e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(8); 1759-1765

Original Research Article

Association between Adjuvant Use and IVF Outcomes in Women Classified Under POSEIDON Groups 3 and 4: A Prospective Observational Cohort Study

Diksha Kumari Chittara[1], Anil Gurjar[2], Saumya Bhagat[3]

[1]Associate Consultant, SPARSH IVF, Udaipur, Rajasthan, India
[2]Professor, Department of OBGY, SMS Medical College, Jaipur, Rajasthan, India
[3]Resident Doctor, Department of OBGY, SMS Medical College, Jaipur, Rajasthan, India

Received: 01-05-2026 / Revised: 15-06-2026 / Accepted: 21-07-2026
Corresponding author: Dr. Diksha Kumari Chittara
Conflict of interest: Nil

Abstract

Background: Women classified under POSEIDON groups 3 and 4 have diminished ovarian reserve and a low probability of achieving live birth following in vitro fertilization. Several adjuvant therapies are used to improve ovarian response and reproductive outcomes. Objective: To evaluate the association between adjuvant use and IVF outcomes among women classified under POSEIDON groups 3 and 4.

Methods: This prospective observational cross-sectional study included 120 women undergoing autologous IVF or intracytoplasmic sperm injection at SPARSH IVF, Udaipur, Rajasthan, India. Participants were recruited consecutively from August 2026 to January 2027 and followed until their final reproductive outcome. Women were categorized according to whether they received any adjuvant in addition to standard ovarian stimulation. Risk ratios with 95% confidence intervals were calculated.

Results: Of the 120 participants, 72 received at least one adjuvant and 48 received no adjuvant. Clinical pregnancy occurred in 36.1% and 25.0% of participants, respectively (risk ratio [RR], 1.44; 95% confidence interval [CI], 0.81–2.58; P=0.200). Live-birth rates were 29.2% with adjuvant use and 18.8% without adjuvant use (RR, 1.56; 95% CI, 0.78–3.10; P=0.197). After adjustment for POSEIDON group and previous IVF treatment, adjuvant use was not significantly associated with live birth. Live birth was numerically more frequent in POSEIDON group 3 than in group 4 (34.2% vs 20.7%), although the difference was not statistically significant. No clear differences in cycle cancellation or adverse outcomes were observed.

Conclusion: Adjuvant use was associated with numerically higher clinical-pregnancy and live-birth rates, but the estimates were imprecise and did not demonstrate a statistically significant benefit. These exploratory findings do not establish adjuvant efficacy. Larger prospective studies using standardized interventions are required to identify whether specific adjuvants benefit selected POSEIDON subgroups.

Keywords: Adjuvant therapy; Diminished ovarian reserve; In vitro fertilization; Live birth; POSEIDON classification.

DOI: 10.25258/ijcpr.18.8.260

Introduction

Poor ovarian response remains one of the most difficult problems in assisted reproductive technology (ART) because a limited follicular cohort restricts the number of oocytes and embryos available from each stimulation cycle. The POSEIDON (Patient-Oriented Strategies Encompassing IndividualizeD Oocyte Number) classification reframed this condition as a low-prognosis state by integrating female age, ovarian-reserve markers, and previous response to stimulation. [1,2] Within this framework, groups 3 and 4 comprise women with a low antral follicle count or anti-Müllerian hormone concentration before treatment; group 3 includes women younger than 35 years, whereas group 4 includes those aged 35 years or older. This age distinction is clinically important because reduced oocyte quantity affects both groups, while increasing age adds a higher probability of embryonic aneuploidy and further reduces reproductive potential. The therapeutic aim in these patients is not simply to increase follicle numbers, but to obtain enough competent oocytes to generate at least one transferable euploid embryo within the shortest reasonable time.1 Nevertheless, observational evidence consistently indicates poorer outcomes in groups 3 and 4 than in women

with an adequate ovarian reserve, with group 4 generally having the least favorable prognosis. [3] Increasing gonadotropin exposure cannot create new recruitable follicles, and conventional, mild, or repeated stimulation strategies have not consistently produced superior live-birth outcomes across all low responders. Consequently, various pharmacological adjuvants have been introduced in an attempt to enhance follicular sensitivity, oocyte competence, embryo development, or endometrial receptivity.

The principal adjuvants proposed for expected poor responders include recombinant luteinizing hormone, dehydroepiandrosterone or testosterone, growth hormone, aromatase inhibitors, and antioxidants such as coenzyme Q10. [4] Androgenic interventions and luteinizing hormone may increase intraovarian androgen activity and follicle-stimulating hormone receptor expression, whereas growth hormone may modify insulin-like growth factor signaling. Coenzyme Q10 has been investigated as a means of supporting mitochondrial bioenergetics and reducing oxidative stress during oocyte development. [4,5] These mechanisms are plausible, but improvements in gonadotropin consumption, oocyte yield, or embryo morphology cannot be assumed to translate into a higher cumulative live-birth rate.

In young women classified in POSEIDON group 3, coenzyme Q10 pretreatment increased oocyte yield and favorable embryo measures, but the trial did not establish a significant improvement in clinical pregnancy or live birth.5 A matched retrospective analysis associated growth-hormone pretreatment with improved fresh-transfer live birth among women in group 4, but not group 3; its non-randomized design and differential disposition of cycles before fresh transfer limit causal interpretation.6 More broadly, randomized evidence concerning hormonal add-ons is characterized by small samples, heterogeneous definitions of poor response, variable regimens, and low or very low certainty. [7] Reflecting these limitations, current ovarian-stimulation guidance does not recommend routine dehydroepiandrosterone use and considers growth hormone and testosterone insufficiently supported for low responders. [8] Evidence specific to POSEIDON groups 3 and 4 therefore remains inadequate to determine whether adjuvant therapy improves outcomes that matter to patients, particularly cumulative live birth per initiated cycle. Age-stratified evaluation is essential because an intervention that modifies ovarian response in younger women may not overcome age-related loss of oocyte competence in older women. Accordingly, the present study aimed to evaluate the association between ovarian-stimulation adjuvants and oocyte yield, embryo development, clinical pregnancy, and live birth in POSEIDON groups 3 and 4.

Materials and Methods

This prospective observational cross-sectional study was conducted at the infertility clinic of SPARSH IVF, Udaipur, and Rajasthan, India. Participants were recruited consecutively from August 2026 to January 2027. Follow-up continued beyond the recruitment period until the final reproductive outcome was documented for each participant.

Women classified as POSEIDON group 3 or 4 who underwent controlled ovarian stimulation for an autologous IVF or intracytoplasmic sperm injection cycle were eligible. POSEIDON group 3 included women aged <35 years with diminished ovarian reserve, whereas group 4 included women aged ≥35 years with diminished ovarian reserve. Diminished ovarian reserve was defined as an anti-Müllerian hormone concentration <1.2 ng/mL and/or an antral follicle count <5.

Only the first eligible treatment cycle of each woman during the study period was included. Women undergoing donor-oocyte, fertility-preservation or gestational-surrogacy cycles were excluded. Repeat treatment cycles from the same woman and cycles with incomplete treatment or outcome documentation were also excluded.

A sample of 120 eligible women was enrolled using consecutive sampling. The sample size was determined according to the expected number of eligible women attending the centre during the six-month recruitment period. As the study included several adjuvant therapies, it was designed primarily to evaluate the association between the use of any adjuvant and IVF outcomes rather than the comparative efficacy of individual adjuvants.

Participants were classified into an adjuvant group and a no-adjuvant group according to the treatment received during the index cycle. Adjuvant therapies included growth hormone, coenzyme Q10, androgen pretreatment, letrozole cotreatment, supplemental recombinant luteinizing hormone and combinations of these interventions. Recombinant luteinizing hormone was classified as an adjuvant only when administered as supplementation beyond the centre's standard stimulation regimen. The selection of adjuvant therapy and stimulation protocol was made by the treating clinician according to age, ovarian reserve, previous treatment response and routine clinical practice. Treatment allocation was not randomized and was not influenced by study participation.

Baseline variables included age, body mass index, residence, education, employment, duration and type of infertility, previous pregnancy, previous

IVF treatment, ovarian surgery and relevant medical conditions. Ovarian-reserve variables included serum anti-Müllerian hormone, antral follicle count and basal follicle-stimulating hormone.

Treatment-related variables included the ovarian-stimulation protocol, type and total dose of gonadotropin, duration of stimulation, ovulation-trigger method, endometrial thickness, and number of oocytes retrieved, metaphase-II oocytes, normally fertilized two-pronuclear embryos, transferable and good-quality embryos, fertilization method, embryo-transfer characteristics and cycle cancellation. Data were recorded prospectively using a standardized case-record form and verified against clinical, laboratory and embryology records.

The primary outcome was live birth per initiated cycle, defined as the delivery of at least one living infant after 24 completed weeks of gestation. Multiple infants resulting from the same pregnancy were counted as one live-birth event. Secondary outcomes included the numbers of retrieved and metaphase-II oocytes, fertilization rate, normally fertilized embryos, good-quality embryos, cycle cancellation, biochemical pregnancy, clinical pregnancy, ongoing pregnancy, miscarriage, ectopic pregnancy, multiple pregnancy and moderate or severe ovarian hyperstimulation syndrome.

Clinical pregnancy was defined as ultrasonographic identification of at least one intrauterine gestational sac. Ongoing pregnancy was defined as a viable intrauterine pregnancy beyond 12 completed gestational weeks. Pregnancy outcomes were calculated per initiated cycle. Fertilization rates were calculated using the number of inseminated or injected mature oocytes as the denominator. Miscarriage and multiple-pregnancy rates were calculated among clinical pregnancies. Written informed consent was obtained from all participants before enrolment. Participant information was coded and analysed without direct personal identifiers.

Statistical Analysis: Data were analysed using SPSS version 27.0. Continuous variables were summarized as mean ± standard deviation when approximately normally distributed and as median with interquartile range when skewed. Categorical variables were presented as frequency and percentage. The adjuvant and no-adjuvant groups were compared using the independent-samples t test or Mann–Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Pregnancy and live-birth outcomes were expressed as risk ratios with 95% confidence intervals. All tests were two-sided, and $P<0.05$ was considered statistically significant.

Results

[Table -1] Among the 120 participants, 82 (68.3%) were aged ≥35 years, while 38 (31.7%) were younger than 35 years. Most resided in urban areas (65.0%), and 75.8% had completed graduate or postgraduate education. Slightly more than half of the participants were employed (55.8%).

[Table -2] Baseline clinical and ovarian-reserve characteristics were comparable between participants who received an adjuvant and those who did not. No statistically significant between-group differences were observed in age, body mass index, infertility duration, infertility type, POSEIDON classification, serum AMH, AFC, basal FSH or baseline estradiol. Previous IVF treatment was more frequent in the adjuvant group than in the no-adjuvant group (54.2% versus 41.7%), although this difference was not statistically significant (P=0.180).

Of the 120 participants, 72 (60.0%) received at least one adjuvant, whereas 48 (40.0%) received no adjuvant. Growth hormone was the most frequently used individual adjuvant (16.7%), followed by coenzyme Q10 (13.3%) and recombinant luteinizing hormone supplementation (10.8%). The proportion of participants receiving any adjuvant was similar in POSEIDON groups 3 and 4 (60.5% versus 59.8%; P=0.936).

[Table -3] Ovarian-stimulation and procedural characteristics were broadly comparable between the exposure groups. The median total gonadotropin dose was numerically lower among participants receiving an adjuvant than among those receiving no adjuvant (2,950 versus 3,100 IU), although the difference was not statistically significant (P=0.290). The median duration of stimulation was 10 days in both groups. The proportions of participants managed using a GnRH-antagonist protocol, dual trigger or ICSI were also similar between groups. Embryo transfer was performed in 87.5% of the adjuvant group and 83.3% of the no-adjuvant group (P=0.521). Mean endometrial thickness did not differ significantly between groups (9.3 ± 1.7 versus 9.1 ± 1.8 mm; P=0.544).

[Table-4] Participants receiving an adjuvant had numerically higher numbers of retrieved oocytes and metaphase-II oocytes than those receiving no adjuvant. The numbers of normally fertilized embryos and good-quality embryos were also numerically higher in the adjuvant group. However, none of the ovarian-response or embryological outcomes differed significantly between the groups. Cycle-cancellation rates were comparable (8.3% versus 10.4%; P=0.753). Biochemical pregnancy,

clinical pregnancy, ongoing pregnancy and live birth were more frequent among participants receiving an adjuvant. The live-birth rate was 29.2% in the adjuvant group and 18.8% in the no-adjuvant group (RR, 1.56; 95% CI, 0.78–3.10; P=0.197). None of the reproductive-outcome comparisons reached statistical significance. Of the 120 women included in the study, clinical pregnancy was achieved in 16 women in group 3 and 22 women in group 4, and the difference did not reach statistical significance (RR, 1.57; 95% CI, 0.94–2.63; P=0.087). Ongoing pregnancy was seen in 14 women in POSEIDON group 3 and 19 women in group 4.

The estimated probability of ongoing pregnancy was higher in group 3, but the estimate remained imprecise (RR, 1.59; 95% CI, 0.89–2.83; P=0.117). Similarly, live birth occurred in 13 women in group 3 (34.2%) compared with 17 women in group 4 (20.7%). This corresponded to a relative risk of 1.65 for group 3 compared with group 4 (95% CI, 0.90–3.04; P=0.113). Among the 38 women in group 3, 23 received at least one adjuvant and 15 received no adjuvant. Live birth occurred in 9 of the 23 women receiving an adjuvant (39.1%) and in 4 of the 15 women receiving no adjuvant (26.7%). the association was not statistically significant (RR, 1.47; 95% CI, 0.55–3.91; P=0.501). Among the 82 women in POSEIDON group 4, 49 received an adjuvant and 33 received no adjuvant. Live birth was achieved by 12 women in the adjuvant group (24.5%) and 5 women in the no-adjuvant group (15.2%), this association was not statistically significant was (RR, 1.62;95% CI, 0.63–4.16; P=0.408) [Table-5] Clinical pregnancy and live birth occurred in 31.7% and 25.0% of participants, respectively.

The numerically highest unadjusted rates were observed with growth hormone (45.0% and 35.0%), followed by coenzyme Q10 (37.5% and 31.3%) and androgen pretreatment (36.4% and 27.3%). Corresponding live-birth rates were 23.1% with recombinant luteinizing hormone, 28.6% with letrozole, 20.0% with multiple adjuvants and 18.8% without adjuvant therapy. No statistically significant variation among adjuvant categories for clinical pregnancy (P=0.766) or live birth (P=0.831).

Table 1: Baseline sociodemographic characteristics of the study participants (N=120)

Characteristic	Category	Frequency	Percentage
Age group (years)	20–29	11	9.2
	30–34	27	22.5
	35–39	43	35.8
	≥40	39	32.5
Residence	Urban	78	65
	Rural	42	35
Educational level	Up to secondary education	29	24.2
	Graduate	61	50.8
	Postgraduate	30	25
Employment status	Employed	67	55.8
	Not employed	53	44.2

Table 2: Baseline clinical and ovarian-reserve characteristics according to adjuvant exposure (N=120)

Characteristic	Any adjuvant (n=72)	No adjuvant (n=48)	P value
Age (years)	37.5 ± 4.2	36.8 ± 4.5	0.393
BMI (kg/m²)	24.9 ± 3.4	25.3 ± 3.7	0.551
Duration of infertility (years)	5.2 ± 3.0	4.8 ± 2.7	0.449
Primary infertility, n (%)	54 (75.0)	34 (70.8)	0.613
Previous IVF attempt, n (%)	39 (54.2)	20 (41.7)	0.18
POSEIDON group 4, n (%)	49 (68.1)	33 (68.8)	0.936
AMH (ng/mL)	0.72 (0.46–0.98)	0.76 (0.49–1.01)	0.621
AFC	4 (3–5)	4 (3–5)	0.884
Basal FSH (IU/L)	10.8 (8.7–13.6)	10.4 (8.5–13.0)	0.552
Baseline estradiol (pg/mL)	42 (31–55)	40 (30–53)	0.647

Table 3: Ovarian-stimulation and procedural characteristics according to adjuvant exposure (N=120)

Characteristic	Any adjuvant (n=72)	No adjuvant (n=48)	P value
Total gonadotropin dose (IU), median (IQR)	2,950 (2,400–3,600)	3,100 (2,500–3,825)	0.29
Duration of ovarian stimulation (days), median (IQR)	10 (9–11)	10 (9–12)	0.41
GnRH-antagonist protocol, n (%)	51 (70.8)	35 (72.9)	0.804
Dual trigger, n (%)	24 (33.3)	14 (29.2)	0.632
ICSI performed, n (%)	59 (81.9)	38 (79.2)	0.705
Embryo transfer performed, n (%)	63 (87.5)	40 (83.3)	0.521
Endometrial thickness (mm), mean ± SD	9.3 ± 1.7	9.1 ± 1.8	0.544

Table 4: Ovarian-response, embryological and reproductive outcomes according to adjuvant exposure (N=120)

Outcome	Any adjuvant (n=72)	No adjuvant (n=48)	Risk ratio (95% CI)	P value
Ovarian-response and embryological outcomes				
Oocytes retrieved, median (IQR)	4 (2–5)	3 (2–5)	—	0.18
Metaphase-II oocytes, median (IQR)	3 (2–4)	3 (1–4)	—	0.22
Normally fertilized 2PN embryos, median (IQR)	2 (1–3)	2 (1–3)	—	0.31
Good-quality embryos, median (IQR)	1 (0–2)	1 (0–2)	—	0.25
Fertilization rate, n/N (%)	154/211 (73.0)	93/132 (70.5)	—	0.613
Cycle cancellation, n (%)	6 (8.3)	5 (10.4)	0.80 (0.26–2.47)	0.753
Pregnancy and live-birth outcomes				
Biochemical pregnancy, n (%)	31 (43.1)	15 (31.3)	1.38 (0.84–2.27)	0.193
Clinical pregnancy, n (%)	26 (36.1)	12 (25.0)	1.44 (0.81–2.58)	0.2
Ongoing pregnancy, n (%)	23 (31.9)	10 (20.8)	1.53 (0.80–2.94)	0.182
Live birth, n (%)	21 (29.2)	9 (18.8)	1.56 (0.78–3.10)	0.197

Table 5: Clinical pregnancy and live birth according to individual adjuvant exposure

Category	Participants	Clinical pregnancy	Live birth
No adjuvant	48	12 (25.0)	9 (18.8)
Growth hormone	20	9 (45.0)	7 (35.0)
Coenzyme Q10	16	6 (37.5)	5 (31.3)
Androgen pretreatment	11	4 (36.4)	3 (27.3)
Recombinant LH	13	4 (30.8)	3 (23.1)
Letrozole cotreatment	7	2 (28.6)	2 (28.6)
Multiple adjuvants	5	1 (20.0)	1 (20.0)
Total	120	38 (31.7)	30 (25.0)

Discussion

Approximately two-thirds of the participants were aged 35 years or older and were consequently classified as POSEIDON group 4, because diminished ovarian reserve becomes increasingly prevalent with advancing reproductive age. The POSEIDON framework separates groups 3 and 4 at 35 years because age is an important surrogate for oocyte competence and embryonic aneuploidy, whereas both groups have a reduced recruitable follicular cohort. [1,2] The finding is consistent with previously published articles showing that group 4 may constitute more than half of the POSEIDON population in some fertility centres. [5,10]

Baseline age, body mass index, duration and type of infertility, POSEIDON classification, AMH, AFC, basal FSH, and estradiol were similar between women who received an adjuvant and those who did not. The median AMH concentration was below 1.0 ng/mL and the median AFC was four in both groups. These ovarian-reserve findings were consistent with the eligibility thresholds used in the POSEIDON definition and in previous investigations of groups 3 and 4. [2,5,7] Cai et al included women with AMH below 1.2 ng/mL in their matched retrospective evaluation of growth-hormone pretreatment.[6] Xu et al. similarly investigated young women with reduced ovarian reserve classified under POSEIDON group 3. [6]

Previous IVF treatment was more frequent among adjuvant users, although the difference was not statistically significant. Previous treatment failure may have influenced the clinician's decision to prescribe an adjuvant. Women with a poorer previous response may have been more likely to receive additional therapy.

Sixty per cent of participants received at least one adjuvant, with growth hormone being the most frequently used, followed by coenzyme Q10 and supplemental recombinant luteinizing hormone. The similar prevalence of adjuvant uses in POSEIDON groups 3 and 4 suggested that chronological age alone did not determine treatment allocation. The variety of interventions reflected the absence of a universally accepted adjuvant regimen for expected poor responders. These treatments have different proposed mechanisms and should not be regarded as a biologically homogeneous exposure. Growth hormone may influence follicular development through insulin-like growth factor signalling, CoQ10 may support mitochondrial bioenergetics, androgens may increase intraovarian androgen activity and FSH-receptor expression, and recombinant LH may support steroidogenesis and follicular maturation. [5]

Stimulation duration, use of a GnRH-antagonist protocol, dual triggering, ICSI, embryo transfer, and endometrial thickness were comparable between exposure groups. The median gonadotropin requirement was 150 IU lower in adjuvant users, but the difference was not statistically significant.

A numerically lower gonadotropin requirement could indicate increased follicular sensitivity, but it could also reflect differences in clinical prescribing rather than a pharmacological effect. Because the stimulation protocol and adjuvant treatment were selected simultaneously by clinicians.

Kahraman and Tulek reported lower total gonadotropin requirements with letrozole cotreatment in both POSEIDON groups 3 and 4. [10] In contrast, Le et al found that conventional stimulation produced better follicular and embryological outcomes than mild stimulation among some group 4 women, particularly those with AFC of at least three, whereas outcomes were similar when AFC was below three.11 These findings suggest that the relationship between gonadotropin exposure and treatment outcome may depend on the extent of residual ovarian reserve.

The comparable endometrial thickness and embryo-transfer rates in the present study suggested no adverse effect of pooled adjuvant exposure on endometrial development or the likelihood of transfer. 103 women underwent embryo transfer and 11 cycles were cancelled, leaving six initiated cycles without transfer that were not classified as cancelled. Adjuvant users had a median of four retrieved oocytes compared with three among non-users, while the median number of mature oocytes was three in both groups. Normally fertilized and good-quality embryo counts were also similar. These results did not demonstrate a statistically significant improvement in ovarian response or embryo production with pooled adjuvant use.

The direction of the ovarian-response findings was partly consistent with the randomized trial by Xu et al [5], in which 60-day CoQ10 pretreatment in 186 POSEIDON group 3 women improved ovarian response and embryological measures. However, that trial was not adequately powered to demonstrate improvement in clinical pregnancy or live birth.

Cai et al [6] reported more good-quality embryos and a higher live-birth rate among growth-hormone-treated women in POSEIDON group 4, whereas no corresponding live-birth benefit was found in group 3. That study included 676 matched retrospective cycles, but its non-randomized design and analysis of treatment-stage subgroups limited causal interpretation. The present findings were similar in showing a direction favouring adjuvant use but differed because no statistically significant association was observed.

Biochemical pregnancy, clinical pregnancy, ongoing pregnancy, and live birth were consistently more frequent among adjuvant users.

Recent evidence syntheses have suggested possible improvements in selected outcomes with some add-on treatments. [7] Correspondingly, the updated ESHRE ovarian-stimulation guideline does not support the routine use of growth hormone, testosterone, or DHEA for low responders because convincing evidence of improved clinically important outcomes remains insufficient. [8]

The cycle-cancellation rates were similar between groups. This finding was consistent with a network meta-analysis of adjuvant therapies for poor ovarian response that did not demonstrate a clear reduction in cancellation across the evaluated interventions. [12] Cancellation depends not only on follicular response but also on clinician and patient decisions.

Clinical pregnancy, ongoing pregnancy, and live birth were numerically more frequent in group 3 than in group 4. The live-birth rate was 34.2% in group 3 and 20.7% in group 4, although the difference was not statistically significant.

Both groups have reduced ovarian reserve, but women in group 4 also experience an age-related

decline in oocyte competence and an increase in embryonic aneuploidy. Published POSEIDON analyses have consistently demonstrated lower cumulative live-birth rates in group 4 than in group 3. In a large retrospective analysis summarized by Roque et al, cumulative live-birth rates were approximately 35.5% in group 3 and 12.7% in group 4.9 Li et al also found that cumulative live-birth rates increased over successive cycles but remained substantially lower in group 4. [13]

Live birth was more frequent among adjuvant users. However, the subgroup estimates were highly imprecise. Cai et al [6], who observed a growth-hormone-associated benefit predominantly in group 4, and from Kahraman and Tulek, who reported significantly higher implantation, clinical-pregnancy, and live-birth rates with letrozole mainly in group 3.10 These differences may reflect intervention-specific effects, different treatment regimens, retrospective selection, sample size, and residual confounding.

Growth hormone had the highest observed clinical-pregnancy and live-birth rates, followed by CoQ [10] and androgen pretreatment, and differences between treatment categories were not statistically significant. The pattern for growth hormone was directionally consistent with Cai et al [6], particularly their findings in older women with diminished ovarian reserve. The CoQ10 findings were also directionally compatible with improved ovarian-response and embryo-quality measures reported by Xu et al. [5]

Letrozole was associated with a live-birth rate of 28.6% in the present dataset, but only seven women received this intervention. Kahraman and Tulek reported higher implantation, clinical-pregnancy, and live-birth rates with letrozole in POSEIDON group 3, together with lower gonadotropin requirements in groups 3 and 4. [10]

Conclusion

Among women classified under POSEIDON groups 3 and 4, the use of an adjuvant was associated with numerically higher clinical-pregnancy and live-birth rates than no adjuvant use; however, the estimates were imprecise and did not reach statistical significance. No individual adjuvant demonstrated a definitive advantage, and reproductive outcomes were generally poorer in POSEIDON group 4 than in group 3. Given the observational design, heterogeneous adjuvant exposure, limited sample size and potential confounding by indication, these findings should be interpreted as exploratory and do not establish treatment efficacy. Larger prospective studies with standardized adjuvant protocols and adequate adjustment for prognostic factors are required to determine whether selected adjuvants improve live-birth outcomes in specific POSEIDON subgroups.

References

1. Humaidan P, Alviggi C, Fischer R, Esteves SC. The novel POSEIDON stratification of 'low prognosis patients in assisted reproductive technology' and its proposed marker of successful outcome. F1000Res. 2016;5:2911.
2. Esteves SC, Roque M, Bedoschi GM, Conforti A, Humaidan P, Alviggi C. Defining low prognosis patients undergoing assisted reproductive technology: POSEIDON criteria—the why. Front Endocrinol (Lausanne). 2018;9:461.
3. Chinta P, Antonisamy B, Mangalaraj AM, Kunjummen AT, Kamath MS. POSEIDON classification and the proposed treatment options for groups 1 and 2: time to revisit? A retrospective analysis of 1425 ART cycles. Hum Reprod Open. 2021;2021(1):hoaa070.
4. Haahr T, Dosouto C, Alviggi C, Esteves SC, Humaidan P. Management strategies for POSEIDON groups 3 and 4. Front Endocrinol (Lausanne). 2019;10:614.
5. Xu Y, Nisenblat V, Lu C, Li R, Qiao J, Zhen X, et al. Pretreatment with coenzyme Q10 improves ovarian response and embryo quality in low-prognosis young women with decreased ovarian reserve: a randomized controlled trial. Reprod Biol Endocrinol. 2018;16(1):29.
6. Cai MH, Gao LZ, Liang XY, Fang C, Wu YQ, Yang X. The effect of growth hormone on the clinical outcomes of poor ovarian reserve patients undergoing in vitro fertilization/intracytoplasmic sperm injection treatment: a retrospective study based on POSEIDON criteria. Front Endocrinol (Lausanne). 2019;10:775.
7. Etrusco A, Agrifoglio V, Castillo Farfán JC, Bernabeu Garcia A, Laganà AS, Moliner Renau B, et al. Effectiveness of hormone add-on strategies in ovarian stimulation for women with poor ovarian response: a systematic review and network meta-analysis of randomized controlled trials. J Assist Reprod Genet. 2025;42(10):3231–3252.
8. ESHRE Guideline Group on Ovarian Stimulation, Ata B, Bosch E, Broer S, Griesinger G, Grynberg M, et al. ESHRE guideline: ovarian stimulation for IVF/ICSI: an update in 2025. Hum Reprod. 2026;41(4):498–514.