



# Correlation of progesterone and Activin A with pregnancy outcome following IVF/ICSI cycle.

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The association between the two hormones (progesterone and Activin A) in infertile women on the day of ova pick up and their relationship with pregnancy status in assisted reproductive programs are both poorly understood. To determine the correlation of progesterone and activin A on the day of ova pick up with pregnancy status of women undergoing IVF/ICSI cycle. The study was conducted on 80 infertile couples. The serum at day of ova pick up was collected. Serum progesterone and activin A analysis were done for all samples for activin A. Out of eighty infertile females twenty-five became pregnant (Pregnancy rate = 31%). Serum progesterone levels at days of oocytes pick up was significantly higher in pregnant females than non-pregnant ( $9.22 \pm 0.54$  vs.  $4.47 \pm 0.44$ ;  $p < 0.001$ ). There was a significantly higher serum activin levels at day of oocytes pick up in pregnant women compared to non-pregnant ( $2.19 \pm 0.04$  vs.  $1.52 \pm 0.04$ ;  $p < 0.001$ ). The cut-off value of serum progesterone at day of oocytes picks up was  $> 7.5$  ng/ml and the cut-off value of serum activin A at day of oocytes pick up was  $> 1.85$  ng/ml. Pregnant women had higher levels of the hormone progesterone and Activin A than non-pregnant women, which is significantly correlated. This result can be utilized to predicate the pregnancy status early in IVF Centers.

ABSTRACT

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#### KEYWORD

Progesterone, Activin A, Pregnancy, IVF/ICSI.

## **1. Introduction**

An increasing number of people at reproductive age have difficulties in achieving pregnancy. Therefore, infertility has been considered as a social disease (Shaaban et al., 2013 [1]). For some couples, the only solution to this problem becomes the methods of IVF programs (LaMarca et al., 2019 [2]). After the end of the IVF / ICSI program and the process of returning the embryos, the diagnosis of pregnancy occurs after 13-14 days (Garg et al., 2022 [3]). Reproductive hormones play a main role in successful fertilization, implantation, and pregnancy (Oliva et al., 2022 [4]). One of these hormones is Progesterone, it is the main hormone in the luteal phase. It plays a key role in preparing the uterus for a possible pregnancy and in maintaining pregnancy term. In assisted reproduction treatments, there is usually a luteal phase deficiency. Therefore, it is necessary to supplement this critical phase to obtain the best

results, not only of implantation but also of ongoing pregnancy (Huang et al., 2023 [5]). Among all the available options, exogenous administration of Progesterone is the most commonly used, as it has proven its efficacy and safety (Kara et al., 2012 [6]). Other reproductive hormones are the Activins, which are dimeric glycoproteins belonging to the transforming growth factor beta superfamily and resulting from the assembly of two beta subunits, which may also be combined with alpha subunits to form inhibins (Xu et al., 2022 [7]). Activins are discovered in 1986 following the isolation of inhibins from porcine follicular fluid and are characterized as ovarian hormones that mediated FSH release by the pituitary gland (Simon et al., 2019 [8]). However, the studies concerned on the correlation between progesterone and activin A to predict pregnancy following IVF programs are limited; therefore, this investigation

is designed to found out the correlation of both hormones and pregnancy status following undergoing ICSI cycle.

## ***2. Patients and Methods***

The study was designed to be a prospective study. The sample size was 80 infertile women undergoing intracytoplasmic sperm injection. Who attended the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, and Al-Zaitoon Specialized Fertility Center, Baghdad /Iraq. The duration of the study is from November 2022 till June 2023. The women's ages ranged from (18 to 40) years old, and they complaining of primary and secondary infertility for a period ranged from more than one year. And two samples were collected from each woman, one in the day of OVA pick-up.

**1- Semen analysis:** A semen analysis was examined and diagnosed by a urologist to understand the cause of infertility. Semen samples from each male partner were collected after (3-5)

days of abstinence from masturbation next to the semen analysis laboratory according to WHO.(1999& 2021)

## **2- Women investigation:**

Women in the study had to have a series of hormone analyzes (E2, LH, FSH, Prolactin, TSH, AMH) for cycle day two or cycle day 3. Progesterone and Activin A were measured on the day of oocyte retrieval. The level of serum progesterone was measured using the Tosho technique. While the level of activin A in the serum was measured using a quantitative sandwich enzyme immunoassay technique. Pregnancy test was measured and recorded after 14 days of embryo transfer to detect the  $\beta$ -hCG titer.

**3-Statistical Analysis:** The data were analyzed using Statistical Package for Social Sciences (SPSS) version 23.0 and Microsoft Office 2010. The groups were compared by applying an independent sample t-test (Unpaired t-test compare between two groups), paired sample t-test

(Comparison of a single variable with two periods) and Chi-square (Comparison of non-continuous variables or percentages). The cut-off value, sensitivity, and specificity were calculated by using the Receiver operative characteristics (ROC) curve

### **3. Results**

#### **1- Pregnancy rate of patients involved in the present study**

Out of eighty infertile females, twenty-five were become pregnant (Pregnancy rate = 31%), as shown in (Figure 1., Table 1). There were no significant differences regarding mean females' age ( $p=0.488$ ), mean body mass indices ( $p=0.326$ ), and body mass indices ranking ( $p=0.713$ ) between pregnant and non-pregnant females (Table 1); in addition, there were no significant differences in types ( $p=0.140$ ) and duration of infertility ( $p=0.581$ ). Comparison of hormonal levels between pregnant and non-pregnant females

#### **2-The comparisons of hormonal levels between pregnant and non-pregnant**

patients were demonstrated in (Table 2). Accordingly, there were also no significant differences ( $p > 0.05$ ) in all hormones involved in the present study.

#### **3- Comparison of serum progesterone and activin levels between pregnant and non-pregnant females**

Serum progesterone levels at both days of oocyte pickup was significantly higher in pregnant females ( $9.22 \pm 0.54$  vs.  $4.47 \pm 0.44$ ;  $p < 0.001$ ) respectively (Table -3). There was also significantly higher serum activin levels at the day of oocyte pickup ( $2.19 \pm 0.04$  vs.  $1.52 \pm 0.04$ ;  $p < 0.001$ ) in pregnant females, as demonstrated in (Table 3).

#### **4- Serum progesterone and activin levels as a predictor of positive pregnancy**

Receiver Operative Characteristic curve (ROC curve) has been used to

calculate the serum progesterone and activin cut-off values at both days of oocyte pick-up as a predictor of a positive pregnancy with acceptable sensitivity, specificity, and good area under the curve .The cut-off value of serum progesterone at the day of oocyte pick up was > 7.5 ng/ml with sensitivity =80%, specificity=78%, and area under the curve = 0.853 .In addition, the cut-off value of serum activin at the day of oocyte pick up was > 1.85 ng/ml with sensitivity = 100%, specificity=86%, and area under the curve=0.966 (Table 4).

#### **5- Correlations between serum progesterone and activin levels with**

#### **patient's age and BMI in pregnant females**

There were no significant correlations between serum progesterone and activin levels at both days of oocyte pickup with age and body mass indices in pregnant females, as illustrated in (Table 5).

#### **6- Correlations between serum progesterone and activin A with other hormones in pregnant females**

There were no significant correlations between both serum progesterone and activin levels with other hormones in pregnant females, as presented in (Table 6).

**(Table 1):** Comparison of demographic features between pregnant and non-pregnant females

Demographic features		Pregnant females n=25	Non-pregnant females	p-value
Age (years) (Mean±SE)		29.44 ± 1.18	28.42 ± 0.83	0.488 F NS
BMI (Kg/m <sup>2</sup> ) (Mean±SE)		26.61 ± 0.51	25.97 ± 0.37	0.326 F NS
BMI ranking n. (%)	Normal	7 (28.0 %)	19 (34.5 %)	0.713 € NS
	Overweight	15 (60.0 %)	32 (58.2 %)	
	Obese	3 (12.0 %)	4 (7.3 %)	
Duration of infertility (years) (Mean±SE)		4.36 ± 0.36	4.09 ± 0.28	0.581 F NS
Type of infertility n. (%)	Primary	12 (48.0 %)	36 (65.5 %)	0.140 € NS
	Secondary	13 (52.0 %)	19 (34.5 %)	

NS: Not significant ( $p > 0.05$ ); BMI: Body mass index; F: Independent sample t-test; €: Chi square

**(Table-2):** Comparison of hormonal levels between pregnant and non-pregnant females

Hormones	Pregnant females (Mean ± SE)	Nonpregnant females (Mean ± SE)	p-value
LH (mIU/ml)	6.17 ± 0.72	5.58 ± 0.34	0.403 F
FSH (mIU/ml)	7.54 ± 0.69	8.68 ± 0.34	0.101 F
AMH (ng/ml)	2.63 ± 0.40	2.07 ± 0.18	0.151 F
E2 (pg/ ml)	21.96 ± 0.62	21.58 ± 0.43	0.620 F
E2 at time of trigger (pg/ ml)	1235 ± 154	1050 ± 99	0.305 F
Prolactin (ng/ml)	10.42 ± 0.81	11.07 ± 0.58	0.532 F
TSH (mIU/ml)	1.64 ± 0.14	1.99 ± 0.13	0.102 F

SE: Standard error; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; E2: Estradiol; AMH: Antimullerian hormone; TSH: Thyroid stimulating hormone; NS: Not significant ( $p > 0.05$ ); F: Independent sample t test

**(Table 3):** Comparison of serum progesterone and activin levels between pregnant and non-pregnant females

Parameter	Pregnant females	Nonpregnant females	p-value
P4 levels (ng/ml) at the day of oocyte pickup	9.22 ± 0.54	4.47 ± 0.44	< 0.001 T S
Activin levels (ng/ml) at the day of oocytes pick up	2.19 ± 0.04	1.52 ± 0.04	< 0.001 T S

ET: Embryo transfer; P4: Progesterone; S: Significant ( $p \leq 0.05$ ); T: Independent sample t test

**(Table -4):** ROC characteristics of serum progesterone and activin levels as a predictor of positive pregnancy

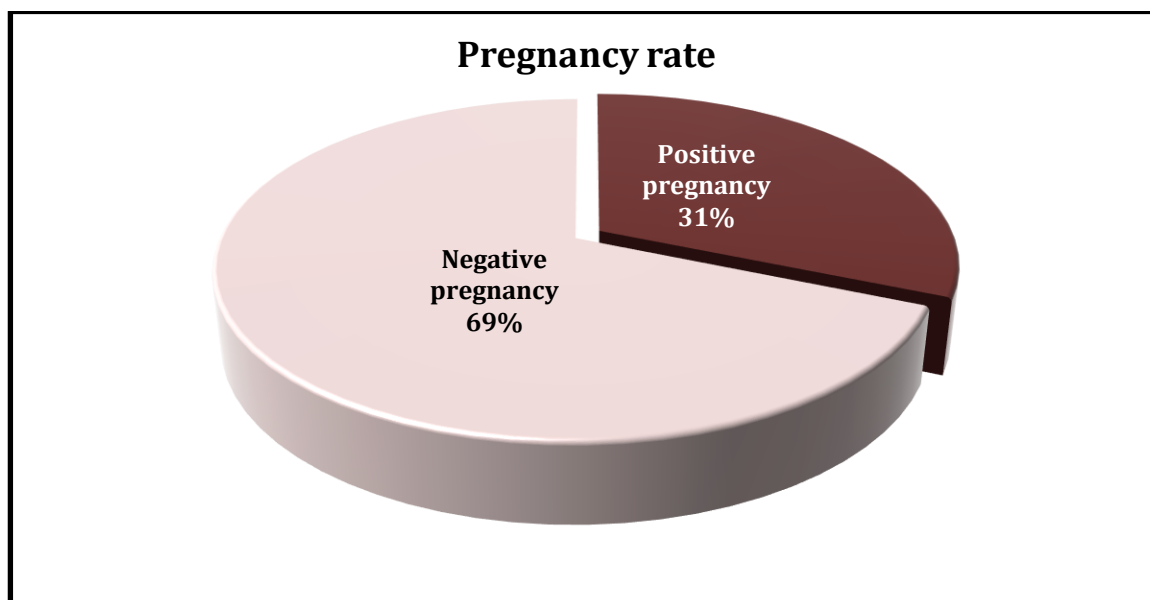
Parameter	AUC	Sensitivity	Specificity	Cut off value
P4 levels (ng/ml) at the day of oocyte pickup	0.853	80 %	78 %	7.5
Activin levels (ng/ml) at the day of oocytes pick up	0.966	100 %	86 %	1.85

ROC: Receiver operative characteristics, ET: Embryo transfer; P4: Progesterone; AUC: Area under curve

**(Table -5):** Correlations between serum progesterone and activin A levels with age and body mass index in pregnant females

Parameters		Progesterone at oocytes picks up	Activin A at oocytes pick up
Age	r	0.064	0.181
	p-value	0.573 NS	0.109 NS
Body mass index	r	-0.010	0.040
	p-value	0.931 NS	0.723 NS

ET: Embryo transfer; P4: Progesterone; r; Pearson's correlation coefficient; NS: Not significant (p > 0.05)



**(Figure 1):** Pregnancy rate of patients involved in the current study



**(Table-6):** Correlations between serum progesterone and activin levels with hormones in pregnant females

Hormones		P4 at oocytes pick up	Activin at oocytes picks up
LH	r	0.102	0.005
	p-value	0.628 NS	0.981 NS
FSH	r	0.309	-0.344
	p-value	0.132 NS	0.092 NS
AMH	r	-0.106	-0.231
	p-value	0.613 NS	0.267 NS
E2 basal	r	-0.151	0.045
	p-value	0.470 NS	0.832 NS
E2 \ trigger	r	-0.086	0.041
	p-value	0.682 NS	0.845 NS

ET: Embryo transfer; P4: Progesterone; r: Pearson’s correlation coefficient; NS: Not significant ( $p > 0.05$ ); S: Significant ( $p \leq 0.05$ )

#### 4. Discussion

Comparison of Serum Progesterone and Activin-A Levels between Pregnant and Non-pregnant Females

The present study showed that there was a significant increase in Progesterone levels in pregnant women

compared to the non-pregnant group.

At the same time. It has been reported that the rise in Progesterone is significantly

associated with the number of oocytes retrieved, which in turn is associated with successful IVF outcomes in fresh cycles. Elevation in Progesterone level

seems to be, therefore, an indirect parameter for predicting successful IVF outcomes in fresh cycles (Wilkinson., et al 2019 [9]).

More recent evidence suggests that serum Progesterone measured in early pregnancy is the most powerful single predictor of pregnancy outcome (Akan et al., 2011 [10]). Progesterone plays an important role in the uterus by increasing the thickness of the endometrium that, preparing it to receive the fetus. It has been proved that Progesterone administration was increased endometrium associated with better pregnancy outcomes (Aktan et al., 2004 [11]).

On the same time, the results obtained from the present work found a significant increase in the level of Activin A hormone in a pregnant group compared to non-pregnant women. It has been shown that Activin A can be a predictor of pregnancy (Piccinni et al., 2021 [12]). Activin A plays an important role in endometrial

differentiation, trophoblast invasion, and embryo implantation, and this hormone was expressed throughout the endometrial cycle in increasing amounts, with the highest levels of human endometrium also expresses Activin A receptors (Obuna et al., 2023 [13]). It has been reported that Activin A is secreted by the human endometrium as decidualization progresses by the effect of Progesterone (Alwan et al., 2013 [14]). Correlations between Progesterone and Activin A with other hormonal Levels in Pregnant and Non-pregnant Females

There was no significant correlation between the most reproductive hormones with progesterone and Activin A, in pregnant females. No correlation between the reproductive hormones with progesterone and activin, An indication of the normal physiological status of the hypothalamus–pituitary–ovary axis through the follicular phase (khalial et al., 2022 [15]) . It has been noticed that pregnant women had

higher estradiol levels are considered good responders (Barber et al., 2023 [16]). Estradiol is required for follicular development and plays an important role in embryo implantation with progesterone (Bloise et al., 2019 [17]). The estradiol /Progesterone ratio leading to facilitate the interaction of Activin A with the endometrial layer to enhance the implantation process.

## **6- Conclusion**

Pregnant women had higher levels of the hormone progesterone and Activin A than non-pregnant women, which is significantly correlated. This result can be utilized to predicate the pregnancy status early in IVF Centers.

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### **Author Contribution**

Noor S. Hamid performed the study, and Saad S. AL-Dujaily Wasan A. AL-Jubory supervised the work .

### **Conflict of Interest**

The authors declare no conflict of interest .

### **Ethical Clearance**

The study was approved by the Ethical Approval Committee.

### **Financial Disclosure**

There is no financial disclosure.

### **Ethical Clearance**

The study was approved by the Ethical Approval Committee

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