

EFFECT OF TRIGGER-DAY SERUM PROGESTERONE LEVEL ON CLINICAL PREGNANCY IN FRESH IN VITRO FERTILIZATION (IVF) CYCLES: A RETROSPECTIVE CHART REVIEW

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INTRODUCTION: Clinical pregnancy rates remain suboptimal in many fresh In Vitro Fertilization (IVF) cycles. Progesterone elevation prior to oocytes retrieval remains a controversial factor that may affect pregnancy rates. There is no single globally accepted serum progesterone threshold level so far. In addition, there are only limited studies done on the issue in low resource countries.

OBJECTIVE: To assess the association between trigger-day serum progesterone level and clinical pregnancy rate in fresh IVF cycles.

METHODS: A three years chart review (2023 – 2025 GC) conducted at Alhikmah Fertility Center, Addis Ababa, Ethiopia. Women undergoing fresh IVF/ICSI cycles who fulfill the eligibility criteria were included. The data was entered and analyzed using SPSS version 25.

RESULT: A total of 214 fresh IVF/ICSI cycles were included. Mean age at ovum pick up was 34.7 ± 6.0 years. The overall clinical pregnancy rate was 23.8%. Progesterone was categorized into three clinically relevant groups based on prior study reports as Group A (<0.7 ng/mL), Group B ($0.70-1.00$ ng/mL) and Group C (>1.00 ng/mL). Clinical pregnancy rate fell as progesterone level rose, from 34.2% in Group A to 16.3% in Group C. The difference across the three groups was significant ($\chi^2=7.80$, 2 df, $p=0.020$). Women with a pre-trigger progesterone level ≤ 1.00 ng/mL had 2.7 times times higher odds of clinical pregnancy compared to those with progesterone >1.00 ng/mL (AOR 2.74, 95% CI 1.34–5.59, $P=0.006$).

CONCLUSIONS: The findings support an inverse association between trigger-day progesterone concentration and clinical pregnancy rate in fresh IVF cycles. The trigger-day progesterone level above 1.00 ng/mL was associated with significantly reduced clinical pregnancy rate.

KEY WORDS: IVF, ICSI, fresh ET, OPU, trigger-day progesterone, Clinical pregnancy, Ethiopia.

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INTRODUCTION

Infertility is a growing global reproductive health problem affecting millions of couples worldwide. Globally, approximately one in six people of reproductive age experience infertility at some stage in their lives^{1, 2}. Assisted reproductive technologies (ART), including in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), have become important components of infertility management and have enabled millions of couples to achieve pregnancy. However, despite advances in ovarian stimulation protocols and embryo culture techniques, clinical pregnancy rates remain suboptimal in many fresh IVF cycles³⁻⁸.

In controlled ovarian hyperstimulation (COH), the primary goal is to produce multiple oocytes to increase the chances of a successful pregnancy. Nevertheless, IVF does not invariably result in implantation or live birth, and the outcome of an individual treatment cycle remains dependent on a complex interaction of maternal, paternal, ovarian, endometrial, embryological, laboratory, and treatment-related factors².

A number of factors are known to influence the probability of clinical pregnancy following IVF. Female age is one of the most consistent and powerful predictor. Increasing age is associated with declining ovarian reserve and quality of embryos⁹. The number of oocytes, the underlying cause and duration of infertility, body mass index (BMI), smoking, alcohol exposure, metabolic abnormalities, and general reproductive health, may also influence IVF outcomes^{1, 10}.

One of the factors increasingly recognized as influencing IVF success is the hormonal environment during controlled ovarian stimulation, particularly progesterone level during the late follicular phase^{7, 8, 11, 12}. During a natural menstrual cycle, progesterone levels remain low during the follicular phase and rise after ovulation. In stimulated IVF cycles, however, supra-physiologic follicular activity induced by exogenous gonadotropins may result in a Premature Progesterone Rise (PPR) during the late

follicular phase, specifically on the day of Human Chorionic Gonadotropin (hCG) trigger^{4, 13-18}.

While the role of progesterone in the luteal phase is well-established, its elevation prior to oocyte retrieval remains a controversial factor^{7,8,12,19}. Several studies have suggested that elevated progesterone levels on the day hCG trigger dose administration may affect endometrial receptivity by causing embryo-endometrial asynchrony, thereby reducing implantation, clinical pregnancy, and live birth rates in those who had fresh embryo transfer (ET) performed^{4, 14, 20}.

There is no universally accepted threshold definition for trigger-day progesterone level. The absence of a universally accepted cut-off contributes to heterogeneity among studies and complicates clinical decision-making. Different studies have used cut off values ranging from 0.5 to 2.0 ng/mL. Differences in assay methodology, patient population, ovarian response, stimulation protocol, and outcome definition contribute to substantial heterogeneity across studies. The two commonly used clinical definitions are serum progesterone concentrations of ≥ 1 ng/mL and ≥ 1.5 ng/mL on the day of hCG trigger^{4, 5, 17, 19, 21, 22}. Many investigators propose lower or individualized thresholds based on ovarian response and stimulation protocol^{6, 8, 18, 23}.

Some other studies suggest that embryo developmental stage and freeze-all strategies may modify the effect of progesterone elevation⁷. Although many IVF centers now employ freeze-all strategies when progesterone elevation occurs, fresh embryo transfer remains widely practiced due to lower cost, reduced treatment duration, and patient preference. Studies suggest that frozen embryo transfer (FET) may overcome the adverse endometrial effects associated with progesterone elevation^{14, 24}. However, whether freeze-all completely eliminates the detrimental effect remains uncertain^{12, 13, 15, 16}.

The lack of consensus on trigger-day progesterone cut-off values in fresh ET creates uncertainty in clinical decision-making and patient management. In addition, the majority of established IVF

progesterone threshold data is derived from Caucasian and Asian cohorts in high-resource, developed nations. There are only very few studies done on the issue in low resource countries especially Africa. Factors such as genetic variations in hormone metabolism, body mass index, and access to different forms of progesterone (e.g., Oral Vs vaginal Vs intramuscular) mean that Western guidelines may not perfectly translate to the African context^{16, 25}.

In many low- and middle-income countries, including resource-limited IVF settings, fresh embryo transfer remains widely practiced because freeze-all approaches may increase treatment cost, treatment duration, and hence reduce accessibility. Therefore, understanding the true effect of trigger-day progesterone elevation on pregnancy outcomes in fresh IVF cycles in low resource setting is essential for optimizing treatment protocols and improving success rates while minimizing unnecessary cycle cancellations or embryo freezing.

The purpose of this study was to assess trigger-day serum progesterone level and its effect on clinical pregnancy rate (CPR) in Fresh IVF cycles. To our knowledge this study is one of the first studies on the topic in our country. The study findings may contribute to evidence-based clinical decision making regarding optimal individualized embryo transfer strategies and improve IVF success rates.

METHODOLOGY

Study Design and setting: This is a three years chart review conducted at Alhikmah fertility center, Addis Ababa, Ethiopia. The center provides comprehensive infertility evaluation and care including assisted reproductive technology (ART) services. According to the study center protocol, GnRH antagonist ovarian stimulation protocol was used for all the cases during the study period. Serum progesterone level was determined 10-12 hours before HcG trigger dose administration in different laboratories close to their residence. Then, ovum pick-up (OPU) was done at 36 hours after the trigger dose administration. Embryo quality

was classified following the European Society of Human Reproduction and Embryology (ESHRE) and Alpha Scientists in Reproductive Medicine (ALPHA) consensus and recommendations.

Study period: The study included all eligible IVF/ICSI cycles performed between January 2023 – December 2025.

Source population: All women who underwent IVF or ICSI treatment at the center during the three-year study period.

Study Population: The study population included women who underwent controlled ovarian stimulation followed by fresh embryo transfer during the study period.

Inclusion Criteria: Women who had documented trigger-day serum progesterone measurement, underwent their first fresh IVF or ICSI cycles in the same cycle, and had a documented clinical pregnancy outcome.

Exclusion Criteria: Women who had frozen embryo transfer (FET) cycles, no recorded trigger-day progesterone value, and whose cycles cancelled before ET for different reasons including trigger day progesterone >2 ng/ml, and no embryo development.

Sample size and Sampling: Complete enumeration sampling was employed and all women who had IVF/ICSI cycles with fresh ET during the study period who fulfill the eligibility criteria were included. A consecutive sampling technique was used.

Data Collection

The study utilized clinical, laboratory, embryological, and pregnancy outcome records of women who underwent fresh IVF/ICSI cycles during the study period. Data was extracted from the medical records using a structured standardized data-extraction spreadsheet which was adapted from prior similar study reports and organised based on the study objectives 4, 7, 8, 11, 13, 16, 18, 19, 21, 22, 24-30. The questionnaire was pre tested on 5% of the expected sample size of participants based on the facility records. Information collected included: Socio-

demographic characteristics (age, address, BMI); reproductive data (previous pregnancy history, duration of infertility, type of infertility, and cause of infertility); ovum collection procedure details (trigger-day progesterone level, number of oocytes retrieved, number of oocytes cleaved, number and quality/grade of embryo transferred, day (age) of embryo transferred); and clinical pregnancy outcomes.

Clinical pregnancy rate was the dependent variable while the trigger-day serum progesterone level (ng/mL) was the primary independent variable. Many prior studies used different progesterone level groups to observe the effect on pregnancy outcomes. Progesterone level in the current study was analyzed as a categorical variable, dividing participants into three groups as: Group A (<0.7 ng/mL), Group B (0.7–1.0 ng/mL), Group C (>1.0 ng/mL), adapting from threshold ranges used in the many published literatures (4-6, 8, 11, 12, 17, 21, 22, 26, 28).

Other independent variables include: Maternal age at OPU; Body Mass Index (BMI); duration, cause and type of infertility; number of retrieved oocytes; number and quality/grade of embryo transferred; and embryo developmental stage (age).

Data Quality Control: To ensure data quality, data collectors were trained before data extraction. Collected data were reviewed for completeness and consistency. Data was appropriately coded before statistical analysis.

Data Analysis

Data were entered and analyzed using statistical software SPSS version 25. Descriptive statistics was used to summarize socio-demographic, reproductive and clinical variables. Continuous variables were assessed for distribution and effect on clinical pregnancy. Normally distributed variables were presented as mean $\pm$ standard deviation, whereas skewed variables were presented as median and inter-quartile range. Categorical variables were presented as frequencies and percentages. The progesterone level categorical variables/ groups were

compared using Chi-square test. A p-value of less than 0.05 was considered statistically significant. Tables and different graphs were used to assist data presentation.

The association between the dependent variable (clinical pregnancy outcome) and the independent variables stated above was analyzed stepwise with logistic regression. The primary independent variable was serum progesterone level determined on the HCG trigger dose administration day. All variables with odds ratio p-value of less than 0.05 in the bivariate analysis were included to the multivariate logistic regression model to control for confounding factors. Adjusted odds ratios (AORs) with 95% confidence intervals is reported. A p-value of <0.05 was considered statistically significant.

Operational Definition

Trigger-day serum progesterone: Serum progesterone level determined on the day of hCG trigger dose administration as recorded in the patient file.

Clinical Pregnancy: Defined per the standard ESHRE/ICMART glossary of ART terminology: a pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs, or by definitive clinical signs of pregnancy, and includes ectopic pregnancy. (31).

RESULT

A total of 214 women with fresh IVF/ICSI cycles were included (70 in 2023, 56 in 2024 and 88 in 2025). Mean age at OPU was 34.7 ± 6.0 years (median 35, IQR 31–39; range 18–49). Mean BMI was 24.8 ± 4.1 kg/m² (median 24.1). A total of 163 women (76.2%) were nulliparous and 40 (18.7%) had one previous birth. Primary infertility accounted for 143 cycles (66.8%) and secondary infertility for 71 (33.2%). The mean duration of infertility was 5.2 ± 4.6 years (median 4, IQR 2–7; range 0.2–25 years).

Causes of infertility: Female factor was recorded in 134 (62.6%), male factor in 70 (32.7%) and unexplained infertility in 10 (4.7%) cycles. The

most frequent specific causes of infertility were tubal factor (70; 32.7%), premature ovarian failure/insufficiency (52; 24.3%) and male-factor semen abnormality recorded as SOAT (45; 21.0%). Azoospermia accounted for 21 (9.8%) cycles and polycystic ovary syndrome for 9 (4.2%); the remaining causes were individually uncommon.

Stimulation and laboratory characteristics: The mean number of oocytes retrieved was 5.69 ± 3.70 (median 5, IQR 3–8; range 1–17). The mean number of embryos cleaved was 3.18 ± 2.23 (median 2, IQR 2–4; range 1–11).

Embryo transfer: Transfer was at the blastocyst stage (day 5) in 49 cycles (22.9%) and at the cleavage stage in 165 (77.1%). Two embryos were transferred in 116 cycles (54.2%), one in 51 (23.8%) and three in 47 (22.0%); the mean number was 1.98 ± 0.68 . At least one grade 1 embryo was transferred in 195 cycles (91.1%); the remaining 19 (8.9%) received grade 2 embryos.

Trigger-day progesterone and clinical pregnancy by group

Progesterone level was available for all 214 cycles (median 0.88 ng/mL, IQR 0.55–2.04). In total, 51 cycles resulted in a clinical pregnancy (CPR 23.8%). For the present analysis, progesterone was categorized into three clinically relevant groups based on prior study reports used as cut off points. Group A (<0.7 ng/mL) contained 79 cycles (36.9%), Group B (0.70–1.00 ng/mL) 37 (17.3%) and Group C (>1.00 ng/mL) 98 (45.8%). CPR fell as progesterone level rose, from 34.2% in Group A to 16.3% in Group C, a relative reduction of more than half (Table 1). The difference across the three groups was significant ($\chi^2=7.80$, 2 df, $p=0.020$), as was the comparison of Group A with Group C ($\chi^2=7.58$, $p=0.006$; unadjusted OR 2.66).

Trigger-day progesterone level cut-off point for favorable clinical pregnancy and associated factors

Table 1. Clinical pregnancy by trigger-day progesterone group in fresh IVF/ICSI cycles, Addis Ababa, 2023–2025 (N=214)

Progesterone group	Clinical pregnancy n (%)	No clinical pregnancy n (%)	Total
A: <0.70 ng/mL	27 (34.2%)	52 (65.8%)	79
B: 0.70–1.00 ng/mL	8 (21.6%)	29 (78.4%)	37
C: >1.00 ng/mL	16 (16.3%)	82 (83.7%)	98
Total	51 (23.8%)	163 (76.2%)	214

To identify the appropriate cut-off point of trigger-day progesterone level for favourable clinical pregnancy rate step wise analysis was done. Initially bivariate logistic regression using clinical pregnancy as the primary dependent variable was done for possible association with age at OPU, BMI, type of infertility, duration of infertility, cause of infertility, trigger-day serum progesterone level, day (age) of embryo, number of embryo transferred and grade of embryo transferred. In the bivariate logistic analysis only trigger-day progesterone level, age at OPU and duration of infertility were significantly associated with clinical pregnancy ($P<0.05$). In

addition, trigger-day progesterone level groups A and B combined (trigger-day progesterone level ≤ 1.00 ng/mL) had higher likelihood of clinical pregnancy than Group C (OR 2.22; 95% CI 1.14–4.31; $p=0.019$). Hence a multivariable logistic regression analysis was done using clinical pregnancy as the dependent variable; and dichotomised trigger-day progesterone level (≤ 1.0 ng/mL versus >1.0 ng/mL), age at OPU, and duration of infertility as the exposure variables. Women with a trigger-day progesterone level of ≤ 1.00 ng/mL had 2.7 times higher likelihood of clinical pregnancy compared to those with

progesterone >1.00 ng/mL (AOR 2.74, 95% CI 1.34–5.59, $P=0.006$). Both age and duration of infertility were also found to be independently associated with clinical pregnancy. (Table 2)

Table 2: Logistic regression analysis result of association between clinical pregnancy and independent variables among women who had fresh embryo transfer in Addis Ababa, 2023-2025. (N=214)

Variable	Category	Clinical pregnancy n (%)	COR	95% CI	P-value	AOR	95%CI	P-value
Urban	≤ 1.00 ng/mL	35 (30.2)	2.22	1.14–4.31	0.019	2.74	1.34–5.59	0.006*
Trigger day progesterone	≤ 1.00 ng/mL	35 (30.2)	2.22	1.14–4.31	0.019	2.74	1.34–5.59	0.006*
	>1.00 ng/mL	16 (16.3)	1.00	-		1.00	-	
Age at OPU	<35 years	35 (34.4)	3.13	1.61–6.12	0.001	3.24	1.59–6.10	0.001*
	≥ 35 years	16 (14.3)	1.00	-		1.00	-	
Duration of infertility	≤ 5 years	41 (29.3)	2.81	1.28–6.18	0.010	2.34	1.03–5.34	0.043*
	>5 years	10 (13.5)	1.00	-		1.00	-	

*P-value <0.05 with 95% CI

OPU: Ovum Pick-up; COR: Crude Odds Ratio; AOR: Adjusted Odds Ratio; CI: Confidence Interval

In addition, age and duration of infertility were further assessed as continuous variables to further describe their association with clinical pregnancy. Age was inversely associated with clinical pregnancy: for each additional year of age, the adjusted odds of clinical pregnancy decreased by 9.7% (AOR 0.903, 95% CI 0.851–0.959, $P<0.001$). Women aged <35 years had more than three times the odds of achieving clinical pregnancy compared to those aged ≥ 35 years (AOR 3.24, 95% CI 1.59–6.10, $P=0.001$). Similarly, duration of infertility was significantly associated with clinical pregnancy. There was a 10.5% reduction in the likelihood of clinical pregnancy per additional year of infertility duration. Duration of infertility ≤ 5 years showed higher likelihood of clinical pregnancy compared with >5 years (AOR 2.34, 95% CI 1.03–5.34, $P=0.043$).

DISCUSSION

This retrospective study assessed the relationship between serum progesterone measured on the day of the hCG trigger and clinical pregnancy among women undergoing fresh IVF/ICSI cycles at a Fertility Center in Addis Ababa. A total of 214 eligible women with fresh ET cycles performed between 2023 and 2025 were included. The overall clinical pregnancy rate was 23.8%. The principal finding was a statistically significant decline in clinical pregnancy as trigger-day progesterone increased. Clinical pregnancy was achieved in 34.2% of cycles with progesterone <0.70 ng/mL, 21.6% of cycles with progesterone between 0.70 and 1.00 ng/mL, and 16.3% of cycles with progesterone >1.00 ng/mL. The difference among the three groups was statistically significant ($\chi^2=7.80$, $p=0.020$).

The observed gradient is clinically important because the pregnancy rate in the lowest progesterone category was more than twice that observed among women with progesterone concentrations above 1.00 ng/mL. Similar dose-response patterns have been described in previous IVF studies and systematic reviews, although the magnitude of the association differs among populations and treatment protocols^{12, 21, 22, 26}.

The regression analysis provided further support for the observed association. After adjustment for maternal age and duration of infertility, women whose trigger-day progesterone was ≤ 1.00 ng/mL had significantly greater odds of clinical pregnancy than women with progesterone >1.00 ng/mL (AOR 2.74, 95% CI 1.34–5.59, $p=0.006$). The present findings are consistent with the substantial body of literature indicating that trigger-day progesterone elevation may adversely affect outcomes following fresh embryo transfer^{12, 21}. The current findings therefore add supportive evidence from an Ethiopian IVF population while also reinforcing the need for caution in applying a single threshold across different clinical settings.

The lack of a universally applicable progesterone cut-off has been repeatedly demonstrated in the literature. Published studies have used thresholds

ranging from approximately 0.5 to 2.0 ng/mL, with 1.5 ng/mL frequently adopted as a conventional definition of progesterone elevation^{4, 5, 11, 12, 15, 19, 21}. One of the notable findings of this study is that the progesterone concentration associated with poorer clinical pregnancy in this population (>1.00 ng/mL) was lower than the 1.5 ng/mL threshold commonly used in many previous studies^{4, 5, 11, 12, 15, 19}. This observation is clinically interesting but should be viewed as providing evidence for a potentially useful threshold for the local population rather than establishing a new international standard. The threshold should not be considered optimal or validated without further multicenter studies and analysis.

Some studies suggest that the principal effect of elevated progesterone is on endometrial receptivity rather than on the embryo itself, whereas other studies have reported possible effects on oocyte competence or embryo development^{6, 7, 17, 29, 30}. Under physiological conditions, progesterone remains relatively low during the follicular phase and increases after ovulation. During controlled ovarian stimulation, increased follicular activity and premature luteinisation can result in progesterone production before the administration of the trigger^{4, 19, 23, 24}. Premature exposure of the endometrium to progesterone may advance endometrial development relative to the developmental stage of the embryo. This can result in a displacement of the period during which the endometrium is optimally receptive to implantation^{14, 19}.

Maternal age was independently associated with clinical pregnancy in the present study. The finding agrees with the well-established relationship between increasing maternal age and declining reproductive potential. Age is associated with progressive reduction in ovarian reserve, diminished oocyte competence and increasing embryo aneuploidy, all of which may reduce implantation and pregnancy potential^{9, 10}.

Duration of infertility was also independently associated with clinical pregnancy. Duration of infertility may partly reflect the underlying severity and duration of reproductive pathology, increasing

maternal age, declining ovarian reserve or other cumulative factors that influence IVF prognosis^{9, 10}. Nevertheless, the association should not be interpreted as a direct biological effect of duration itself, because duration of infertility is closely related to several other patient characteristics.

The present findings are particularly relevant to IVF practice in Ethiopia and other resource-constrained settings. Most published evidence regarding premature progesterone elevation has originated from Europe, Asia and other relatively well-resourced settings, whereas evidence from African populations remains limited^{13, 16, 22, 24}. Differences in patient characteristics, stimulation protocols, laboratory procedures, progesterone assays and embryo-transfer practices may affect the relationship between progesterone and IVF outcomes. The findings from this study therefore provide useful preliminary local evidence that can inform further investigation and protocol development.

CONCLUSIONS AND RECOMMENDATIONS

Overall, the findings support an inverse association between trigger-day progesterone concentration and clinical pregnancy in fresh IVF/ICSI cycles. The observed association persisted after adjustment for age and duration of infertility, and the strongest signal was observed at a locally derived threshold of 1.00 ng/mL though the 1.00 ng/mL threshold should not be considered optimal or validated without further analysis. The study provides important preliminary evidence from an Ethiopian fertility center and supports continued investigation of trigger-day progesterone as a potential marker for individualized fresh embryo-transfer planning. Nevertheless, because of the retrospective design, modest sample size and potential residual confounding, the findings should be interpreted as evidence of association rather than proof of causality. Larger prospective and multicenter studies in Ethiopia and other African populations are required to validate the threshold.

LIMITATIONS

The patient population and clinical practices

of the Fertility Center may differ from those of other private or public fertility services in Ethiopia. Hence, the findings may therefore not be directly generalizable to all Ethiopian women undergoing IVF/ICSI treatment or to other African populations. The progesterone level was determined in different laboratories as a result quality control issues were not addressed in the study. In addition, the retrospective observational design prevents determination of causal relationship.

ETHICAL APPROVAL

Ethical clearance was obtained from the institutional review board (IRB) of College of Health Sciences (Ref. No: 065/26/GynObs), Addis Ababa University. Permission to conduct the study was obtained from Alhikmah Fertility Center. Since this is a retrospective study using secondary data, informed consent of participants was waived. Patient confidentiality was maintained and participants were not personally identified in any way.

List of abbreviations:

ART: Assisted reproductive technologies; COH: Controlled ovarian hyper-stimulation; CPR: Clinical pregnancy rate; ET: Embryo transfer; FET: Frozen embryo transfer; ICSI: Intra-cytoplasmic sperm injection; IVF: In vitro fertilization; OPU: ovum pick-up.

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