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Comparable Clinical and Embryological Outcomes in Luteal and Follicular Phase Controlled Ovarian Hyperstimulation: A Retrospective Cohort Study

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Objective: To study whether luteal phase stimulation provides clinical and embryological outcomes comparable to follicular phase stimulation in controlled ovarian hyperstimulation cycles.
Design: Retrospective cohort study.
Subjects: A total of 12,442 patients undergoing 18,062 in vitro fertilization cycles between January 1, 2018, and December 21, 2021, across 6 assisted reproductive technology centers within a large US fertility network.
Exposure: Patients underwent controlled ovarian hyperstimulation using either follicular phase or luteal phase initiation. Cycles involving fresh transfers, day 3 transfers, or poor endometrial receptivity were excluded.
Main Outcome Measures: The primary outcomes were clinical pregnancy rates and cumulative live birth rates. The secondary outcomes included the number of oocytes retrieved, oocyte maturation rate, fertilization rate, blastocyst biopsy rate, and euploid embryo rate.
Results: The clinical pregnancy rates were similar between follicular (68.44%) and luteal (67.67%) phase stimulations (odds ratio, 0.975; 95% confidence interval [CI], 0.751–1.266). Luteal phase stimulation required a higher total follicle-stimulating hormone dose (4,350.92 IU vs. 3,989.11 IU); however, stimulation duration did not differ significantly. Follicular phase stimulation yielded more oocytes on average (12.61 vs. 11.85), although luteal phase stimulation produced more oocytes in paired analyses (8.54 vs. 7.31). Among patients aged <35 years, the blastocyst biopsy rates were higher in luteal cycles (61.01% vs. 55.37%). No significant differences were found in the oocyte maturation, fertilization, or euploid embryo rates. The cumulative live birth rates were comparable across age groups and transfer attempts.
Conclusion: Luteal phase stimulation offers clinical and embryological outcomes comparable to follicular phase stimulation in in vitro fertilization. In patients aged <35 years, it may provide higher blastocyst biopsy rates, supporting its use as a flexible and effective stimulation option. (F S Rep® 2025;6:289–98. ©2025 by American Society for Reproductive Medicine.)

Key Words: Luteal phase stimulation, follicular phase stimulation, clinical pregnancy rates, cumulative live birth rates

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Controlled ovarian stimulation is an essential component of assisted reproductive technologies involving the development of multiple follicles under the influence of gonadotropins. The physiologic mechanisms of recruitment and selection of antral follicles in women are not fully understood to date. Increasing evidence has shown that multiple waves of antral follicles are recruited during the menstrual cycle (1). In a large population of healthy women, 68% of women exhibited 2 waves of follicle recruitment during the interovulatory cycle, whereas the remaining 32% exhibited 3 waves (2). Baerwald et al. (2) demonstrated that small antral follicles could be in the early stages of follicular development during the luteal phase, suggesting that the ovaries could be continuously stimulated in the same menstrual cycle. Conventional controlled ovarian stimulation starts in the early follicular phase. In the past 10 years, however, ovarian stimulation starting in the luteal phase is emerging as an alternative. Luteal phase stimulation has been tested in healthy (3, 4) and poor responders on the basis of the Bologna criteria (5–7), although it was originally reserved for women with cancer whose oncological treatment required urgent stimulation without waiting for the follicular phase to start (8, 9). It has been shown that luteal phase stimulation is comparable with follicular phase stimulation in terms of efficacy in young women with poor ovarian reserve (6, 10, 11). The prospective study by Kuang et al. (10) showed that luteal phase stimulation is appropriate for producing competent oocytes, thus producing embryos with good pregnancy and live birth outcomes with healthy responders aged <38 years. The same group later demonstrated the safety of the luteal phase stimulation protocol for offspring (7). The rates of blastocysts and euploid blastocysts were similar between follicular and luteal phase stimulations in several studies (12–14) in donor-recipient cycle for patients aged <35 years. Besides its time convenience, other hypothetical advantages of ovarian stimulation initiated in the luteal phase include a reduced risk of ovarian hyperstimulation syndrome, cycle cancellation, or premature luteinization (15).

Buendgen et al. (3) found that a higher dose of follicle-stimulating hormone (FSH) was required for luteal phase stimulation than for follicular phase stimulation (3,495 IU vs. 2,014 IU) and follicular and luteal phase stimulation demonstrated no difference in maturity, fertilization, and embryo development (4). Another study by Martinez et al. (16) found that the total dose of FSH and the number of days for FSH stimulation were comparable (2,261 IU vs. 2,147 IU and 10.4 days vs. 9.9 days). Biasoni et al. (17) have termed the ratio of total gonadotropin dose to the number of oocytes as ovarian sensitivity index (OSI). It has been shown that OSI is a better representation of ovarian responsiveness as opposed to either retrieved oocyte number or gonadotropin dose alone when considering the varying daily dosages of gonadotropins administered to different patients (17, 18). Thus far, different research groups have proposed 3 main methods to calculate OSI (18, 19), which share the same concepts that measure the ovarian response to the total FSH dose or antimullerian hormone (AMH) levels.

The cumulative live birth rates have been considered a more relevant variable, although it may take years from the start of a cycle until these data can be collected (20–24). To date, no high-quality evidence has been found for cumulative live birth rates for the luteal phase stimulation protocol.

It is well established that compared with 20–29 years, fertility is reduced by 31% in women aged 35–39 years and 60% less likely to conceive in any given cycle in ages above 40 years (25, 26). Substantial increases in aneuploidy were noted in embryos from women aged >42 years (27). In addition, poor response to ovarian stimulation and much worse embryo quality were observed in women aged ≥40 years than in women aged <40 years (28). The results support the concept that oocyte quality, embryo competence, euploidy rates, and pregnancy or live birth outcomes do not decline in a linear fashion with advancing age but instead show marked decreases around the ages of 35, 40, and 42 years. Stratifying variables such as egg quality, embryo competence, and pregnancy/live birth rates by age is a common statistical technique (29).

This retrospective study aimed to compare the effects of initiating controlled ovarian hyperstimulation in the luteal vs. follicular phase of the menstrual cycle on various outcomes. These include oocyte retrieval numbers, maturation rates, OSI, rates of blastocyst formation, rates of euploid blastocysts, clinical pregnancy rates, and cumulative live birth rates, both in general and across different age groups. To our knowledge, this represents the largest retrospective analysis to date, evaluating patients of all ages and specific age categories to determine the relative effectiveness of luteal and follicular phase stimulation on clinical pregnancy success, cumulative live birth rates, and embryological outcomes.

MATERIALS AND METHODS

Ethics approval

The retrospective study of "A Comparative Study of Controlled Ovarian Luteal Phase vs. Follicular Phase Stimulation" (Pro00063766) was approved by Advarra Institutional Review Board on June 17, 2022.

To safeguard patient privacy, patient confidentiality was rigorously maintained throughout the study by deidentifying all patient data before analysis. This process involved the removal of any personally identifiable information from the data set, ensuring that individual patients could not be traced back from the study results.

Study design and participants

This is a retrospective study using data collected from all in vitro fertilization (IVF) cycles occurring between January 1, 2018, and December 21, 2021, across 6 clinical centers within a large network in the United States, including 12,442 patients and 18,062 IVF cycles. The patients who underwent fertility (oocyte or embryo) cryopreservation treatment, fresh and day 3 transfers, cycles with known poor

endometrial receptivity, non–preimplantation genetic testing (PGT) for aneuploidy (PGT-A) cycles, and random start stimulation cycles were excluded in this study. The patients were stratified into 4 age groups for data analysis: ages of <35 years; 35–39 years (≥35 years and <40 years); 40–41 years (≥40 and <42 years); and ≥42 years. Age groups are based on maternal age at oocyte retrieval, not at transfer.

Luteal phase stimulation

This protocol was provided on the basis of individual characteristics, prior outcomes, physician preferences, or when it allowed for more convenient scheduling of banking cycles. Luteal phase stimulation begins after ovulation has occurred, typically around the middle to late luteal phase of the menstrual cycle. Similar to traditional IVF protocols, ovarian stimulation medications including FSH and human menopausal gonadotropin were administered to stimulate the ovaries and promote multifollicular development for 8–15 days. gonadotropin-releasing hormone antagonists were introduced when the lead follicle reached approximately 14 mm in diameter or on the basis of serum estradiol levels to prevent premature luteinization. During stimulation, patients undergo regular monitoring with transvaginal ultrasound and serial blood measurements of estradiol and progesterone to assess follicular development. When follicular development is deemed optimal, a trigger shot of human chorionic gonadotropin and/or gonadotropin-releasing hormone agonist was administered to induce final oocyte maturation and prepare for oocyte retrieval, which takes place 36 hours later, with a narrow range of 34–36 hours in practice (30).

Follicular phase stimulation

For patients pretreated with oral contraceptive pills, ovarian stimulation was typically initiated 5–7 days after discontinuation, following clinic protocols to allow for adequate hormonal suppression and endometrial shedding. Ovarian stimulation begins during the early follicular phase of the menstrual cycle, typically on cycle day 2 or 3 or a few days after stopping oral contraceptive pills. Monitoring, assessment, and triggering ovulation were similar to the luteal phase stimulation protocol.

Oocyte retrieval and fertilization

Oocyte retrieval was performed by transvaginal ultrasound-guided puncture 36 hours after the administration of human chorionic gonadotropin or Lupron according to clinic protocol. Cumulus and corona cells were enzymatically removed 3.5 hours after retrieval before intracytoplasmic sperm injection (ICSI). Only morphologically normal mature oocytes with a visible first polar body by the time of ICSI procedure were microinjected. Successful fertilization was defined as 2 clean pronuclei being present 16–18 hours after insemination.

Embryo grading, vitrification, and warming

Blastocysts were graded using the Gardner and Schoolcraft scoring system (31). All good morphology blastocysts including blastocysts with grades that were better than or equal to 4BB on day 5 and better than or equal to 4CC on day 6 or 7 after oocyte retrieval were frozen by the Kitazato vitrification method (32). Embryos graded as 4CC on day 5 were cultured further and re-evaluated on day 6 or 7 before deciding on biopsy and vitrification. Warming the blastocysts followed the Kitazato method (32).

Frozen embryo transfer

Endometrial preparation and frozen embryo transfer were performed in either a natural cycle or a stimulated cycle as described (30).

Outcome measures

Clinical pregnancy was defined as the presence of a gestational sac with or without fetal cardiac activity visualized by transvaginal ultrasound at approximately 5–7 weeks of gestation after embryo transfer. The cumulative live birth rate was defined as the proportion of IVF cycles resulting in at least 1 live birth from a single oocyte retrieval, after using all resulting embryos through multiple frozen embryo transfers (30). Our analysis evaluated clinical pregnancy rates after the first, second, and third euploid embryo transfers across various age groups.

The embryological outcome measures consisted of the number of oocytes retrieved, oocyte maturity, OSI, fertilization rate, usable blastocyst development rate, and euploid rate. The clinical and embryological data were collected from the electronic medical records. Continuous variables are presented as means (standard deviations and 95% confidence intervals [CIs]). The oocyte maturity rate was calculated by dividing the number of metaphase II oocytes by the total number of oocytes retrieved. The oocyte sensitivity index was calculated by dividing the total administered FSH dose by the number of retrieved oocytes (33). The fertilization rate was calculated by dividing the number of fertilized oocytes (2 pronuclei) by the number of oocytes injected by ICSI or conventional insemination. The usable blastocyst rate was calculated by dividing the number of biopsied blastocysts by the number of fertilized oocytes (2 pronuclei). A euploid blastocyst was defined as an embryo with 23 pairs of chromosomes that are detected in the trophectoderm biopsy by a single PGT-A platform. The euploidy rate was calculated by dividing the number of euploid blastocysts by the number of biopsied blastocysts.

Statistical analysis

Multivariate regression analysis. Generalized estimating equations analysis in R was used to calculate coefficients and *P* values for our variables of interest while adjusting

for confounding factors, namely, age, AMH, body mass index (BMI), insemination type, and recruitment site. Age was recorded in years; AMH was recorded in ng/mL; BMI was calculated as weight (lb)/[height (in)]^2 × 703; insemination type was categorized as conventional, conventional/ICSI, and ICSI; and recruitment sites were recorded the name of clinical centers and deidentified as A, B, C, D, E, and F.

Post hoc analysis. A post hoc analysis was conducted to explore the clinical relevance of the differences observed between luteal and follicular phase stimulations. For this purpose, a 5% threshold was used as an exploratory reference to assess whether the observed differences in the clinical pregnancy rates could be considered clinically meaningful.

Odds ratios (ORs) and risk differences (RDs), along with their 95% CIs, were calculated to assess the relative and absolute differences in the clinical pregnancy rates between luteal and follicular phase stimulations (34).

Survival analysis. The cumulative proportion surviving of live birth during the study period was estimated with the Kaplan-Meier method in R according to the IVF cycle number. Censoring was defined at the juncture where no additional opportunities for embryo transfers existed for a patient beyond the last observed instance at the time of data analysis. When the data were stratified, the log-rank test (Mantel-Cox), Breslow (generalized Wilcoxon) and Tarone-Ware were used to compare survival curves and Cox regression models to control for potential confounders and calculate hazard ratios (35).

Imputation of missing data. Multiple imputation techniques were used to handle missing data for covariates such as age, AMH, and BMI (36).

RESULTS

Supplemental Table 1 (available online) provides a comprehensive summary of patient demographics and cycle information, including age, AMH levels, BMI, number of cancellations along with their rates and specific reasons—ranging from low ovarian response and lack of normal embryo transfer after PGT to opting out of PGT and various personal factors—as well as the types of insemination used.

Primary outcomes

Clinical pregnancy and cumulative live birth rates. In the overall cohort, the first euploid embryo transfer resulted in clinical pregnancy rates of 68.44% for the follicular phase and 67.67% for the luteal phase, with an adjusted OR of 0.975 (95% CI, 0.751–1.266) and an RD of −0.57% (95% CI, −6.46% to 4.92%). The pregnancy rates slightly declined with each subsequent transfer (second and third transfers detailed in Table 1 and Fig. 1). After adjustment for age, AMH, BMI, recruitment site, and insemination type, no significant differences were observed in the pregnancy rates across groups or transfers. In the <35-year age group, the first transfer pregnancy rates were 70.49% for follicular and 78.16% for luteal phase stimulations (OR, 1.623; 95% CI, 0.932–2.827; P = .087; RD, 7.67%; 95% CI, −1.10% to

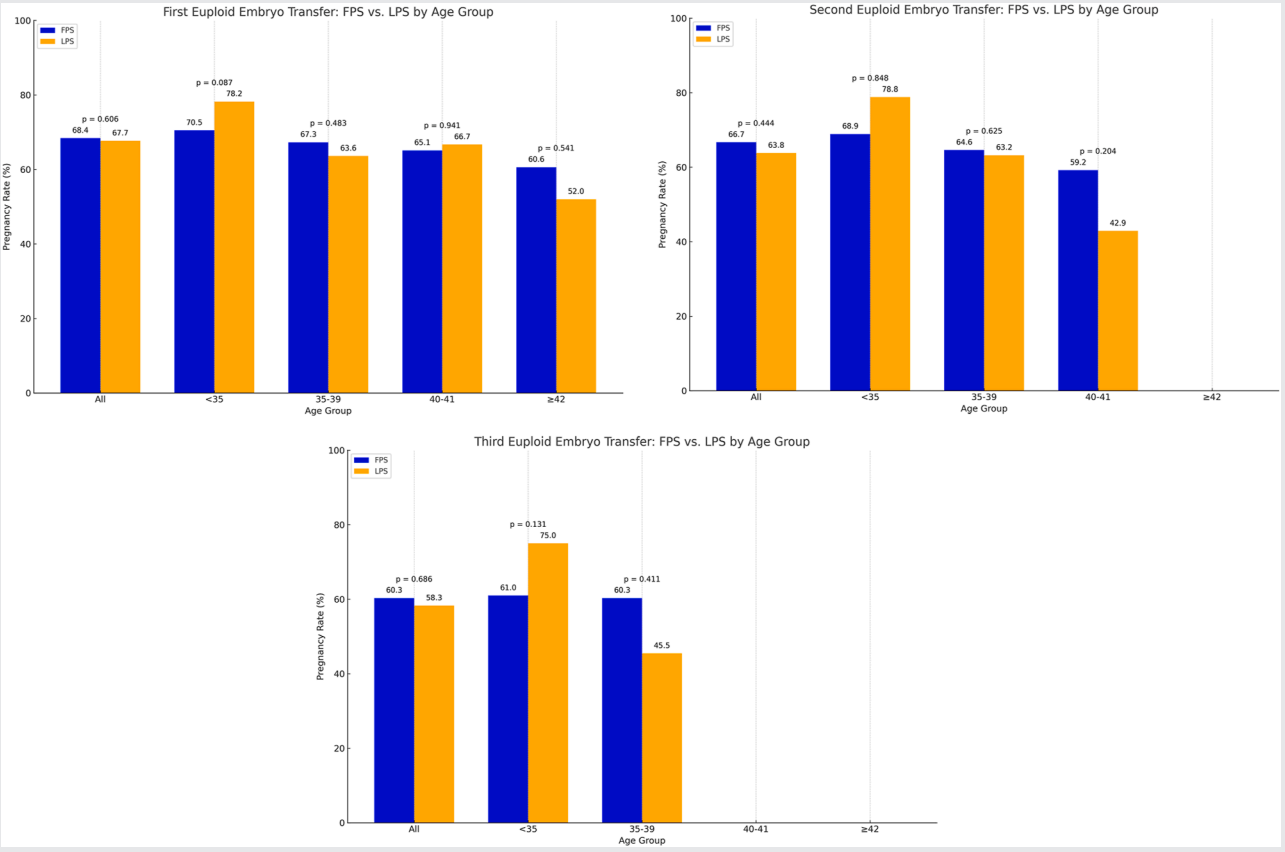
TABLE 1

The clinical pregnancy rates and estimates of odds ratio and risk differences after the first, second, and third euploid embryo transfers.

Age groups	Transfer number	FPS	LPS	Odds ratio[a]	95% confidence interval	*P* value	Risk difference	95% confidence interval
All	First euploid embryo transfer	68.44% (7,121/10,405)	67.67% (180/266)	0.975	0.751–1.266	.606	−0.77%	−6.46% to 4.92%
	Second euploid embryo transfer	66.69% (2,727/4,089)	63.75% (51/80)	0.829	0.513–1.340	.444	−2.94%	−13.57% to 7.69%
	Third euploid embryo transfer	60.33% (800/1,326)	58.33% (14/24)	1.192	0.508–2.799	.686	−2.00%	−21.90% to 17.90%
<35 y	First euploid embryo transfer	70.49% (3,504/4,971)	78.16% (68/87)	1.623	0.932–2.827	.087	7.67%	−1.10% to 16.44%
	Second euploid embryo transfer	68.90% (1,635/2,372)	78.75% (22/32)	0.926	0.422–2.031	.848	9.85%	−4.45% to 24.15%
	Third euploid embryo transfer	60.96% (523/858)	75% (9/12)	3.222	0.705–14.715	.131	14.04%	−10.68% to 38.76%
35–39 y	First euploid embryo transfer	67.35% (2,844/4,223)	63.64% (77/121)	0.866	0.579–1.295	.483	−3.71%	−12.40% to 4.98%
	Second euploid embryo transfer	64.56% (951/1,473)	63.16% (24/38)	0.837	0.410–1.707	.625	−1.40%	−16.93% to 14.13%
	Third euploid embryo transfer	60.28% (258/428)	45.45% (5/11)	0.597	0.174–2.043	.411	−14.83%	−44.92% to 14.96%
40–41 y	First euploid embryo transfer	65.06% (568/873)	66.67% (22/33)	1.031	0.467–2.275	.941	1.61%	−14.78 to 18.00%
	Second euploid embryo transfer	59.18%(116/196)	42.86% (3/7)	0.386	0.089–1.678	.204	−16.32%	−53.62% to 20.98%
	Third euploid embryo transfer	n/a	n/a	n/a	n/a	n/a	n/a	n/a
≥42 y	First euploid embryo transfer	60.65%(205/338)	52% (13/25)	0.771	0.335–1.773	.541	−8.65%	−28.92% to 11.62%
	Second euploid embryo transfer	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	Third euploid embryo transfer	n/a	n/a	n/a	n/a	n/a	n/a	n/a

FPS = follicular phase stimulation; LPS = luteal phase stimulation; n/a = not available.
[a] Adjusted odds ratios are provided for the variable "group LPS vs. FPS" after controlling for age, antimullerian hormone, body mass index, recruitment site, and insemination type.
Gao. Luteal vs. follicular: comparable results. F S Rep 2025.

FIGURE 1



Pregnancy rates after 3 euploid embryo transfers, stratified by age group and stimulation protocol. This bar chart compares pregnancy outcomes between follicular phase stimulation (FPS) and luteal phase stimulation (LPS) across age groups. The pregnancy rates are shown as percentages, with FPS in blue and LPS in orange. *P* values are annotated above each age group to indicate statistical comparisons. No statistically significant differences were observed between FPS and LPS across age groups. Detailed sample sizes for each group are provided in Table 1.

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16.44%). By the third transfer, the rates were 60.96% and 75.00%, respectively (OR, 3.222; $P = .131$), although differences remained nonsignificant. In the 35–39-year age group, the first transfer rates were 67.35% (follicular) and 63.64% (luteal) (OR, 0.866; RD, −3.71%; 95% CI, −12.40% to 4.98%), with a general decline across subsequent transfers. Among patients aged 40–41 years, the first transfer rates were 65.06% and 66.67% (OR, 1.031), and the second transfer rates declined to 59.18% and 42.86% (OR, 0.386; $P = .204$). In the ≥42-year age group, the first transfer rates were 60.65% (follicular) and 52.00% (luteal) (OR, 0.771; RD, −8.65%; 95% CI, −28.92% to 11.62%); no data were available for later transfers.

The cumulative live birth rates by age and transfer number showed higher sustained rates in patients aged <35 years, moderate increases in the 35–39-year age group, and lower but improving rates in patients aged ≥40 years. No significant differences were observed between stimulation groups after adjustment. Table 2 and Figure 2 provide detailed cumulative live birth data.

Secondary outcomes

Furthermore, to understand underlying factors contributing to the clinical outcomes, we conducted a comprehensive analysis of embryological outcomes. Supplemental Table 2 (available online) presents the statistical comparison results of all variables both overall and when stratified by age after adjusting for potential confounding factors. The days of luteal phase stimulation were statistically significantly longer than those of follicular phase stimulation across all age groups, except for the ≥42-year age groups. The total number of oocytes retrieved was significantly lower in luteal phase stimulation than in follicular phase stimulation for the <35-year age group (luteal, 12.61, vs. follicular, 17.19; $P = .0007$). Similar trends were found in all other age groups but did not reach statistical significance. The total dose of FSH administered to the luteal phase stimulation group was significantly higher than to the follicular phase stimulation group across all age groups. The OSI in luteal phase stimulation was significantly higher than that in follicular phase stimulation for the <35-year age group (luteal, 558.71, vs.

TABLE 2

Cumulative live birth rates comparing follicular phase stimulation vs. luteal phase stimulation.

The cumulative proportion surviving of live birth rates	Stimulation	No. of embryo transfer time	cycles	Coefficient*	CI95%	P value**
All age	FPS	1	9217	58.21%	[57.19 ,59.20]	0.52
		2	2908	79.48%	[78.55 ,80.36]	
		3	967	88.71%	[87.87 ,89.49]	
		4	325	93.85%	[93.05 ,94.56]	
		5	47	95.81%	[94.73 ,96.68]	
		6	16	97.12%	[95.69 ,98.08]	
		7	6	97.60%	[95.89 ,98.60]	
		9	1	100.00%	[NA ,NA]	
	LPS	1	210	58.10%	[50.86 ,64.26]	
		2	49	76.91%	[68.87 ,82.87]	
		3	17	86.42%	[77.66 ,91.74]	
		4	5	89.13%	[78.91 ,94.40]	
		5	1	89.13%	[78.91 ,94.40]	
<35	FPS	1	4995	59.86%	[58.48 ,61.20]	0.33
		2	1392	81.46%	[80.19 ,82.64]	
		3	408	89.46%	[88.26 ,90.53]	
		4	124	94.13%	[92.90 ,95.15]	
	LPS	1	87	63.22%	[51.55 ,72.08]	
		2	20	87.13%	[75.15 ,93.33]	
		3	6	93.56%	[81.87 ,97.72]	
		4	1	93.56%	[81.87 ,97.72]	
35-39	FPS	1	4242	54.76%	[53.24 ,56.24]	0.07
		2	1032	76.29%	[74.64 ,77.82]	
		3	252	86.54%	[84.72 ,88.15]	
		4	59	90.88%	[88.67 ,92.66]	
	LPS	1	121	48.76%	[39.03 ,56.94]	
		2	26	68.47%	[55.25 ,77.78]	
		3	9	75.48%	[59.79 ,85.04]	
		4	3	83.65%	[58.12 ,93.62]	
40-41	FPS	1	877	52.34%	[48.91 ,55.53]	0.62
		2	148	73.91%	[69.32 ,77.82]	
		3	22	83.40%	[76.32 ,88.36]	
		4	4	87.55%	[75.72 ,93.62]	
	LPS	1	33	51.52%	[31.08 ,65.89]	
		2	5	61.21%	[31.96 ,77.89]	
>=42	FPS	1	341	48.68%	[43.09 ,53.72]	0.92
		2	38	63.54%	[54.21 ,70.96]	
		3	3	87.85%	[38.80 ,97.59]	
	LPS	1	25	48.00%	[24.22 ,64.32]	
		2	2	74.00%	[0.00 ,93.82]	
		3	1	74.00%	[0.00 ,93.82]	

Note: This table shows the cumulative proportion of live births achieved after sequential embryo transfer cycles, comparing follicular phase stimulation and luteal phase stimulation across various age groups (all ages, <35, 35–39, 40–41, and ≥42 years). For each group, the cumulative live birth rates are reported as percentages after each successive embryo transfer attempt. Statistical significance (*P* values) was adjusted for age, antimullerian hormone, body mass index, recruitment site, and insemination type. CI = confidence interval.

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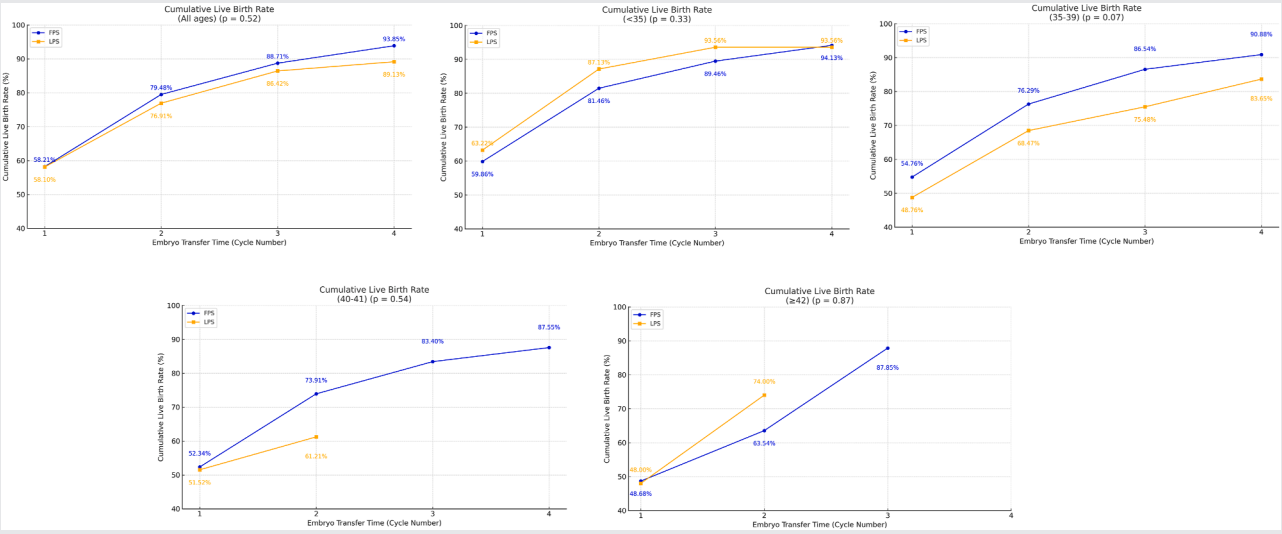
follicular, 370.10; $P = .021$). Regarding the oocyte maturation and fertilization rate, no statistically significant differences were found for any age groups between luteal and follicular phase stimulations.

In the <35-year age group, luteal phase stimulation resulted in significantly higher biopsied blastocysts than follicular phase stimulation (61.01% vs. 61.01%, $P = .014$). In the ≥42-year age group, luteal phase stimulation resulted in 35.57% biopsied blastocysts compared with 29.41% with follicular phase stimulation ($P = .05$). It is important to note that despite the differences observed in the percentage of biopsied blastocysts between luteal and follicular phase stimulations in different age groups, there was no significant distinction in the euploidy rates between the 2 stimulation protocols on any of the days (5, 6, and 7)) per patient.

Exploratory subgroup analysis

To assess how stimulation methods varied across subgroups, we conducted a subgroup analysis of 770 participants who underwent follicular or luteal phase stimulation, categorized into follicular phase start (472 IVF cycles) and luteal phase start (298 IVF cycles) groups (Supplemental Table 3, available online).The mean participant age was approximately 38 years, with no significant differences in age, AMH levels, or BMI between groups. The luteal phase group required a significantly higher total FSH dose (4,350.92 IU vs. 3,989.11 IU, $P < .001$), although the number of stimulation days did not differ significantly ($P = .079$). In the paired analysis subgroup, more oocytes were retrieved after luteal phase stimulation (8.54 vs. 7.31, $P = .014$), contrasting with the overall cohort where follicular phase stimulation yielded

FIGURE 2



Cumulative live birth rates by stimulation protocol (follicular phase stimulation [FPS] vs. luteal phase stimulation [LPS]) and oocyte retrieval age. The live birth rates (y-axis) are plotted against the number of embryo transfers (x-axis) for each age category (<35, 35–39, 40–41, and ≥42 years). FPS is shown in blue circles and lines, and LPS is shown in orange squares and lines. Data labels indicate cumulative live birth rates at each transfer. Detailed sample sizes for each group are provided in Table 2.

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more oocytes. No significant differences were observed in euploidy rates across day 5, 6, or 7 embryos between groups. After the first euploid embryo transfer, the clinical pregnancy rates were similar (56.56% for follicular phase stimulation vs. 58.72% for luteal phase stimulation; OR, 1.092; 95% CI, 0.650–1.834; $P = .74$), with no significant differences observed across age groups (<35, 35–39, 40–41, and ≥42 years). Data were insufficient to perform a cumulative live birth rate analysis in this subgroup.

DISCUSSION

Our study aimed to compare the clinical and embryological outcomes of luteal phase stimulation vs. follicular phase stimulation in controlled ovarian hyperstimulation cycles. Although we did not predefine a hypothesis regarding clinical equivalence, a 5% difference was considered post hoc as a threshold for clinical relevance. In our study, the RD for clinical pregnancy after the first euploid embryo transfer was −0.57% with a 95% CI of −6.46% to 4.92%. Because the lower bound of this CI (−6.46%) falls below the 5% threshold, the results suggest that luteal phase stimulation results in slightly lower clinical pregnancy rates; however, the difference is not large enough to be clinically significant.

A unique aspect of our study is that the sample size is large and contains an unselected patient population, which allows for robust statistical performance. The data used for analysis were retrieved from multiple clinical centers within the same network of institutions sharing the same clinical, embryology, and andrology laboratory methods, which ensured homogeneous embryo grading as well as embryo culture processes. Moreover, each group was adjusted for the confounding factors including age, AMH, BMI, insemination type, and recruitment site, which greatly reduced the impact of confounding factors.

Changing analysis of live birth rates to cumulative live birth rates has been recommended as a more comprehensive indicator of success in IVF outcomes because cryopreservation has become an integral part of IVF (35, 37, 38). The cumulative live birth rates of short or medium term can be reported as live birth episodes per woman per oocyte retrieval cycle over a 2–5-year period to account for the first live birth (39). Traditionally, censored data in survival analyses reflect cases where outcomes such as conception or live birth are not observed within the study period. By redefining censoring on the basis of embryo transfer opportunities, our analysis better reflects the realities of fertility treatment, recognizing the finite nature of transfer chances.

This patient-centered approach enhances clinical relevance but limits direct comparison with studies using traditional time-based methods.

The total dose of FSH administered in the luteal phase stimulation group was significantly higher than the dose given to the follicular group for all age groups. These results were consistent with previous studies in healthy and poor responders (3, 4, 11, 40) suggesting that ovarian responsiveness is lower in the luteal phase stimulation than in the follicular phase group. The study by Minegishi et al. (41) has shown that the total number of FSH receptors in the leading follicles increases by approximately twofold at the

midfollicular phase compared with those at other phases. Their results suggest that antral follicles in the luteal phase have fewer FSH receptors than the dominant and other follicles in the follicular phase.

Our study found differences in oocyte yield results between Supplemental Tables 2 and 3. Supplemental Table 2, which includes all patients, shows that follicular phase stimulation generally yields more oocytes. In contrast, Supplemental Table 3, which presents a paired analysis of the same patients undergoing both protocols, shows that luteal phase stimulation results in more oocytes. This discrepancy suggests that individual responses to stimulation can vary, indicating that some patients may benefit more from luteal phase stimulation because of unique ovarian physiology or previous treatment responses. These findings highlight the potential benefits of personalized IVF treatments on the basis of specific patient characteristics.

A previous study has indicated equivalent or higher euploid rates in luteal phase stimulation than in follicular phase stimulation (42). In our study, despite some differences in oocyte yield and blastocyst biopsy rates between protocols, we observed no statistically significant differences in the euploidy rates between stimulation types across any age group. This supports the idea that luteal phase stimulation can produce embryos with comparable chromosomal integrity to those from traditional follicular phase protocols.

In addition to protocol comparisons, our data set revealed a notable age-related trend. Interestingly, we also observed relatively high euploidy rates among patients aged $\geq$40 years. This finding appears counterintuitive given the expected age-related decline in oocyte quality and chromosomal competence. We believe that this may be because of selection bias because only embryos that reached the blastocyst stage and were eligible for biopsy were included in the analysis. Older patients who generate such embryos may represent a biologically favorable subset, potentially inflating the apparent euploidy rate in this age group. Additionally, smaller sample sizes in older cohorts may contribute to wider CIs and potential overestimation.

Patients undergoing both follicular and luteal phase stimulations may represent a distinct IVF subgroup, often with low ovarian reserve or suboptimal response. Luteal phase stimulation is sometimes preferred for such patients because of potential benefits in oocyte quality and hormonal milieu (43, 44). In our subgroup analysis, the clinical pregnancy rates after euploid embryo transfer were comparable between stimulation groups across all ages.

These results suggest that although luteal phase stimulation improves oocyte yield, it does not necessarily enhance pregnancy rates, underscoring the importance of factors such as uterine receptivity.

We did not include any paternal data; thus, we could not attribute any outcome changes on the basis of paternal age or sperm quality. However, paternal contribution to the formation of blastocyst and euploidy has shown to have an effect of less than 10% (45–47); therefore, we have assumed that its effect is minimal.

Limitations

Although our study provides valuable insights into luteal and follicular phase stimulation in IVF, several limitations should be noted. As a retrospective analysis, it is subject to potential biases and confounding because of the lack of randomization. Patient selection for luteal phase stimulation on the basis of clinical characteristics and physician preference may limit generalizability. Variations in the timing of luteal phase stimulation across patients could also influence outcomes, underscoring the need for standardized protocols. Finally, differences between overall outcomes and paired subgroup analyses highlight the need for cautious interpretation and more controlled studies.

CONCLUSION

Our study demonstrates that both luteal and follicular phase stimulation protocols are effective for IVF treatment, with comparable outcomes across various clinical and embryological measures. Future research should aim to identify patient-specific factors that may influence the effectiveness of each protocol and conduct prospective randomized controlled trials to further explore and validate the comparative benefits of luteal phase stimulation in diverse patient populations.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT 4.0 to enhance language clarity. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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CRediT Authorship Contribution Statement

Feng Gao: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Conceptualization. **Nicolás Garrido:** Writing – review & editing, Methodology, Conceptualization. **Juan Manuel Mascarós Martínez:** Software, Methodology, Data curation. **Christine Whitehead:** Validation, Data curation. **Odgerel Badamjav:** Validation. **Katharine Baxter:** Validation. **Jonathan Kort:** Writing – review & editing, Supervision, Conceptualization.

Declaration of Interests

F.G. has nothing to disclose. N.G. has nothing to disclose. J. M.M.M. has nothing to disclose. C.W. has nothing to disclose. O.B. has nothing to disclose. K.B. has nothing to disclose. J.K. has nothing to disclose.

SUPPLEMENTAL MATERIAL

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