



## The correlation between progesterone/MII oocyte ratio on the day of trigger and ICSI outcome

Nassrin Malik Aubead\*

Department of Obstetrics and Gynecology-College of Medicine /University of Babylon-Hilla-Iraq



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### ABSTRACT

The World Health Organization (WHO) defines subfertility as the inability to get pregnant in couples who have more than 12 months maintaining frequent sexual intercourse without the use of contraceptives methods. Subfertility affects approximately 10-15% of couples in fertile age and this figure is increasing. Assess the level of serum progesterone MII oocyte ratio at the day of a trigger is to determine that if associated with poor ICSI-embryo transfer outcome. A retrospective cohort study carried in the period from Nov.1, 2018 to the end of Nov. 2019, when 50 patients were enrolled within the age between 20-35 years old with mean age ( $29 \pm 5$ ) years and the main age group were in between (25-30) years. The most common cause of subfertility was oligospermia (48.0%) and the HCG was positive in (20.0%) of the patients and negative in (80.0%), Significant association were found between implantation rate and P/MII oocyte ratio ( $P=0.008$ ), while highly significant association were noticed between pregnancy rate and P/MII oocyte ratio ( $P<0.001$ ). Progesterone increase should be avoided that lead to advance maturation of the endometrium and impaired endometrial receptivity, so from these results, we concluded that raised serum progesterone MII oocyte ratio at the day of the trigger is related with reduced ICSI-embryo transfer outcome.

### \*Corresponding Author

Name: Nassrin Malik Aubead

Phone: +9647829364566

Email: maliknassrin@yahoo.com

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The inability to gestate is a problem that involves the two members of a couple. 85% of couples conceive within one-year; increasing to 92% at two years and 93% at three (Mackens *et al.*, 2017). Since the first pregnancy was obtained by in vitro fertilization (IVF) in 1978, the intracytoplasmic sperm injection (ICSI) has been one of the most important contributions in assisted reproduction. To perform this technique requires a complex assisted reproduction laboratory. However, the high costs of IVF / ICSI treatments prevent many couples with subfertility from accessing these treatments (Henkel *et al.*, 2005).

### INTRODUCTION

The World Health Organization (WHO) defines subfertility as the inability to get pregnant in couples who have more than 12 months maintaining frequent sexual intercourse without the use of contraceptives methods. Subfertility affects approximately 10-15% of couples in fertile age and this figure is increasing (Mascarenhas *et al.*, 2012).

Intracytoplasmic sperm injection was presented in 1992 to improve fertility outcomes in the situation of male infertility and has developed treatment choices with improved results (Palermo, 1992; Sherins *et al.*, 1995). However, its use has extended to other areas, including those that respond poorly ( $\leq 4$  oocytes collected), the elderly of the mother and under conditions of a previously failed in vitro fertilization cycle. Some medical centers use ICSI

extensively (Carrell *et al.*, 2015; Guo *et al.*, 2018).

In the normal menstrual cycle, progesterone level is rising after luteinizing hormone (LH) surge and ovulation in the luteal phase. During IVF cycles, progesterone levels sometimes rise in the follicular phase on the day of human chorionic gonadotropin injection. This premature progesterone rise was called premature luteinization, referred to as a premature LH surge. With the introduction of GnRH analogs in IVF cycles, the progesterone level (P4) was decreased and premature LH surge was inhibited. This is because suppressing of granulosa cell steroidogenic activity (Abolfotouh *et al.*, 2019).

### The aim of the study

The objective of this study is to determine if elevated serum progesterone MII oocyte ratio at the day of a trigger is associated with poor ICSI-embryo transfer outcomes.

## PATIENTS AND METHODS

### Study population

A retrospective cohort study carried in Fertility center- AL Sadder Medical city- AL Najaf Iraq, in the period from Nov.1, 2018 to the end of Nov. 2019. 50 patients were enrolled in the current study within the age of 20-35 years old.

### Methods

In, all fresh cycles of women who underwent ICSI cycles in 2019 with flexible GnRH antagonist protocol and HCG for oocytes trigger, were followed up. The exclusion of Frozen cycles was done. After reviewing all patients' files for subfertility treatment at that period, 73 patients were eligible to be included in our study, 23 patients were canceled for different reasons (9 patients had failed fertilization, 5 showed poor response, one developed ovarian hyperstimulation, 3 with no oocytes retrieved, one had an endometrial polyp, 2 had immature oocytes, and 2 had arrested embryos).

### Exclusion criteria

All those patients who had recurrent implantation failure were excluded from the study.

### Ethical concept

All respondents signed a written informed paper after we informed them about the purpose of the study and all this information with confidentiality.

### Statistical analysis

Data entered by the researcher by use of computerized statistical software; Statistical Package of the Social Sciences (SPSS) version 23. Descriptive statistics are presented in the form (mean  $\pm$  standard

deviation). To compare more than two means, we used one-way ANOVA. In all statistical analyses, the significance level (p-value) was set at  $\leq 0.05$  and the result was presented in tables and/or graphs.

## RESULTS AND DISCUSSION

### Study participants

This study was included 50 patients within the age between (20-35) years old with mean age ( $29 \pm 5$ ) years and the main age group was between (25-30) years. The most common cause of subfertility was oligospermia (48.0%), then oligoasthenospermia (26.0%), unexplained subfertility (24.0%) and tubal factor in (2.0%). HCG was positive in (20.0%) of the patients and negative in (80.0%) (Table 1) & (Figure 1). Increasing P4 levels on the day of HCG activation are not uncommon in ladies undergoing IVF / ICSI.

The increase in HCG P4 is a bad predictor of IVF results. In our retrospective study, we examined the relationship between P4 concentration at trigger day and clinical pregnancy rate in fresh embryo transfer cycles. The current study showed that the pregnancy rate was 20%, which is less than that in (Ashmita *et al.*, 2017) study when the pregnancy rate was 30.6% and 34% in (Mascarenhas *et al.*, 2015).

This may be due to a difference in sample size collection. No significant differences were found regarding age, BMI and also same that found by (Ashmita *et al.*, 2017). In an observational study to assess the level of serum progesterone on the day of trigger and its association with outcome of IVF / ICSI. Two study groups were made; group A with  $P4 \leq 1.5$  ng/ml and group B with  $P4 > 1.5$  ng/ml. Like the present study, the P4 serum cut point was taken as 1.5 ng/ml.

Current pregnancy rates were inversely proportional to serum progesterone levels on the day of HCG (Table 2). Patients with progesterone  $\leq 1.5$  ng/ml had significantly higher pregnancy rates than patients with progesterone  $> 1.5$  ng / ml (46.6% vs. 17.24%;  $p = 0.028$ ) (Gill *et al.*, 2016).

Table 3 shows that there is a significant association was found between embryo grades II, III with negative HCG, while no association was found regarding other parameters.

Mean age in-group 1 was ( $28 \pm 5$ ) years and increase in-group 2 ( $30 \pm 4$ ) years, but with no significant difference ( $P=0.1$ ), no significant difference was found between both groups according to the cause of subfertility ( $P=0.7$ ). BMI of the group1 was ( $29.89 \pm 4.8$ ) while ( $28.12 \pm 4.7$ ) for group 2 with no difference ( $P=0.19$ ).

**Table 1: Patient's distribution according to age and cause of sub fertility**

	Variable	No.	%
Age Group	<25	9	18.0
	25-30	21	42.0
	>30	20	40.0
	Mean±SD		29±5
Cause of subfertility	oligoasthenospermia	13	26.0
	oligospermia	24	48.0
	unexplained	12	24.0
	tubal factor	1	2.0

**Table 2: Correlation between pregnancy rate and different parameters of the study**

Variables	HCG		P-value
	Positive (n=10) Mean±SD	Negative (n=40) Mean±SD	
Age	27±4	30±5	0.08 Ns
Body mass index (BMI)	24±2	24±2	-
Estradiol pg/ml	2187.11±935.4	2311.4±899.8	0.6 Ns
Progesterone ng/ml	1.58±1.27	1.89±1.28	0.4
Endometrial thickness (mm) at the day of trigger	10.7±1.9	10.7±1.5	-
No. of oocytes retrieved	10±5	10±7	-
No. of MII oocytes	7±4	8±6	0.6 Ns
No. Of fertilized oocytes	5±3	5±3	-
No of cleaved embryos	4±2	5±3	0.3 Ns
Embryo grade I	3±1	3±2	-
Embryo grade II	1±1	3±2	0.003
Embryo grade III	0	1±0	< 0.001
No. of transferred embryos	3±1	2±2	0.1 Ns
No. of frozen embryo	2±1	3±2	0.1 Ns

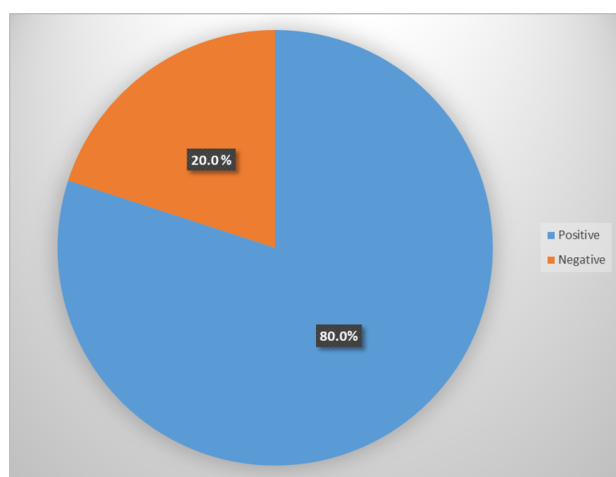
MI: number of oocytes in metaphase II.

**Table 3: Correlation between progesterone level on the day of HCG trigger and different parameters**

Variables	Progesterone level at HCG day		P-value
	Group 1 (n=26) <1.5 ng/ml	Group 2 (n=24) ≥1.5 ng/ml	
Age (mean ± SD)	28±5	30±4	0.1
Causes of Subfertility	oligoasthenospermia	7	6
	oligospermia	14	10
	unexplained	5	7
	tubal factor	0	1
Total	26	24	
Body mass index (BMI)	29.89 ± 4.8	28.12 ± 4.7	0.19
Pregnancy rate (HCG)	Positive	7 (70.0%)	3 (30.0%)
	Negative	19 (47.5%)	21 (52.5%)
Endometrium thickness(mm)	11.03 mm ± 1.06	10.08± 1.7	0.02
Estradiol pg/ml (mean ± SD)	2127.4±628.6	2521.4±671.9	0.03

**Table 4: Impact of serum progesterone level, P/e, and P/MII ratios on fertilization, implantation and pregnancy rates**

Variable	Progesterone ng/ml		P value	P/E2 ratio		P value	P/MII ratio		P value
	<1.5 (n=26)	≥1.5ng/ml (n=24)		<1 (n=28)	>1 (n=22)		≤ 0.32 (n=31)	> 0.32 (n=19)	
Fertilization rate (%)	56.7±8	55±11	0.5	52.8±9	53.1±10	0.9	57.1±5	56.7±11	0.8
Implantation rate (%)	22.0±23	20.3±30.2	0.8	22.5±25.5	21.9±29	0.9	27.2±30	7±14	0.008
Chemical pregnancy (%)	57±6	55±5	0.2	43±4	42±5	0.4	59±4	22±5	<0.001

**Figure 1: Pregnancy rate**

There is an increase in pregnancy rate in progesterone level < 1.5 ng/ml than that in > 1.5 ng/ml but no significant difference was found between. Significant increase in Endometrium thickness in progesterone level <1.5 ng/ml than that in > 1.5 ng/ml (P=0.02). Estradiol pg/ml were significantly increased in progesterone level >1.5 ng/ml than that in other groups (P=0.03) (Table 3). This was in agreement with the (Ashmita *et al.*, 2017), who reported a higher pregnancy frequency with E2 ≥2500 IU. (Bosch *et al.*, 2010) concluded that estrogen values on the day of the HCG trigger were associated with an increase in progesterone levels (P <0.0001).

A significant association was found between implantation rate and P/MII oocyte ratio (P=0.008), and highly significant association were found between pregnancy rate and P/MII oocyte ratio (P<0.001) (Table 4).

In the current study, since high progesterone levels with no effect on the fertilization rate, while reduced the implantation rate significantly, it can be estab-

lished that high levels of progesterone decrease the endometrial receptivity. According to previous studies, because the main sources of productive progesterone are follicles, under the effect of FSH, the level of progesterone produced per mature oocyte is the better predictor for IVF results (Fleming and Jenkins, 2010). In the present study, we found that there is a positive relationship between the number of mature oocyte and concentrations of serum progesterone, which is in agreement with that mentioned by (Aflatoonian *et al.*, 2014).

## CONCLUSION

It was concluded that increase level of progesterone should be avoided that leads to advance maturation of the endometrium and impaired endometrial receptivity. If progesterone exceeds 0.32 per metaphase II of an oocyte, fresh embryo transfer must be canceled and considered freeze all embryos for later transfer, up to increase acceptance of the endometrium and thereby increase the success rate.

## Fund

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## Ethical clearance

From the Ministry of Health and Environment/ scientific committee

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