ISSN: 03875547
Volume 45, Issue 01, February, 2022

The Association of Serum CA-125 and Inhibin B Levels with Outcome in Ovarian Hyper stimulation and ICSI Cycles

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Keywords:
Serum CA-125, Inhibin B, Ovarian Hyper Stimulation, IVF, ICSI Cycles.

ABSTRACT

Looking for a simple, noninvasive, easy to perform, predictor to the ovarian response and outcome in ICSI cycle. We tried to evaluate the prognostic value of serum CA-125 and Inhibin B measurements in predicting ovarian response to gonadotropin stimulation as well as in predicting the outcome of ICSI cycle. Sixty infertile women were divided into three groups each of 20 women. 20 polycystic ovary diagnosed by Rotterdam criteria, 20 normal responders and 20 poor responders according to history of previous IVF trial, age and ovarian reserve parameters (AMH, Antral follicular count). All the women on the same protocol (antagonist). We compared the CA-125 and inhibin B levels of three groups of patients at 3 times of treatment cycles: first day of treatment, the day of ovulation trigger and at the day of oocyte retrieval. There was a significant difference in the mean levels of both CA-125 and Inhibin B among three groups of patients, with a significant positive and linear correlations between Inhibin B (pg/ml) and CA-125 (U/ml) at time of ovulation trigger among normal responders and poor responders which may aid the prediction of response and outcome in these groups. The aim of this study is to evaluate the association of serum CA-125 and Inhibin B levels with the outcome of ovarian hyper stimulation.

1. INTRODUCTION

Inhibin B has been suggested as an immediate organic chemistry marker of sex gland [1], and because of being made by granulosa cells and with the more understanding of the synthesis and secretion of the inhibin and their inherent endocrine role in the menstrual cycle, an awareness has been conducted to the likelihood of this family of peptides to produce a direct index and early sensitive predictor of ovarian reserve and an improved predictor of ART outcome [2]. Inhibins are dimeric polypeptide composed of &-subunit and BA-subunit (inhibin A) or BB subunit (inhibin B) [3]. It is believed that inhibin B is produced by a cohort of recruited follicles and might mirror the quantity of follicles at baseline [4]. Recently, CA-125 was advised as a possible predictor of IVF treatment outcome [5]. CA-125 is Cancer antigen which is a Trans membrane

glycoprotein expressed on the surface of germinal epithelium and other tissue derived from embryonic coelomic epithelium [6]. It was suggested that, the production of CA-125 is correlated with ovarian activity and the variation in its concentration during menstrual cycle may be due to cyclical changes in the female genital tract [7]. In addition, as the most convenient method of prediction of endomaterial receptivity is a non-invasive one and because CA-125 is produced by the endometrium, this made a suggestion that CA-125 can be used as a marker for endometrial receptivity and a predictor to the outcome in patients undergoing ART [8].

2. Material and Method

This is a prospective cross sectional study carried out on 60 infertile women referred to the fertility clinic in AL-Sadder teaching hospital AL Najaf-Iraq. The study conducted from 10th January 2021 to 10th September 2021, verbal consent was obtained from all patients. Full history, examinations and investigation done, and according to the findings, we divided the infertile women into 3 groups, 20 women for each one. 20 women with polycystic ovary diagnosed according to Rotterdam criteria, with exclusion of other causes of hyperandrogenemia. 20 non polycystic ovary who expected to be normal responder with adequate ovarian reserve parameters [AMH=1.2-3.5 ng/ml, Antral follicular count 4-14], non-advanced maternal mage (<35 years). other 20women who expected to be poor responder depending on the presence of two of 3 criteria, inadequate ovarian reserve test [AMH=0.5-1,1ng/ml, AFC 5-7]. Advanced maternal age (> 35 years) or other cause of poor ovarian response and previous incidence of poor ovarian response. We excluded male factor infertility, patient with endocrinological disease like DM, Thyroid disease also we exclude patient with uterine abnormality that may affect implantation like polyp and fibroid. Venous blood samples were taking to assay for CA-125 and inhibin B in the first day and before giving stimulation treatment, on the day of ovulation trigger and on the day of oocyte retrieval respectively. Samples were stored at -20C until assayed. The CA-125 concentrations were determined using Human Carbohydrate Antigen 125 [CA-125 ELIZA Kit [SunLong Biotech Co., LTD] with sensitivity range 0.05 U/ml. Dimeric Inhibin B was measured using Human Dimeric Inhibin B [DINH-B] ELIZA KIT, SunLong Biotech Co., LTD with sensitivity of 0,1 ng/l. All the women on flexible antagonist protocol with ovarian stimulation begun on the 2nd or 3rd day of spontaneous menstrual cycle by either, Recombinant FSH or with Human Menapausal Gonadotropin [HMG]. Monitoring of ovarian stimulation by serial tans vaginal sonography, while the leading follicle arrive a mean diameter of 14mm 0.25mg of GnRH antagonist {Cetrotide} was administered with the adjusted dose of Gonadotropins until the day of trigger by human chorionic gonadotropin [HCG] or by GnRH Agonist. Based on follicular size and E2 concentration retrieval of oocyte done 35 hrs., later under trans vaginal ultrasound guidance. Retrieved oocytes were fertilized with ICSI technique.0ne to three embryos per women were replaced 2 or 3 days after oocyte retrieval. Pregnancy test by β-HCG was done after two weeks of embryo transfer. Viability of pregnancy is confirmed by ultrasound at 5 ± 1 week of gestation, which considered main outcome of this study.

2.1 Data Analysis

Statistical analysis was carried out using SPSS version 25. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Independent samples t-test was used to compare means between two groups. ANOVA test was used to compare means between three groups or more. Pearson chi-square test was used to find the association between categorical variables. Pearson correlation coefficient (r) between (-1 to +1) was used to assess the relationship between two continuous variables. A p-value of ≤ 0.05 was considered as significant.

3. Results

ISSN: 03875547
Volume 45, Issue 01, February, 2022

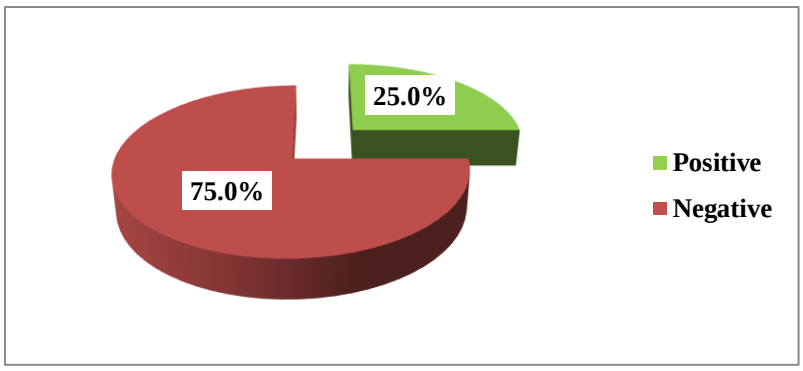

Figure (1): distribution of patients according to pregnancy outcome (N=60)

There were a significant differences between means of hormones including (FSH (P<0.001), LH (P<0.001), E2 (P<0.001) AMH (P<0.001) and TSH (P 0.021)) according to study groups Table (2).

Table (1): The mean differences of study variables according to study groups

Study variables	Study groups	N	Mean ± SD	F-test	P-value
FSH (IU/l)	Normal responders	20	5.23 ± 0.56	**78.157**	**<0.001***
	Poor responders	20	8.78 ± 1.78		
	Polycystic ovary	20	4.48 ± 0.73		
LH (IU/l)	Normal responders	20	3.73 ± 0.78	**123.328**	**<0.001***
	Poor responders	20	2.91 ± 0.68		
	Polycystic ovary	20	7.76 ± 1.47		
E2 (pg/ml)	Normal responders	20	55.24 ± 6.11	**46.244**	**<0.001***
	Poor responders	20	38.28 ± 7.50		
	Polycystic ovary	20	58.46 ± 7.66		
AMH (ng/ml)	Normal responders	20	2.76 ± 0.56	**180.091**	**<0.001***
	Poor responders	20	0.67 ± 0.26		
	Polycystic ovary	20	4.54 ± 0.92		
TSH (mIU/l)	Normal responders	20	2.43 ± 1.01	**4.126**	**0.021***
	Poor responders	20	3.41 ± 1.11		
	Polycystic ovary	20	2.64 ± 1.28		
Prolactin (ng/ml)	Normal responders	20	14.33 ± 7.91	0.244	0.784
	Poor responders	20	14.42 ± 7.88		
	Polycystic ovary	20	15.99 ± 9.41		

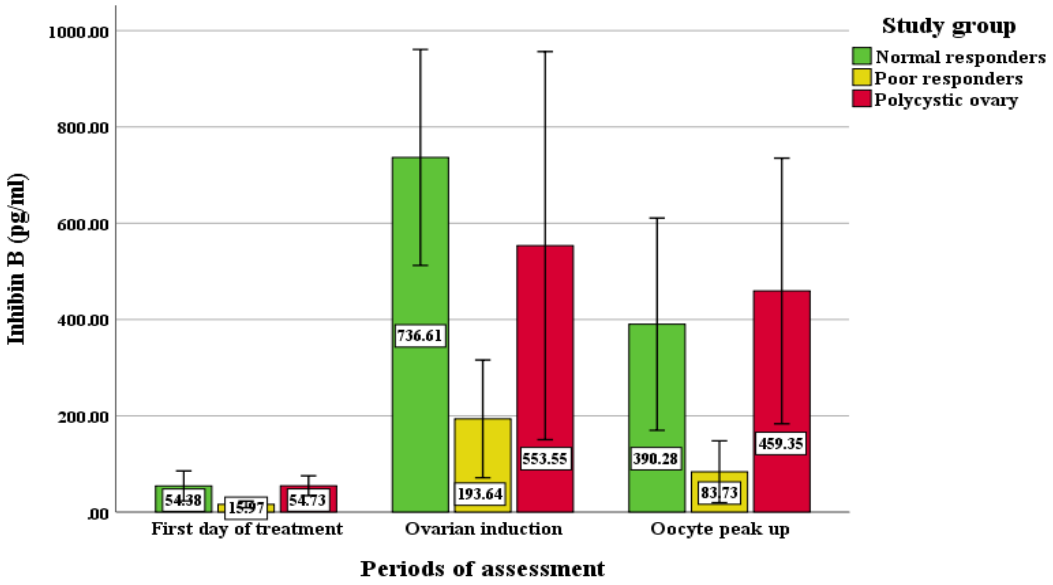

Figure (2): The mean differences of inhibin B (pg/ml) at three periods according to study groups

Regarding the mean levels of inhibin B (pg/ml) at three periods of assessment including (first day of treatment, at ovulation trigger and at Oocyte retrieval) according to study groups (normal responders, poor responders and Polycystic ovary patients), it was found that, there were significant differences (P <0.001) in the means of inhibin B (pg/ml) at three periods according to study groups with lower level of Inhibin B means at all three periods of assessment in poor responder women compared with normal responders and Polycystic ovary women while higher mean level of Inhibin B in Polycystic ovary patients at two time of assessment; first day of treatment (54.73 ± 10.28 pg/ml) versus (54.38 ± 15.54pg/ml) in normal responder and (15.97 ± 3.42 pg/ml) in poor responder and at time of oocyte retrieval (459.35 ± 137.90 pg/ml) in Polycystic ovary patients compared to normal responders (390.28 ± 110.20 pg/ml) and Poor responders (83.73 ± 32.12 pg/ml). In addition the higher level of inhibin B at ovulation trigger time was among normal responder women (736.61 ± 112.15) compared to polycystic ovary patients (553.55 ± 201.50 pg/ml) and poor responder patients (193.64 ± 61.17 pg/ml).

Regarding the CA-125, our results showed that, there were significant differences (P <0.001) between means of CA-125 (U/ml) at three periods of assessment according to study groups. The means of CA-125 were higher among PCO women in three times of assessment than normal and poor responder women, while lower mean levels of CA-125 at first day of treatment (13.20 ± 1.04) and at oocyte retrieval (16.72 ± 1.55) was among normal responder and lower mean levels of CA-125 at ovulation trigger day (14.08 ± 2.02) was among poor responder.

ISSN: 03875547
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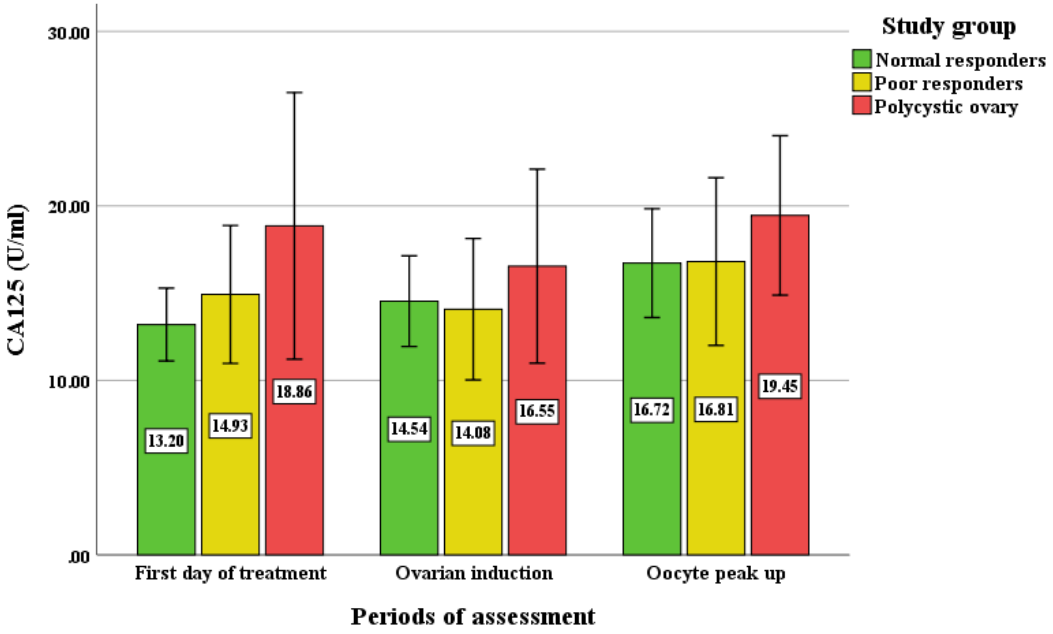

Figure (3): The mean differences of CA-125 (U/ml) at three periods according to study groups

Table (2): The mean differences of Inhibin B and CA-125 according to pregnancy outcome in three periods of assessment among normal responders, poor responders and polycystic ovary (N=20)

Study variables	Pregnancy	N	Mean ± SD	t-test	P-value
First day of treatment (normal responders)					
Inhibin B (pg/ml)	Positive	6	58.75 ± 13.26	0.815	0.426
	Negative	14	52.51 ± 16.51		
CA-125 (U/ml)	Positive	6	13.43 ± 0.89	0.645	0.527
	Negative	14	13.10 ± 1.11		
Ovulation trigger (normal responders)					
Inhibin B (pg/ml)	Positive	6	778.35 ± 69.65	1.095	0.288
	Negative	14	718.72±123.97		
CA-125 (U/ml)	Positive	6	17.91 ± 0.67	**3.422**	**0.003***
	Negative	14	16.20 ± 1.55		
Oocyte retrieval (normal responders)					
Inhibin B (pg/ml)	Positive	6	382.71 ± 91.78	-0.196	0.847
	Negative	14	393.52± 120.30		
CA-125 (U/ml)	Positive	6	14.25 ± 1.29	-1.54	0.141
	Negative	14	15.20±1.13		
First day of treatment (poor responders)					
Inhibin B (pg/ml)	Positive	6	16.66 ± 4.83	0.374	0.713
	Negative	14	15.84 ± 3.29		
CA-125 (U/ml)	Positive	6	14.30± 3.21	-0.584	0.566
	Negative	14	15.03 ± 1.80		

Ovulation trigger (poor responders)					
Inhibin B (pg/ml)	Positive	6	213.30 ± 17.81	1.219	0.244
	Negative	14	190.17 ± 65.71		
CA-125 (U/ml)	Positive	6	14.16 ±2.14	0.436	0.668
	Negative	14	13.60 ± 1.37		
Oocyte retrieval (poor responders)					
Inhibin B (pg/ml)	Positive	6	77.60 ± 12.66	-0.647	0.534
	Negative	14	84.80 ± 34.59		
CA-125 (U/ml)	Positive	6	16.38 ± 2.32	-2.049	0.055
	Negative	14	19.23 ± 1.02		
First day of treatment (polycystic ovary)					
Inhibin B (pg/ml)	Positive	6	58.21 ± 9.37	0.99	0.335
	Negative	14	53.24 ± 10.62		
CA-125 (U/ml)	Positive	6	17.75 ± 1.92	-1.121	0.277
	Negative	14	19.32 ± 4.37		
Ovulation trigger (polycystic ovary)					
Inhibin B (pg/ml)	Positive	6	526.85 ± 220.15	-0.379	0.709
	Negative	14	564.99 ± 200.58		
CA-125 (U/ml)	Positive	6	17.22 ± 3.02	**2.427**	**0.026***
	Negative	14	14.96 ± 1.12		
Oocyte retrieval (polycystic ovary)					
Inhibin B (pg/ml)	Positive	6	410.18 ± 137.68	-1.046	0.309
	Negative	14	480.4 ± 137.51		
CA-125 (U/ml)	Positive	6	19.26 ± 1.95	-0.235	0.817
	Negative	14	19.53 ± 2.47		

In Table (2), the mean differences of Inhibin B (pg/ml) and CA-125 (U/ml) according to pregnancy outcome (positive and negative) in three periods of assessment including (first day of treatment, at ovulation trigger and at Oocyte retrieval).

In normal responders women the results showed that, there were significant difference of CA-125 (P 0.003) at Ovulation trigger according to pregnancy outcome. The mean of CA-125 was increased (17.91 ± 0.67) in positive pregnancy outcome compared with negative pregnancy outcome (16.20 ± 1.55), while no significant differences of inhibin B according to pregnancy outcome (positive and negative) in three periods of assessment among normal responders. In poor responders the mean differences of Inhibin B (pg/ml) and CA-125 (U/ml) according to pregnancy outcome (positive and negative) in three periods of assessment the study results showed that, there were no significant differences of inhibin B and CA-125 according to pregnancy outcome in three periods of assessment. While in PCO women the mean differences of Inhibin B (pg/ml) and CA-125 (U/ml) according to pregnancy outcome (positive and negative) in three periods of assessment the study found that, there were a significant difference of CA-125 (P 0.026) at ovulation trigger according to pregnancy outcome among PCO women. The mean of CA-125 was increased (17.22 ± 3.02) in positive pregnancy outcome compared with negative pregnancy outcome (14.96 ± 1.12), while no significant

differences of inhibin B according to pregnancy outcome (positive and negative) in three periods of assessment including (first day of treatment, at ovulation trigger and at Oocyte retrieval) among polycystic ovary and there were no significant differences of CA-125 according to pregnancy outcome (positive and negative) at first day of treatment and Oocyte retrieval among polycystic ovary.

The correlations between Inhibin B (pg/ml) and CA-125 (U/ml) in three periods of assessment including (first day of treatment, at ovulation trigger and at Oocyte oocyte retrival) among study groups including (normal responders, poor responders and polycystic ovary) were significant positive linear correlation between Inhibin B and CA-125 at time of ovulation trigger among normal responders (r=0.594, P=0.006*) and among poor responders (r=0.453, P=0.045*) as shown in Figure (4), (5).

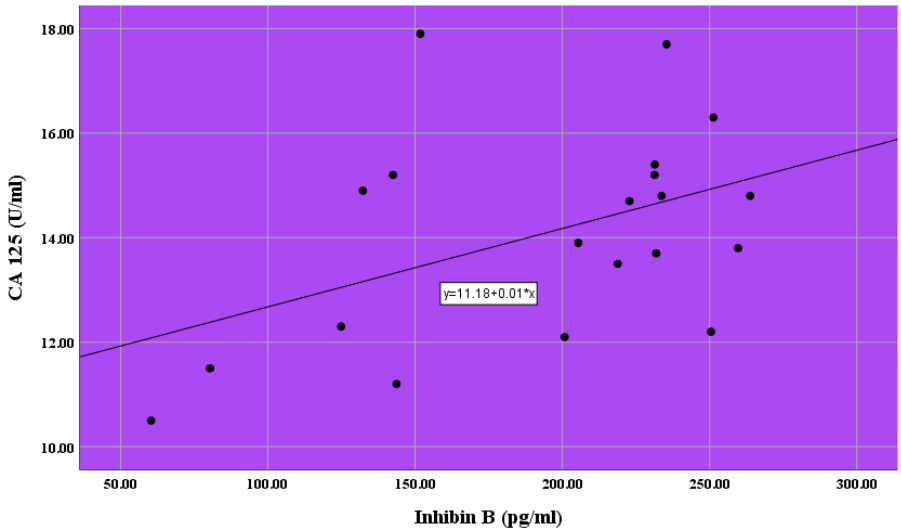

Figure (4): Correlations between Inhibin B (pg/ml) and CA-125 (U/ml) at ovulation trigger (r= 0.453, P=0.045*) among poor responders

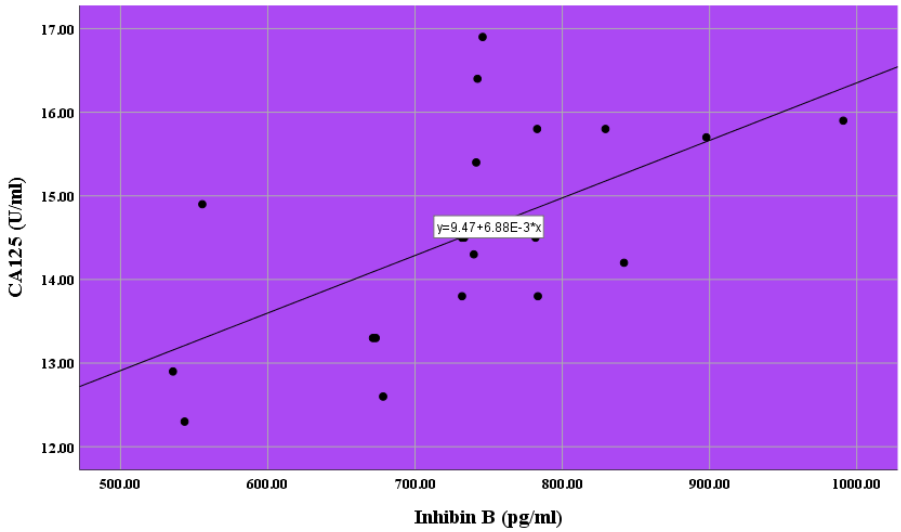

Figure (5): Correlations between Inhibin B (pg/ml) and CA-125 (U/ml) at ovulation trigger (r= 0.594, P=0.006*) among normal responders

4. Discussion

As far as we know there was no previous study compare the 3 heterogeneous groups of infertile women

(normal responder, poor responder and PCO) to evaluate the relationship of inhibin B and CA-125 in predicting the outcomes of ICSI in fresh ART cycles. This heterogeneity was clear in their differences in physical, hormonal and endocrinological characteristics. In our study, there was a significant difference of mean inhibin B (figure2) and CA-125 (figure3) at three periods of measurement according to the study groups. In polycystic ovary patients, the serum inhibin B concentration was increased with higher level at the first day of treatment and at the time of oocyte retrieval in comparison to other groups. This may be due to the fact that, polycystic ovary often contains more antral follicles than normal ovaries, which could be a potential source of inhibin B. In addition, the elevated levels of androgen secreted by the hypertrophied thecal layer in polycystic ovary may increase stimulation of inhibin B secreation from granulosa cells [9], this may be in similar to previous study of [10], who found that, the mean inhibin B concentration in polycystic ovary women after rFSH stimulation was higher than normal ovaries, which could be due to the higher sensitivity of granulosa cells in PCO to FSH treatment and to the suggestion of its abnormal endocrinological property than normal granulosa cells lead to more response to stimulation treatment. Regarding CA-125 In polycystic ovary. Our study found that, the highest mean concentration of CA-125 was among polycystic ovary patients at all three times of assessment according to the study groups, but generally within the normal range (<35 U/ml) [11] (figure3), this might reflect the higher number follicular development in PCO. This is agree with [12] who noted that, the increasing CA-125 serum concentration is well related to the growth of dominant follicle, and [13] who concluded that, the production of CA-125 may in some way reflect the proliferative activity of ovarian tissue, this involves angiogenesis and proliferative activity of the theca and granulosa cells, if considering CA-125 is coming from one of these ovarian compartment [14].

As well as, this elevation in CA-125 levels in polycystic ovary patients may be an indicator of an ovarian abnormalities in polycystic ovary [15]. There is a significant difference of CA-125 concentration according to pregnancy outcome (earliest fetal viability), we found that, positive pregnancy outcome associated with increased mean level of CA-125 at ovulation trigger time (table2). The normal responder patients in our study revealed a highest mean inhibin B concentration at ovulation trigger day (figure 2), this may postulated that, the inhibin B takes part in the mechanism of terminating ovulatory FSH signal [16], which may predict the outcome of stimulation treatment , this result may simulate the finding of [17] that the women who achieved successful pregnancy after IVF, inhibin B concentration on the day of HCG administration were greater than those women who did not become pregnant [18]. In comparison to PCO and normal responder, the suspected poor responder women had a lower mean inhibin B levels at all 3 times of assessment which may aid the idea of potential endocrine role of inhibin B, and it's critical paracrine regulation of follicular and oocyte quality as it was reported to be decrease with reproductive aging and being the earliest marker of the decline in follicle number and may be a marker of follicular quality [19]. When compare CA-125 concentration between normal and suspected poor responder women, it was lower at the first day of treatment and at the time of oocyte retrieval among normal responder but higher at ovulation trigger (figure3) and there was a significant difference of CA-125 according to pregnancy outcome with higher mean at the ovulation trigger time in positive pregnancy among normal responder patients while there is no significant difference according to pregnancy outcome in suspected poor responders (table2). This finding may indicates that, there is a relation between the low levels of CA-125 at the time of ovulation trigger and poor pregnancy outcome which may be due to either poor ovarian response or poor endometrial receptivity or may be both of them, a theory which may be supported by [20], who displayed that, higher CA-125 levels in pregnant than in non-pregnant cycle on the day of ovulation trigger. While at the time of oocyte retrieval although it wasn't a significant relation in the study groups but we found that the pregnancy positive outcome associated markedly with the decreased CA125 concentration similar to [21] who found significantly lower CA-125 concentration in pregnant than in non-pregnant women at oocyte retrieval. It is possible that, measurement of CA-125 on the day of oocyte retrieval reflects the actual state of the endometrium and may predict its tendency to shading [22].

It seems that, the endometrium is more compact without any trend to shading and somehow more `receptive' to embryo implantation when CA-125 values are low at the time of oocyte retrieval. This agree with [23] who found, rising CA-125 concentration during menstruation, which may be due to an easier access of CA125 from endometrial epithelial lining into the circulation. However, a functional rather than quantitative changes of the endometrium may still be the origin of CA-125 changes [24]. In our study, there were a positive correlation between serum inhibin B and CA-125 levels at time of ovulation trigger in both normal responder and poor responder women. The suggested explanation for this positive correlation may be because of the decrease in ovarian blood tissue barrier, this barrier may prevent CA-125 from getting out of follicular fluid to circulation [25], but due to follicular stimulation by gonadotropin and the result angiogenesis in the luteinized ovaries allowing CA-125 to escape from follicular fluid to the circulation [26], which may be due to displacing CA-125 into the circulation by elevated follicular fluid inhibin and/or E2, causing increase levels of circulating CA-125 as well as inhibin B [27].

5. Conclusions

Measurement of inhibin B level at the beginning of ovarian stimulation might help us to identify type of ovarian response to treatment in all infertile women (normal, poor and high) responder and may allow for choosing treatment. In polycystic ovary patients, the serum inhibin B concentration was increased with higher level at the first day of treatment and at the time of oocyte retrieval in comparison to other groups. In normal responder patients in our study revealed a highest mean inhibin B concentration at ovulation trigger day while the suspected poor responder women had a lower mean inhibin B levels at all 3 times of assessment. There was a significant difference of mean inhibin B and CA-125 at three periods of measurement according to the study groups with a positive correlation between serum inhibin B and CA-125 levels at time of ovulation trigger in both normal responder and poor responder which may aid prediction of treatment outcome in them at that time. higher mean level of CA-125 was among PCO women at all three times of assessment according to the study groups with a significant association of early viable pregnancy and increased mean level of CA-125 at ovulation trigger time but, in spite of its increased concentration in response to ovarian stimulation in a different way in the different groups there is a marked association of deceased level of CA125 at the time of oocyte retrieval and early pregnancy viability in all 3 different groups which may indicates its relation to endometrial receptivity as a functional changes of the endometrium may result in that CA-125 concentrations changes.

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