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The Relationship between Progesterone Oocyte Index, Follicular Progesterone Index, and Progesterone Estradiol Ratio with IVF Outcomes at the IVF Clinic of Prima Medika General Hospital Denpasar

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ABSTRACT

Reliable biomarkers for predicting in vitro fertilization (IVF) outcomes remain limited, and progesterone-derived indices may reflect ovarian response more comprehensively than serum progesterone alone. This retrospective study evaluated the association of serum progesterone, the Progesterone–Oocyte Index (POI), the Progesterone–Follicular Index (PFI), and the Progesterone–Estradiol Ratio (PER) with chemical pregnancy in 119 IVF–intracytoplasmic sperm injection (ICSI) cycles performed at the IVF Clinic of Prima Medika General Hospital, Denpasar, between September 2023 and December 2024. Serum progesterone and estradiol on the day of human chorionic gonadotropin (hCG) administration, the number of retrieved oocytes, and the number of follicles >14 mm were recorded, and POI, PFI, and PER were calculated. Cycles were dichotomized into low and high groups at the sample means of each variable, and associations with chemical pregnancy were assessed by logistic regression. None of serum progesterone, POI, PFI, or PER was significantly associated with chemical pregnancy (all $p > 0.05$). Low PFI showed the strongest, though non-significant, tendency toward a favorable outcome (odds ratio 2.186; 95% confidence interval 0.539–8.865). These findings suggest that progesterone-derived indices, particularly PFI, may add interpretive value when assessing ovarian response but cannot yet be regarded as independent predictors of IVF success. Prospective multicenter studies with larger samples and clinical pregnancy or live birth endpoints are needed.

Keywords: progesterone oocyte index; progesterone follicular index; progesterone estradiol ratio; IVF; chemical pregnancy

INTRODUCTION

Controlled ovarian stimulation is central to in vitro fertilization (IVF), promoting the growth of multiple follicles from which the best embryos are selected for transfer. Follicle-stimulating hormone (FSH) drives follicular development, and adequate antral follicle responsiveness to FSH is a marker of normal reproductive function. An appropriate ovarian response is a prerequisite for pregnancy, and differences in response influence IVF outcomes (Esteves et al., 2021; A. Li et al., 2020; P. Li & Chen, 2022). Predicting cycle success remains a central clinical challenge, because outcome depends not only on the number of developing follicles and retrieved oocytes but also on the hormonal milieu of the late follicular phase (Guadix, 2021).

Among the hormonal parameters assessed during IVF, progesterone has attracted particular attention. A rise in serum progesterone before human chorionic gonadotropin (hCG) administration has been linked to premature luteinization and altered endometrial receptivity, potentially reducing implantation (Hsia et al., 2023). Some studies report poorer pregnancy outcomes with elevated late-follicular progesterone, whereas others do not confirm this association, leaving its clinical significance unresolved. This inconsistency is clinically consequential, as the interpretation of progesterone elevation may determine whether a fresh embryo transfer is continued or deferred (Nagy et al., 2019; Silitonga et al., 2021; Simon et al., 2019).

Established markers of ovarian response, basal FSH, anti-Müllerian hormone, and antral follicle count, have limited ability to predict IVF success (P. Li & Chen, 2022). Quantitative indices such as the follicular output rate, ovarian sensitivity index, and follicle-to-oocyte index were introduced to better capture the relationship between ovarian reserve, follicular recruitment, and oocyte yield, but their predictive value for pregnancy remains inconsistent across populations and protocols (Carosso et al., 2022; Chen et al., 2023). Absolute serum progesterone may likewise fail to represent follicular function adequately, because progesterone secretion depends on both the number of growing follicles and the endocrine activity of each follicle; elevation may reflect either impaired receptivity or simply greater follicular activity (L.-J. Huang et al., 2023; Tulic et al., 2020; Zhang et al., 2024).

For this reason, ratio-based parameters, the Progesterone–Oocyte Index (POI), the Progesterone–Follicular Index (PFI), and the Progesterone–Estradiol Ratio (PER), have been proposed as more informative measures, normalizing progesterone to oocyte number, follicle number, or estradiol during stimulation (Braga et al., 2024; Novia et al., 2020). However, most studies have evaluated a single progesterone-related parameter rather than comparing several indices within one cohort and clinical setting (L. Huang et al., 2022; Merviel et al., 2021; Zhang et al., 2024), and evidence from Indonesian IVF centres is scarce, limiting local applicability (Novia et al., 2020). It therefore remains unclear which progesterone-related parameter offers the most useful interpretation for predicting IVF outcomes. This study evaluated serum progesterone, POI, PFI, and PER simultaneously as predictors of chemical pregnancy in patients undergoing IVF at the IVF Clinic of Prima Medika General Hospital, Denpasar.

MATERIALS AND METHODS

Study design and setting

This retrospective, non-interventional observational study was conducted at the assisted reproduction unit of the IVF Clinic, Prima Medika General Hospital, Denpasar, Indonesia.

Participants

Patients undergoing IVF–ICSI between September 2023 and December 2024 were eligible. Cycles were included when complete data were available for serum progesterone, serum estradiol, and the number of follicles >14 mm on the day of hCG administration. A total of 119 IVF–ICSI cycles met these criteria and were analyzed.

Ovarian stimulation and laboratory procedures

All patients underwent controlled ovarian stimulation with a short antagonist protocol, using recombinant FSH (Gonal-F), highly purified human menopausal gonadotropin (HP-hMG; Menopur), or a combination, according to the centre's clinical protocol. Serum estradiol and progesterone concentrations and transvaginal ultrasonography were used to monitor follicular development. Final oocyte maturation was triggered by 250 µg hCG (Ovidrel; Merck Serono) 36 hours before oocyte retrieval. ICSI was performed in all cycles according to semen parameters. Embryo transfer was carried out 48–72 hours after retrieval, with a maximum of two embryos transferred based on clinical history and embryo quality.

Progesterone-derived indices

POI was calculated as serum progesterone (ng/mL) on the hCG day divided by the total number of retrieved oocytes. PFI was calculated as serum progesterone (ng/mL) on the hCG day divided by the number of follicles >14 mm at the last ultrasound examination on the same day. PER was calculated as serum progesterone (ng/mL) divided by serum estradiol (pg/mL) on the hCG day.

Outcome

The primary outcome was chemical pregnancy, defined as a positive serum β-hCG test performed [insert interval, e.g. 12–14 days] after embryo transfer [confirm assay, threshold, and timing].

Statistical analysis

Continuous variables are summarized as mean ± standard deviation. For association testing, each continuous variable (maternal age, duration of infertility, number of follicles >14 mm, number of retrieved oocytes, estradiol, progesterone, POI, PFI, and PER) was dichotomized at its sample mean into low and high categories. The association of each variable with chemical pregnancy was assessed separately using univariable logistic regression, with results expressed as odds ratios (OR) and 95% confidence intervals (CI). A two-sided p-value <0.05 was considered statistically significant. Analyses were performed using [software and version, e.g. IBM SPSS Statistics v26].

Ethical considerations

This study was approved by the Health Research Ethics Committee, Wangaya Regional General Hospital (RSUD Wangaya), Denpasar (approval No. 000.9.2/4420/RSUDW). Because the study used anonymized secondary data from medical records with no patient contact or intervention, the requirement for informed consent was waived. Names, medical record numbers, and other identifiers were removed before analysis, and all data were analyzed in aggregate for research purposes only.

RESULTS

A total of 119 IVF–ICSI cycles were analyzed. The mean maternal age was 32.3 ± 4.2 years. The chemical pregnancy rate was 45.4%, and the non-pregnancy rate was 54.6%. All cycles used a short antagonist protocol. On the hCG day, the mean serum progesterone was 0.93 ± 0.4 ng/mL, and the mean serum estradiol was 2135.7 ± 676.2 pg/mL. The mean number of retrieved oocytes at ovum pick-up was 6.51 ± 3.2, and the mean number of follicles >14 mm was 7.52 ± 3.3. Mean POI, PFI, and PER were 0.193 ± 0.19, 0.156 ± 0.16, and 0.000548 ± 0.0007, respectively.

Table 1 shows the distribution of baseline and stimulation variables. Most cycles were in patients ≤32 years (54.6%) with an infertility duration ≤6 years (57.1%). The majority had ≥7 follicles >14 mm (55.5%) and ≥6 retrieved oocytes (60.5%). Estradiol was above the mean in 57.1% of cycles, whereas progesterone was at or below the mean in 59.7%. Most cycles fell into the low group for POI (70.6%), PFI (69.7%), and PER (73.1%). Overall, the cohort comprised predominantly younger patients with a moderate ovarian response and low progesterone-derived index values.

TABLE 1: Distribution of maternal age, duration of infertility, follicle number, oocyte number, estradiol level, progesterone level, POI, PFI, and PER (N = 119).

Variable	n	%
Maternal age		
≤32 years	65	54.6
>32 years	54	45.4
Duration of infertility		
≤6 years	68	57.1
>6 years	51	42.9
Number of follicles >14 mm		
≥7 follicles	66	55.5
<7 follicles	53	44.5
Number of oocytes at OPU		
≥6 oocytes	72	60.5
<6 oocytes	47	39.5
Estradiol level (pg/mL)		
Low (≤2135.7)	51	42.9
High (>2135.7)	68	57.1
Progesterone level (ng/mL)		
Low (≤0.933)	71	59.7
High (>0.933)	48	40.3
POI		
Low (≤0.193)	84	70.6
High (>0.193)	35	29.4
PFI		
Low (≤0.156)	83	69.7
High (>0.156)	36	30.3
PER		
Low (≤0.000548)	87	73.1
High (>0.000548)	32	26.9

OPU, ovum pick-up; PER, progesterone–estradiol ratio; PFI, progesterone–follicular index; POI, progesterone–oocyte index.

Univariable associations with chemical pregnancy are shown in Table 2. No variable was significantly associated with chemical pregnancy (all $p > 0.05$). Chemical pregnancy was numerically more frequent with lower progesterone, lower POI, lower PFI, and lower PER. Low PFI carried the highest odds ratio (OR 2.186; 95% CI 0.539–8.865), although this did not reach statistical significance.

TABLE 2: Univariable logistic regression of maternal age, duration of infertility, follicle number, oocyte number, estradiol level, progesterone level, POI, PFI, and PER with chemical pregnancy (N = 119).

Variable	p-value	OR	95% CI
Maternal age	0.715	1.190	0.468–3.023
Duration of infertility	0.799	1.120	0.469–2.678
Number of follicles >14 mm	0.879	0.917	0.299–2.808
Number of oocytes at OPU	0.549	1.398	0.468–4.181
Estradiol level	0.914	1.062	0.358–3.143
Progesterone level	0.284	0.596	0.232–1.536
POI	0.656	0.725	0.176–2.986
PFI	0.274	2.186	0.539–8.865
PER	0.272	0.519	0.161–1.674

CI, confidence interval; OR, odds ratio; OPU, ovum pick-up; PER, progesterone–estradiol ratio; PFI, progesterone–follicular index; POI, progesterone–oocyte index.

DISCUSSION

Maternal age and infertility duration were not associated with chemical pregnancy, likely reflecting the relatively homogeneous age distribution and the multifactorial nature of IVF success. The number of follicles >14 mm and retrieved oocytes were similarly unassociated, indicating that quantitative ovarian response alone does not determine outcome; success also depends on oocyte competence, embryo quality, endometrial receptivity, and embryo–endometrium synchrony (Reshef et al., 2022; Tomic et al., 2020; Ubaldi et al., 2019; Zhao et al., 2023).

Estradiol was not associated with chemical pregnancy; although a marker of follicular activity, serum estradiol may not reflect follicular quality or embryo implantation potential. Serum progesterone was likewise not significantly associated with the outcome, although pregnancy was numerically more frequent in the low-progesterone group, supporting the view that the clinical meaning of late-follicular progesterone cannot be captured by absolute concentration alone (X. Li et al., 2019; Lu et al., 2024; Volovsky & Seifer, 2024; Yang et al., 2021).

The absence of significant associations for POI, PFI, and PER indicates that these indices do not function as independent predictors of chemical pregnancy in this population. The tendency toward higher pregnancy rates with lower POI, PFI, and PER nonetheless suggests that lower progesterone exposure relative to oocyte yield, follicle number, or estradiol may reflect a more favorable endocrine environment. PFI showed the strongest numerical association (OR >2.0), implying that the relationship between progesterone and the number of mature follicles may be more informative than progesterone alone, although the sample size was insufficient to reach statistical significance (Merviel et al., 2021; Simon et al., 2019).

The role of late-follicular progesterone elevation remains contested. Supraphysiological progesterone may impair endometrial receptivity and reduce implantation, or it may simply indicate greater follicular activity without compromising oocyte or embryo competence (Novia et al., 2020; Zhang et al., 2024). In high responders, elevated progesterone may represent cumulative secretion from multiple follicles rather than abnormal steroidogenesis in each follicle, so absolute concentration has limited value unless interpreted alongside follicular response (Cortés-Vazquez et al., 2024).

This rationale underlies ratio-based indices such as POI and PFI, in which progesterone normalized to oocyte number or follicular response may outperform absolute progesterone (Guadix, 2021; Merviel et al., 2021). Consistent with this, low PFI tended to be associated with better chemical pregnancy outcomes in the present cohort, possibly reflecting lower progesterone secretion per mature follicle and a more physiologic late-follicular environment (Nagy et al., 2019; Silitonga et al., 2021; Zhang et al., 2024).

These findings align with reports that composite indices of ovarian response do not consistently outperform their components. Carosso et al. (2022) found that FOI, FORT, and OSI were no better than their constituent variables at predicting live birth, with maternal age remaining a reliable predictor. Braga et al. (2024) observed slower embryo development at lower FOI, suggesting that these indices track biologically relevant processes without necessarily predicting pregnancy. Novia et al. (2020) reported that elevated progesterone at hCG administration may impair oocyte maturation and fertilization in IVF–ICSI. Together, these support the biological plausibility of progesterone-related indices while underscoring their context-dependent clinical utility.

STRENGTHS AND LIMITATIONS

The main strength of this study is the simultaneous evaluation of several progesterone-derived indices in a single, uniformly managed IVF cohort. Several limitations should be considered. First, the retrospective single-centre design and modest sample size (119 cycles, approximately 54 pregnancies) limited statistical power, as reflected in the wide confidence intervals; the study was not powered to detect the observed effect sizes, so null findings should not be interpreted as evidence of no association. Second, each continuous variable was dichotomized at its sample mean; this data-dependent cut-off reduces power and may obscure dose–response relationships, and analysis on the continuous scale would be preferable. Third, associations were tested for each variable individually, without multivariable adjustment or correction for multiple comparisons, so residual confounding and type I error cannot be excluded. Fourth, the mean serum progesterone (0.93 ng/mL) was well below the thresholds commonly associated with impaired outcomes (approximately 1.5 ng/mL), so few cycles had clinically meaningful progesterone elevation, limiting the ability to detect a progesterone effect. Finally, chemical pregnancy is an early surrogate endpoint that does not capture clinical pregnancy or live birth. Prospective, multicentre studies with larger samples, continuous-variable and multivariable analyses, and clinically meaningful endpoints are needed to define the prognostic value of these indices.

CONCLUSION

Serum progesterone, POI, PFI, and PER were not significantly associated with chemical pregnancy in this IVF–ICSI cohort. Lower progesterone-derived indices, particularly PFI, showed a non-significant tendency toward more favorable outcomes. These indices may add interpretive value when assessing ovarian response but cannot yet be considered independent predictors of IVF success. Given the retrospective single-centre design, limited sample size, and use of chemical pregnancy as the endpoint, prospective multicenter studies with larger sample sizes and clinical pregnancy or live birth outcomes are needed to define their prognostic value and clinical utility.

DECLARATIONS

Ethics approval and consent to participate: This study was approved by the Health Research Ethics Committee, Wangaya Regional General Hospital (RSUD Wangaya), Denpasar (approval No. 000.9.2/4420/RSUDW). Because the study used anonymized secondary data from medical records with no patient contact, the requirement for informed consent was waived.

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