the two groups (42.2% vs. 41.7%; RR ¼ 1.06; 95% CI, 0.95–1.06). No differences were identified in live birth rates per transfer	Young women diagnosed with DOR or POR exhibited equivalent aneuploidy rates and live birth rates per euploid embryo transfer in a large, matched	Low

		compared with matched controls.		between women with and without DOR after euploid single-embryo transfers (56.0% and 60.5%, respectively). The prevalence of cycles with "no euploid embryos" in the POR cohort was higher (26% vs. 13%); however, rates of cases with a single embryo available for biopsy were lower in the DOR group, relative to controls (11% vs. 31%).	population, based on age, body mass index, and IVF cycle initiation. The lower percentage of cycles with no euploid embryo available for transfer in DOR and POR patients is because of the decreased total number of oocytes/developing embryos and not because of increased aneuploidy rates in these groups.	
Karlıkaya G, Boynukalin FK, Gultomruk M, Kavrut M, Abalı R, Demir B, Ecemis S, Yarkiner Z, Bahceci M. Euploidy rates of embryos in young patients with good and low prognosis according to the POSEIDON criteria. Reprod Biomed Online. 2021 Apr;42(4):733-741.	Cohort Study (Prospective and Retrospective Study)	A total of 133 patients in POSEIDON group 1 (suboptimal responder; female age <35 years, antral follicle count [AFC] ≥5, number of oocytes retrieved <10) (group A), 133 patients in POSEIDON group 3 (expected low responder; female age <35 years, AFC <5) (group B) and 323 in the non-low-prognosis group (female age <35 years, AFC ≥5 and number of oocytes retrieved >9) (group C) were included. The mean female age was significantly higher in group B than in groups A and C (32 [31–34] versus 32 [29.50–33] and 32 [29–33], respectively; P = 0.013). BMI was significantly higher in group C than in groups A and B (24.22 [21.72–26.64] versus 22.92(20.41–26.21] and 23.39 [21.48–25.08], respectively; P = 0.003). In accordance with the logic of the grouping, AFC was lowest in group B, and group A had a lower AFC than group C (4 [2–5], 12 [9–14] and 16 [14–25]; P < 0.001, respectively).	Association between ovarian reserve, ovarian response and embryonic euploidy	There was no significant difference in euploidy rate per embryo among the three groups (61.7% [145/235] for group A versus 53.5% [68/127] for group B versus 62% [625/1008] for group C; P = 0.13). The cancellation rate in cycles without a euploid blastocyst was significantly lower in group C than groups A and B (8.4% versus 12.8% and 16.5%; P = 0.034). Multivariate regression analysis indicated that the ovarian response group did not significantly affect the probability of obtaining a euploid embryo.	These results confirm that POSEIDON group 1 and group 3 and non-low-prognosis patients have different probabilities of euploid embryos being obtained per cycle. However, euploidy rates per embryo are not affected by the patient's ovarian reserve and response.	Very Low

				Trophectoderm score 'C' (odds ratio 0.520, P = 0.007) and inner cell mass score 'C' (odds ratio 0.480, P < 0.001) were associated with a decreased probability of obtaining a euploid embryo.		
Deng J, Hong HY, Zhao Q, Nadgauda A, Ashrafian S, Behr B, Lathi RB. Preimplantation genetic testing for aneuploidy in poor ovarian responders with four or fewer oocytes retrieved. J Assist Reprod Genet. 2020 May;37(5):1147-1154.	Cohort study	All patients had ovarian reserve testing (anti-Mullerian hormone test) within 8 months before IVF treatment. The mean level of AMH was 0.7 ng/ml in the PGT-A group and 0.63 ng/ml in the non-PGT group. Patients in the PGT-A groups were slightly older than patients in the non-PGT group (40.8 vs 39.4, p< 0.001). The patient groups did not differ in BMI, parity, average number of previous miscarriages, and average number of previous failed IVF cycles. Cycles. The most selected protocol was GnRH antagonist (72.3% in the PGT-A group and 71.8% in the non-PGT group). More cycles were using the micro dose flare protocol with GnRH agonist in the PGT-A group compared with the non-PGT group (26.1% vs 16.1%). Clomid and letrozole with or without gonadotropins were used more in the non-PGT group (8.9%) than in the PGT-A group (1.6%). GnRH agonist long protocol was not used in either group. The total dose of gonadotropins was higher in PGT-A groups while the serum peak oestradiol level, the average number of eggs retrieved, and the average number of 2PN zygotes were similar in both groups	Retrospective cohort study of IVF cycles from 2016 to 2019 at a single academic fertility centre. IVF cycles with POR and four or fewer oocytes retrieved were stratified into PGT-A (n=241) and non-PGT (n=112) groups. In PGT-A cycles, trophectoderm biopsy, next-generation sequencing with 24-chromosome screening, and single euploid frozen embryo transfer were performed. In non-PGT cycles, fresh or frozen transfer of untested embryos on day 3 or 5 was performed.	Number of retrieval cycles 241 112 (PGT-A and Non PGT-A) No. of oocytes retrieved 2.7 ± 1.0, 2.5 ± 1.1 p-value=0.062 Fertilization rate 66.2% 63.1% p-value 0.331 No. of 2PNs 1.5 ± 1.1 1.4 ± 1.0 p-value 0.056 Rate of cycles with embryo available for transfer 13.7% (33/241) 70.6% (79/112) p-value < 0.001 No. of embryo transfer cycles 34,79 Clinical pregnancy rate per retrieval 7.1% (17/241) 8.9% (10/112) p-value 0.526 Miscarriage rate per retrieval 0.4% (1/241) 3.6% (4/112) p-value 0.036 Miscarriage rate per pregnancy 5.9% (1/17) 40% (4/10) p-value 0.047 Live birth rate per retrieval 6.6% (16/241) 5.4% (6/112) p-value 0.814	In conclusion, proceeding with PGT-A in extremely poor ovarian responders with four or fewer oocytes retrieved did not provide a better live birth rate per intent-to-treat cycle compared with untested embryo transfers on day 3 or day 5. Overall, the live birth rate and miscarriage rate per retrieval were low in both PGT-A and non-PGT groups. Although PGT-A was associated with reduced odds of miscarriage compared with non-PGT, a substantial number of PGT-A cycles would be needed to prevent one miscarriage in this specific patient population. The decision to proceed with PGT-A in the setting of	Very Low

					low oocyte numbers should consider patient preferences and values as well as the expected outcomes of each decision. Future research regarding patient experience, time to pregnancy, and cost-effectiveness are needed.	

12.4. Does In-Vitro Oocyte Maturation Improve Efficacy in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Liu Y, Jiang H, Du X, Huang J, Wang X, Hu Y, et al., Contribution of rescue in-vitro maturation versus double ovarian stimulation in ovarian stimulation cycles of poor-prognosis women. Reprod Biomed Online. 2020 Apr;40(4):511–7.	Cohort Study	146 women with poor prognosis who received rescue in-vitro maturation (IVM) (n = 50) or double ovarian stimulation (DuoStim) (n = 96)	rescue in-vitro maturation (IVM) (n = 50) or double ovarian stimulation (DuoStim) (n = 96)	The rates of mature oocytes, available embryos, and top-quality embryos from luteal phase stimulation (LPS) of DuoStim were all significantly higher than those derived from the immature oocytes of rescue IVM ($P < 0.05$). The relative contributions of LPS in the DuoStim group for proportion of mature oocytes, available embryos and top-quality embryos were all significantly higher than IVM in	Rescue IVM and DuoStim can contribute more competent oocytes and viable embryos in the shortest possible time for poor-prognosis women, of which DuoStim may be more efficient.	Very Low

				the rescue IVM group (P < 0.001). The overall cancellation rate of no oocyte or available embryo significantly decreased from 30.21% to 9.38% (P < 0.001) when DuoStim was carried out, which decreased from 24.00% to 12.00% with no significant difference in the rescue IVM group when immature sibling oocytes were matured in vitro.		
Braga DP de AF, Figueira R de CS, Ferreira RC, Pasqualotto FF, Iaconelli A, Borges E. Contribution of in-vitro maturation in ovarian stimulation cycles of poor-responder patients. Reprod Biomed Online. 2010 Mar;20(3):335–40.	Cohort Study	The study included 440 patients undergoing intracytoplasmic sperm injection cycles in which fewer than five metaphase II (MII) oocytes and at least one immature oocyte were retrieved after follicle aspiration.	Patients were allocated into two groups based on the injected oocytes' nuclear maturation status: MII group (n=330), in which only embryos derived from MII oocytes were transferred, and RSM group (n=110), in which at least one embryo derived from an RSM oocyte was transferred.	No differences between the MII and RSM groups were observed for pregnancy (16.7% versus 16.5%) or miscarriage (25.5% versus 29.4%) rates, respectively. The RSM group had a higher number of transferred embryos (1.87+/-1.24 versus 2.35+/-1.22; P<0.001), a lower embryo transfer cancellation rate (14.5% versus 6.36%; P=0.025) and lower implantation rate (15.4+/-31.5% versus 10.5+/-22.3%; not significant).	These findings suggest that RSM did not contribute to the outcomes in poor-responder cycles.	Very Low

13.Ovarian Rejuvenation

13.1. Does Intraovarian Platelet Rich Plasma (PRP) Improve Efficacy or Safety in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Cakiroglu Y, Yuceturk A, Karaosmanoglu O, Kopuk SY, Korun ZEU, Herlihy N, Scott RT, Tiras B, Seli E. Ovarian reserve parameters and IVF outcomes in 510 women with poor ovarian response (POR) treated with intraovarian injection of autologous platelet rich plasma (PRP). Aging (Albany NY). 2022 Mar 22;14(6):2513-2523.	Before-After Study	Reproductive age women (N=510; age range 30-45yo) diagnosed with POR based on Poseidon criteria were included in the study.	The intraovarian injection was performed in the operating room under conscious sedation within two hours of PRP preparation. PRP was injected using a 35 cm 17 G single lumen needle (Cook, USA), into at least one ovary transvaginally under ultrasound guidance. Intraovarian injection of PRP was performed within 10 days after completion of menstrual bleeding. The volume of PRP injected was not indicated in the study	AFC: 2.6 ± 1.3 vs. 4.2 ± 2.4 p<0.001 AMH: 0.35 ± 0.32 vs. 0.53 ± 0.39 p<0.001 FSH: No. Mature oocytes: Conception rate: 22 women (4.3%) conceived spontaneously, 14 (2.7%) were lost to follow-up, and 474 (92.9%) attempted IVF. Among women who attempted IVF, 312 (65.8%) generated embryos and underwent embryo transfer, 83 (17.5%) achieved a pregnancy, and 54 (11.4%) achieved sustained implantation/live birth (SI/LB). PRP resulted in an improvement of ovarian reserve parameters, a pregnancy rate of 20.5% and an SI/LB rate of 12.9%.	Our findings suggest that PRP treatment may be considered in women with POR. For wider clinical application, its clinical efficacy will need to be demonstrated in prospective randomized clinical trials.	Very Low
Li X, Liu H, Lin G, Xu L. The effect of ovarian injection of autologous platelet rich plasma in patients with poor ovarian responder: a	Meta-Analysis	10 studies consisting of 793 participants were included in the meta-analysis.	evaluate the effects of ovarian injection of autologous platelet rich plasma (aPRP) on patients	A review of existing evidence showed that intraovarian	The pooled results suggest that intra-ovarian	Low

systematic review and meta-analysis. Front Endocrinol.2023;14:1292168		with poor ovarian responder (POR)	injection of PRP has significant therapeutic effects in increasing levels of anti-Müllerian hormone (AMH) (SMD=0.44,95% CI [0.07,0.81], p=0.02), antral follicle count (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). We compared the relevant data of patients before and after treatment after 2 months of intervention. Ovarian injection of PRP treatment for 2 months has better effects in reducing FSH levels, increasing AMH levels, increasing antral follicle count, and increasing the number of oocytes and embryos (p<0.05). When the dose of PRP injected into each ovary was ≥ 4ml, there was also a significant correlation (p<0.05) with improving the number of AFC, oocytes, and embryos. Significant	injection of PRP can promote ovarian regeneration and improve the reproductive outcomes of patients with ovarian dysfunction. This therapy may have significant clinical potential in improving sex hormone levels, increasing AFC, oocyte count, and embryo count. However, this findings still requires more rigorous and extensive trials worldwide to determine the value of intra-ovarian injection of PRP in POR patients.

				heterogeneity existed among the studies.		
Panda SR, Sachan S, Hota S. A Systematic Review Evaluating the Efficacy of Intra-Ovarian Infusion of Autologous Platelet-Rich Plasma in Patients With Poor Ovarian Reserve or Ovarian Insufficiency. Cureus. 2020 Dec 12;12(12):e12037.	Systematic Review	663 sub-fertile women To study the efficacy of intra-ovarian infusion of autologous PRP on the improvement of ovarian reserve parameters and the subsequent artificial reproductive technique (ART) cycle outcomes in infertile women with poor ovarian reserve or premature ovarian insufficiency Reviewed 4 studies- Cakiroglu et al. 2020- 311 patients Melo et al. 2020- 46 Cases 37 controls Sfakianoudis et al. 2020- 4 cohorts 30 subjects per cohort (POR, POI, perimenopause, and menopause) Sills et al. 2020- 182 patients	Cakiroglu et al. 2020- Injection of approximately 2-4 ml PRP into each ovary was performed under transvaginal ultrasound guidance Melo et al. 2020- 200-µL PRP injection received once between days 7 and 9 of the menstrual cycle for three consecutive cycles (cycles 1, 2, and 3). Sfakianoudis et al. 2020- Injection of approximately 4 ml PRP into each ovary was performed under transvaginal ultrasound guidance. Sills et al. 2020- 1 mL of activated PRP via transvaginal USG guidance	No quantitative meta-analysis	Intra-ovarian PRP infusion appears to be effective in ovarian rejuvenation, and the results of the subsequent intracytoplasmic sperm injection (ICSI) cycle are encouraging. PRP intervention was found to be beneficial in terms of an improvement in ovarian reserve parameters (increase in serum anti-mullerian hormone or antral follicle count or decrease in serum follicular stimulating hormone). ICSI cycle performance in terms of the total number of oocytes retrieved, number of two-pronuclei embryos, fertilization rate, number of cleavage stage embryos, number of good quality embryos, and cycle cancellation rate were found	Very Low

					to be improved after intra-ovarian PRP infusion as compared to their previous cycle without PRP infusion.	

13.2. Does Intraovarian Stem Cell Therapy Improve Efficacy or Safety in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Zafardoust S, Kazemnejad S, Fathi-Kazerooni M, Darzi M, Sadeghi MR, Sadeghi Tabar A, et al., The effects of intraovarian injection of autologous menstrual blood-derived mesenchymal stromal cells on pregnancy outcomes in women with poor ovarian response. Stem Cell Res Ther. 2023 Nov 15;14(1):332.	Cohort Study	180 infertile individuals with POR who declined oocyte donation.	Those who received bilateral MenSCs intraovarian injection and those who received no intervention.	The MenSC therapy exhibited a favourable tolerability profile and did not raise any safety concerns. Following the 2-month follow-up period, women who received MenSC treatment demonstrated a significantly higher rate of spontaneous pregnancy (P < 0.005) and an improvement in anti-Müllerian hormone (AMH) levels (P = 0.0007) and antral follicle count (AFC) (P < 0.001), whereas the control group demonstrated a considerable decline in these parameters (Both P < 0.001). The MenSC therapy led to a greater number of mature oocytes and embryos among women who underwent ICSI/IVF. Our age subgroup	The results of our study indicate that MenSCs treatment may be a viable option for treating women experiencing POR. However, to be widely implemented in clinical practice, the clinical effectiveness of MenSCs therapy will need to be established through rigorous prospective randomized clinical trials.	Very Low

				analysis demonstrated a significant difference in the number of spontaneous pregnancies and ICSI/IVF outcomes between the treatment and control groups only among individuals below 40 years of age.		
Tandulwadkar S, Karthick MS. Combined Use of Autologous Bone Marrow-derived Stem Cells and Platelet-rich Plasma for Ovarian Rejuvenation in Poor Responders. J Hum Reprod Sci. 2020;13(3):184-190.	Cohort Study (Prospective and Retrospective Study)	The inclusion criteria were as follows 1. Age group of 20–45 years 2. Poor responder POSEIDON[22] Group 3 and 4 (the expected poor responder group where AFC <5 and anti- Mullerian hormone (AMH) <1.1 ng/ml) 3. Normal karyotype. 4. Normal semen parameters.	Synergistic effect of ABMDSCs with PRP 150 ml of bone marrow was aspirated. Sixteen-milliliter BMDSC was separated using the fully automated cell separator, which uses optical sensor technology and simultaneous application of centrifugation and sedimentation. Stem cell count (using flow cytometer and hemocytometer) varies from 05 million to 13 million cells per ml of the final stem cell concentrate. Around 20 ml of peripheral blood in the heparinized syringe was taken and 2 ml of PRP was prepared after double centrifugation. This was mixed with 16 ml of ABMDSCs. Intraovarian instillation was performed either transvaginally USG guided or laparoscopically. Inject up to 06 ml of ABMDSCs per ovary at multiple sites along the long axis of the ovary.	No patient had instillation- related adverse effects. The **total AFC increase** was statistically significant (P = 0.0001) 3.35±0.98 preinstillation versus 5.7±1.75 post installation also observed an **increase in AMH values** in a few patients, but it was not statistically significant (P = 0.584) 5.7±1.75 versus 0.632±0.205 The study indicated a correlation between the AFC increase and the oocytes retrieved 0.763 (no p-value or CI provided)	In conclusion, intraovarian instillation of ABMDSCs combined with PRP is safe and efficacious. It could represent a paradigm shift for fertility treatment for poor responders. Further work is needed to validate results in a larger and homogeneous population, before considering ABMDSCs or PRP as a real alternative to managing poor responder patients. Increased understanding of its mechanism will promote its wide clinical application and give a ray of hope to infertile	Very Low

					couples who do not wish to opt for donor- assisted reproductive techniques.	
Herraiz S, Romeu M, Buigues A, Martínez S, Díaz-García C, Gómez-Seguí I, Martínez J, Pellicer N, Pellicer A. Autologous stem cell ovarian transplantation to increase reproductive potential in patients who are poor responders. Fertil Steril. 2018 Aug;110(3):496-505.e1	Cohort Study (Prospective and Retrospective Study)	Seventeen women who are poor responders.	An SC dose of 10 mg/kg/d of G-CSF was administered during 5 days. On the fifth day, stem cell collection was performed if patients reached a threshold of CD34+ circulating cells in peripheral blood >=10 cells/microL. Cell collection was performed using standard procedures, including continuous flow apheresis in an OPTIA cell separator (Caridian). The target was to reach a minimum of 4 x 10^6 CD34+ cells/kg. Samples were immediately analyzed by flow cytometry after collection to quantify the CD133+ population. A volume of whole apheresis containing 50 x 10^6 CD133+ cells was then prepared for infusion. Patients were referred to the Interventional Radiology Unit for delivery of the apheresis concentrates to the ovarian artery by intra-arterial catheterization.	**Previous vs. After ASCOT** **Antral follicles (total)** 4±1.9 5.8±1.7 (p value 0.036) **Antral follicles total- Infused ovary** 1.9 ±0.7 2.9 ±1.4 (p-value 0.026) Women displayed an **increase in total AFC of three or more follicles** after ASCOT **and/or** showed two consecutive increases **(+2 SD) in AMH level**. Using these criteria, the ovarian reserve improved in 13 of the 16 patients (81.3%) **AMH pmol:** 1.0 (0.9–3.0) vs. 2.8 (0.7–3.7) p-value <0.001	Our results suggest that ASCOT optimized the mobilization and growth of existing follicles, related to fibroblast growth factor-2 and thrombospondin-1 within apheresis. The ASCOT improved follicle and oocyte quantity enabling pregnancy in women who are poor responders previously limited to oocyte donation.	Low

13.3. Does In-Vitro Activation of Ovarian Tissue Improve Safety and Efficacy in Poor Responders?

Article citation	Type of Study	Patient	Intervention	Effect Size	Conclusion	Quality
Lunding SA, Pors SE, Kristensen SG, Landersoe SK, Jeppesen JV, Flachs EM, Pinborg A, Macklon KT, Pedersen AT, Andersen CY,	Cohort Study	20 women with DOR were treated at the fertility clinic, in Rigs Hospital, Denmark, from April 2016–December 2017.	Patients were randomized to have four biopsies taken from either the left or the right ovary by laparoscopy followed by fragmentation of the cortical tissue to an approximate size of 1 mm3 and autotransplanted to a peritoneal pocket. The other	No difference in the **number of mature follicles after ovarian stimulation 10 weeks after the procedure** in the biopsied versus the control ovaries was observed (1.0 vs. 0.7 follicles, P = 0.35). In only three patients, **growth of four follicles was detected at**	Although 12 out of 20 patients became pregnant during the follow-up period, the current study does not indicate that biopsying, fragmenting and autotransplanting of ovarian cortical tissue increase the number of recruitable follicles	Low

Andersen AN. Biopsying, fragmentation and autotransplantation of fresh ovarian cortical tissue in infertile women with diminished ovarian reserve. Hum Reprod. 2019 Oct 2;34(10):1924-1936		Non-pregnant patients were on average followed for 280 days (range 118–408), while women who conceived were followed until delivery. The study included infertile women aged 30–39 years with preserved menstrual cycles, indication for IVF/ICSI and repeated serum measurements of anti-Müllerian hormone (AMH) ≤ 5 pmol/L.	ovary served as a control.	**the graft site** 24–268 days after the procedure. From one of these follicles, a metaphase II (MII) oocyte was retrieved and fertilized, but embryonic development failed. Overall **AMH levels** did not change significantly after the procedure (P = 0.2). The **AFC increased by 0.14 (95% CI: 0.06;0.21) per week (P < 0.005)**, and the biopsied ovary had on average 0.6 (95% CI: 0.3;−0.88) follicles fewer than the control ovary (P = 0.01). **Serum levels of androstenedione and testosterone** increased significantly by 0.63 nmol/L (95% CI:0.21;1.04) and 0.11 nmol/L (95% CI: 0.01;0.21) 1 week after the procedure, respectively, and testosterone increased consecutively over the 10 weeks by 0.0095 nmol/L (95% CI: 0.0002;0.0188) per week (P = 0.045). In 7 of the 20 patients, there was a **serum AMH elevation 5 to 8 weeks after the procedure**. In this group, mean AMH increased from 2.08 pmol/L (range 1.74–2.34) to 3.94 pmol/L (range 3.66–4.29) from Weeks 1–4 to Weeks 5–8. A **clinical pregnancy was obtained in 12 of the 20 (60%) patients** with and without medically assisted reproduction (MAR) treatments. A **cumulated live birth rate per started IVF/ICSI cycle of 18.4%.**	for IVF/ICSI after 10 weeks. However, a proportion of the patients may have a follicular response in Weeks 5–8 after the procedure. It could therefore be relevant to perform a future study on the possible effects of biopsying per se that includes stimulation for IVF/ICSI earlier than week 10.	
Díaz-García C, Herraiz S, Pamplona L, Subirá J, Soriano MJ, Simon C, et al., Follicular activation in women previously diagnosed with poor ovarian	Randomized Controlled Trial	Thirty-four women with POR according to the European Society of Human Reproduction and Embryology criteria.	Women with POR were randomly allocated to receive ovarian fragmentation in 1 ovary or to no intervention (control group). Ovarian reserve markers were followed at 2-week intervals for 6 months. In vitro fertilization cycles were initiated when the antral follicle count (AFC) doubled or at the end of	Ovarian fragmentation for follicular activation resulted in an increase in AFC in the intervention ovary compared with the control ovary and an increase in total AFC in the OFFA group compared with controls. Serum antimüllerian hormone and follicle-stimulating-hormone levels did not improve in the OFFA group throughout the	Ovarian fragmentation for follicular activation in women with POR resulted in an increase in AFC but did not modify IVF outcomes when compared with controls.	Very Low

response: a randomized, controlled trial. Fertil Steril. 2022 Apr;117(4):747–55.	follow-up.	follow-up period. Fifteen patients from each arm underwent IVF. In the control group, 33 MII oocytes were retrieved and 18 embryo transfers were performed, with a 20% pregnancy rate and an 18.7% live birth rate per cycle. In the OFFA group, 23 MII oocytes were retrieved and 11 embryo transfers were performed, with a 13.3% pregnancy rate and a 6.7% live birth rate per cycle. Reproductive outcomes did not significantly differ between the groups. Hippo pathway inhibition was confirmed by an 18.8% reduction in the phospho-YAP/YAP (Yes-associated protein 1) ratio and BIRC and CCN overexpression after fragmentation.