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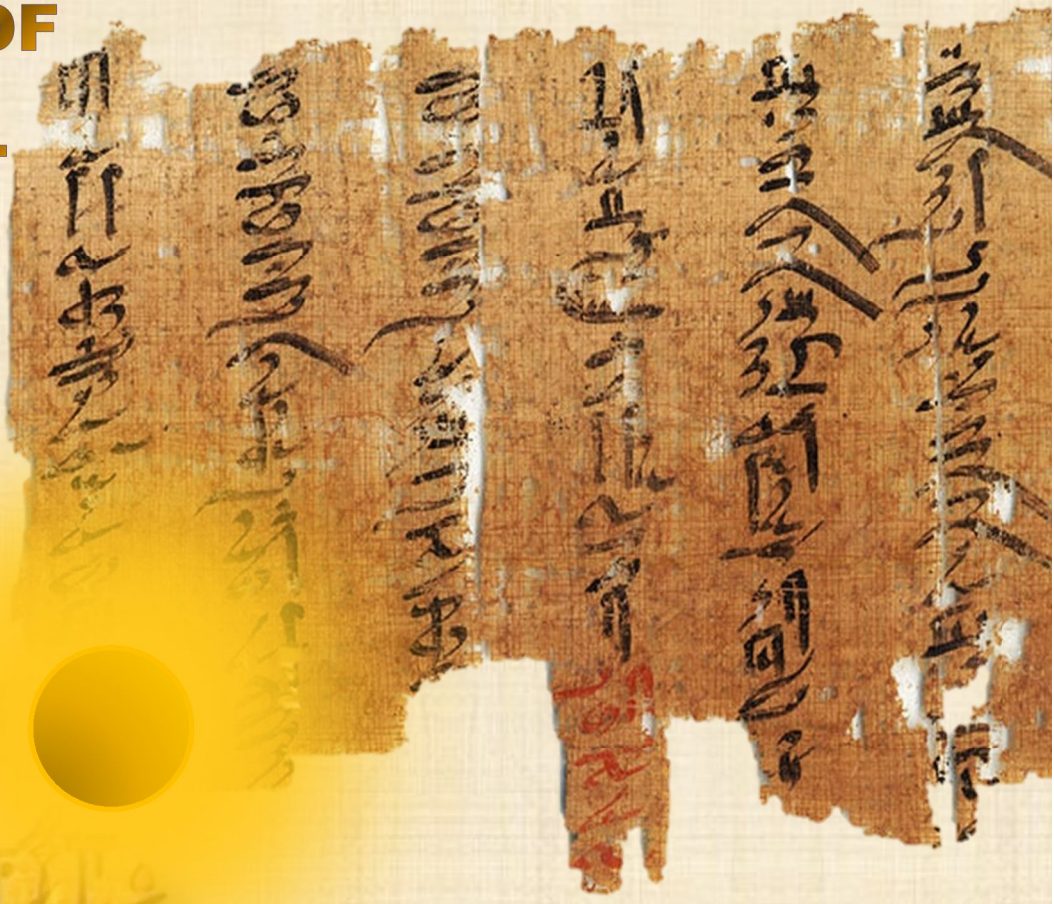

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Original article

The Value of Serum Progesterone Level at The Day of Triggering in Prediction of Intracytoplasmic Sperm Injection [ICSI] Outcome

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ABSTRACT

Background: The potential association of serum progesterone on the day of human chorionic gonadotropin administration with the outcome of intracytoplasmic sperm injection [ICSI] cycles has been one of the major controversies in the endocrinology of ovarian stimulation.

Aim of the work: This study was conducted to estimate the net effect of progesterone elevation on the day of human chorionic gonadotrophin [hCG] on pregnancy outcome in women undergoing fresh embryo transfer in control ovarian stimulation using long agonist and antagonist protocols.

Patients and Methods: This is a prospective study included a total of 177 patients who were indicated for ICSI. The included cases were divided into three groups according to progesterone level at the day of hCG. Both progesterone and E2 were estimated at the day of triggering.

Results: Serum progesterone levels did not differ between cases who got pregnancy and who did not (p=0.435). Estrogen/Progesterone ratio was not significantly different between pregnant and non-pregnant females (p= 0.842).

Conclusion: Progesterone level on the day of hCG administration does not have any effect on ICSI outcome.

Keywords: Progesterone; ICSI; Estrogen/progesterone ratio; Triggering; Outcome

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

The presence of receptive endometrium, functional embryo, along with synchronization between embryo and endometrium are essential prerequisites for a pregnancy to occur[1]. Therefore, the success of in-vitro fertilization will be limited if there is failure to achieve receptivity and synchrony. Endometrial receptivity is driven by time of progesterone exposure after sufficient exposure to estrogen. The time period at which the endometrium is ready to receive and support the trophoblast is called 'window of implantation', and it is limited in time[2].

With the introduction of gonadotrophin releasing hormone [GnRH]-analogue as an ovarian stimulation protocol for IVF, 'premature luteinization' (progesterone rise during the late follicular phase) could be avoided[3]. However, that premature rise of progesterone in stimulated IVF cycles occurs frequently in daily practice (38% of cases), despite the administration of GnRH-analogue [4].

Premature elevation of progesterone levels with GnRH-analogue administration in the presence of normal luteinizing hormone [LH] levels is due to ovarian overstimulation not due to premature luteinization [5]. There is an emerging evidence suggesting that premature elevation of progesterone levels has a negative outcome on the stimulated cycles[6]. In a previous prospective study, Bosch and his associates reported significant lower pregnancy rates when progesterone-levels were more than 1.2ng/ml. Authors also reported that cases with higher progesterone levels had higher doses of follicle stimulating hormone [FSH] along with more prolonged stimulation. Therefore, enhanced FSH-stimulation may be the cause of progesterone rise[7]. In a larger meta-analysis that included more than 60,000 cycles, a significant negative correlation had been detected between pregnancy rates and progesterone levels of≥ 0.8ng/ml[6].

AIM OF THE WORK

This study was conducted to evaluate the predictive value of progesterone level estimation at the day of triggering and its relation to the reproductive outcome after intracytoplasmic sperm injection [ICSI].

PATIENTS AND METHODS

This is a prospective study, which had been conducted over a period of one year, from June 2017 to May 2018.

It included females who undergoing ICSI at assistive reproductive technique [ART] unit, Al-Azhar University.

A total of 177 females were included in the study with the following criteria: Age < 38 years, FSH < 10 mIU/ml, and fresh embryo transfer. Exclusion criteria were: patients with endocrine disorders or endometriosis, mullerian duct anomalies, and patients with chronic diseases like diabetes, hypertension.

Patients were classified according to progesterone level at the day of hCG into three groups. ***Group1,*** included 91 patients with serum progesterone less than 1 ng/ml. ***Group2*** included 48 cases with serum progesterone between 1 and 1.5 ng/ml. ***Group3,*** included 38 cases with serum progesterone level ≥ 1.5 ng/ml.

All patients had been started ovarian stimulation and were commenced on either long agonist (98 cases) or antagonist protocols (79 cases) for ICSI.

Ovulation induction started at the second day of bleeding by 150-225IU of recFSH (hMG, Menogon, 75 IU, Ferring Pharmaceuticals).

Follicular tracking was continued until scanning showed at least three mature follicles. Triggering had been performed by intramuscular injection of hCG (Pregnyl 10000 IU, Organon, Klooster-straat, Nether-lands).

On the day of hCG administration, serum progesterone evaluation was performed. All blood samples for hormone measurements were analyzed in our laboratory by the VIDAS equipment analyzer with ELFA (enzyme linked fluorescent assay) technique. Each blood sample was analyzed on the day of collection.

Ovum pick up had been performed 36 hours later. Embryo transfer was done at day 2-5 after pick up.

Luteal phase support by vaginal progesterone gel (Crinone gel 8%, Merck-Serono, Germany) was given for two weeks until clinical pregnancy was confirmed, and then it was continued during the first

trimester. Pregnancy rate was calculated and documented. The primary outcome of the current study was to evaluate the effect of the predictive value of progesterone level estimation at the day of triggering and its relation to the reproductive outcome after ICSI. The implantation rate was our secondary objective.

Ethical consideration: A written informed consent was obtained from all patients before participating in the study. Besides, the study was approved by the local ethical committee of Al-Azhar University [IRB0012367 (17-04-001)].

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher exact were used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean±SD (Standard deviation).

Independent samples *t*-test was used to compare between two independent groups of normally distributed variables (parametric data) while Mann Whitney [U] test was used for non-normally distributed Data (non-parametric data). Three or more groups of quantitative data were analyzed by analysis of variance (ANOVA) with a Tukey post hoc test to test the intergroup significance.

RESULTS

The patients' characteristics were illustrated in table [1]. The mean age of was 29.34 years (range 18–40). Long agonist protocol was commenced for 98 cases (55.4%), whereas the antagonist protocol was commenced for 79 cases (44.6%).

According to progesterone levels at trigger, patients with values < 1ng/ml were 91(51.4%), those with values from 1 – 1.5ng/ml were 48 (27.1%) and patients with values ≥ 1.5ng/ml were 38 (21.5%).

According to the total pregnancy rate, 82 cases got pregnant (46.32%), whereas no pregnancy were recorded in 95 cases (53.67%) [Table 2]. Age was significantly lower in the group with lowest progesterone levels, while it was relatively older in the third group (p = 0.001). Conversely, no significant difference was detected regarding the protocol used (p = 0.18) [Table 3].

As shown in [Table 4], no significant difference was detected between the three groups regarding laboratory values apart from progesterone and E2/P ratio. The former was significantly lower in the first group and thus, E2/P ratio was significantly higher at the same group.

Pregnancy rate was not significantly different between different groups [Table 5]. None of the studies parameters including progesterone or E2/P ratio differed significantly between pregnant and non-pregnant ladies [Table 6].

Table [1]: Patient characteristics among studied populations

Items		Studied patients (n=177)
Age	Mean±SD	39.34±5.3
	Median	30
	Min.- Max.	18-40
Regimen	Long agonist	98 (ᵓ5.4%)
	Antagonist	79 (44.6%)

Table [2]: Pregnancy rate among studied populations

Items	Study cases [n=177]
Positive	82 (46.32%)
Negative	95 (53.67%)

Table [3]: Relation between patient characteristics and progesterone level.

		E/P ratio						Test	p
		< 1 (N=91)		1-1.5 (N=48)		≥ 1.5 (N=38)			
Age (years)		28.96 ± 5.31		27.21 ± 4.57		31.36 ± 4.89		F= 7.244	P = 0.001*
Regimen	Long agonist	47	51.6%	32	66.7%	19	50%	χ2= 3.432	P= 0.180
	Antagonist	41	48.4%	16	33.3%	19	50%		

Table (4): Hormonal levels in relation to progesterone level.

	E/P ratio			Test	p
	< 1 (N=91)	1-1.5 (N=48)	≥ 1.5 (N=38)		
FSH (IU/ml)	5.9 (4.8-7.3)	5 (4.22-6.55)	5.5 (4.05-7.25)	2.453	0.293
LH (IU/ml)	3.6 (2.6- 5)	3.4 (3.2-4.65)	3.35 (2.53-5.05)	1.208	0.547
PRL (ng/ml)	14.31 (10.46-21.26)	17.26 (11.61-23.41)	14.76 (12.14-18.26)	1.120	0.571
AMH (ng/ml)	0.95 (0.63-4.35)	0.81 (0.65-1.24)	0.84 (0.65 – 1.58)	1.285	0.526
E2 (ng/ml)	0.043 (0.033-0.055)	0.046 (0.036-0.062)	0.045 (0.034-0.061)	1.107	0.575
TSH (IU/ml)	2.1 (1.5-3)	2.5 (1.9-3.3)	2.1 (1.5-3)	5.845	0.054
E2 at trigger (ng/ml)	2.92 (2 -3.54)	2.67 (2.02-3.43)	2.68 (2.06-3.77)	0.802	0.670
Progesterone at trigger (ng/ml)	0.76 (0.51-0.78)	1.2 (1.09-1.30)	1.9 (1.7 -2.5)	17.273	< 0.001*
E/P	4.33 (3.19-5.25)	2.17 (1.66-2.88)	1.41 (0.97- 1.72)	13.217	< 0.001*

Table [5]: Comparison of the pregnancy outcomes according to progesterone level categories.

		E/P ratio						Test of significance
		< 1 (N=91)		1-1.5 (N=48)		≥ 1.5 (N=38)		
Pregnancy	Positive	40	44%	26	54.2%	16	42.1%	χ2= 1.665
	Negative	51	56%	22	45.8%	22	57.9%	P= 0.435

Table [6]: comparison between pregnant and pregnant cases regarding E2 at trigger, Progesterone at trigger and E/P ratio

Parameter	Pregnant cases(no. =47)	Non pregnant cases (no.=53)	Test and P -value
E2 at trigger (ng/ml)	2.8 (2.11-3.75)	2.71 (1.9-3.49)	z= -0.678 P = 0.498
Progesterone at trigger (ng/ml)	1 (0.67-1.33)	0.88 (0.63-1.41)	z= -0.102 P = 0.919
E/P ratio	2.68 (2.03-4.17)	2.92 (1.55-4.61)	z= -0.199 P = 0.842

Discussion

Despite the wide use of GnRH analogues for pituitary down-regulation in controlled ovarian stimulation (COS) cycles for IVF, subtle increases in serum progesterone levels are still observed at the end of the follicular phase in many cases[8]. The clinical impact of this has been highly controversial for many years, with some studies that could not find any association between progesterone levels and pregnancy rates[9-11], whereas others have reported a negative impact on cycle outcome when serum progesterone levels are increased on the day of hCG administration[7, 12-13]. It must be taken into consideration that the majority of studies that failed to demonstrate an association between serum progesterone levels and pregnancy rate used a threshold value of 0.9ng/ml, which was mostly chosen arbitrarily without performing a trend analysis to identify an association between progesterone levels and pregnancy[9]. This clinical trial aimed to estimate the net effect of progesterone elevation on the day of hCG on pregnancy outcome in female undergoing fresh embryo transfer in controlled ovarian stimulation using long agonist and antagonist protocols. Another study handling the same perspective included a total of 302 cases. Patients were started on antagonist (n=241), short (n=47) or long (n=14) agonist protocols, according to their infertility evaluation[14]. Comparable to the present work, one study included a total of 12 cases and patients were divided according to progesterone level into two equal groups; one with progesterone levels

<1.5ng/ml, while the other group had higher levels[15].

In our study, younger age was significantly associated with progesterone levels < 1 ng/ml, while the group with highest progesterone level were relatively older (average, 31.36 years). A previous study also reported a significant difference regarding age between progesterone level-based groups (p=0.017). However, age was significantly higher in the group with lower progesterone levels[15]. In contrary to this study, some studies reported that age was not a significant factor between the study cases after classifying them according to progesterone level. Cases with progesterone level < 1.5 ng/ml had a mean age of 32.97 years, while cases with higher levels had a mean of 32.43 years[14]. Endometrial receptivity could rely on the supra-physiological levels of ovarian steroid hormones. Therefore, age should not be considered as a confounding factor[16], except for cases of very advanced maternal age [17]. The protocol used did not differ between our three study groups (p = 0.180). The long agonist protocol was used in 51.6, 66.7, and 50% in the 3 groups respectively. **Abolfotouh *et al.*** reported also no significant difference between the study groups regarding the used protocol. The agonist protocol was used in 49.2 and 50.8% of cases in both groups respectively (p = 0.28)[14].

In our study, progesterone level at trigger day was significantly different between the three groups. Therefore, E/P ratio was significantly higher in the first group (p < 0.001) in relation to the other two groups. Another study reported the same significance regarding progesterone levels at the trigger day (p < 0.001). It had a mean of 0.54 and 2.39 ng/ml in cases with progesterone level <1.5 and > 1.5 ng/ml respectively [15].

Pregnancy rate in the current work reached 46.32%, and serum progesterone levels did not differ between pregnant and non-pregnant patients. A pooled analysis of data from six trials (n=1890 cycles) by Griesinger et al. supported that progesterone elevation (> 1.5 ng/ml) does not seem to compromise ongoing pregnancy rates in high responders (> 18 oocytes)[18]. Another study had confirmed these finding as there was no relationship between progesterone level on the day of hCG administration and pregnancy events (p=0.89)[19]. Another study reported that pregnancy rate in the followed-up cases was 36.7%. A significant negative association was detected between progesterone level at hCG day and the pregnancy outcomes, as serum progesterone has significantly high in non-pregnant compared to pregnant cases (2.26 vs 1.84, p = 0.018)[14].

Miller *et al.* showed that the elevation of progesterone levels in 293 patients subjected to controlled ovarian stimulation [COS] with hMG and/or FSH in a GnRH agonist protocol did not affect oocyte quality and pregnancy rate[20]. The findings of Miller *et al.* were corroborated by **Hamdine *et al.*** who conducted a prospective interventional study with 158 in vitro fertilization [IVF]-ICSI patients. The authors showed that the incidence of progesterone elevation [PE] (>1.5 ng/ml) was 13.3%, but ongoing pregnancy rates [OPRs] were not significantly different between patients with normal progesterone levels and PE (27.0 versus 19.0%)[21]. Conversely, a rise of progesterone during the late follicular phase (P4) has been considered a negative predictive factor for clinical outcome in both GnRH agonist[22-23] and antagonist protocols[8, 24].

Huang *et al.* in a study of 2566 patients, reported that E/P ratio negatively correlated with live birth in fresh embryo transfer cycles[25]. Data from large previous retrospective and prospective studies supported the notion that pregnancy rates are inversely related to P4 levels, especially when a threshold of 1.5ng/ml is adopted[24, 26].The relationship between PE and pregnancy rate has been analyzed by using different thresholds of serum progesterone on the day of hCG. The thresholds were varied and found to be between 0.4ng/ml and 3ng/ml[6]. The analysis of a large series by Bosch, et al.; the optimal progesterone threshold over which a detrimental effect on IVF outcome might be observed has been estimated at 1.5ng/ml [24].

In our study, E/P ratio was not significantly different between pregnant and non-pregnant females (p= 0.842). It had a mean of 2.68 in the pregnant ladies, while non-pregnant cases had a mean of 2.92. E2/P ratio is thus a supposed marker for endometrial receptivity which up regulates adhesion molecules on the endometrial pinopods and equivalent ligands on the blastocyst for

successful implantation[27]. Research has been done to evaluate the role of E2/P ratio in the luteal phase however; the results are debatable [21, 27- 28]. Another study has reported that measurement of E2/P ratio in ICSI cycles is not of clinical value to predict clinical pregnancies [27].

Conclusion: progesterone level on the day of hCG administration does not have any effect on pregnancy outcome. To reach decisive and final result, further and broader studies with same classified progesterone level in this area should be conducted.

Financial and Non-Financial Relationships and Activities of Interest

Authors declare that, there was no competing interest

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