

Does the E2/P Ratio Predictor have a Role in the IVF Outcome during Ovulation Induction?

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Abstract: *Objective:* The present study investigates the role of hCG day serum P/E ratio in predicting the chemical pregnancy rate in cycles subject to *in vitro* fertilization - intracytoplasmic sperm injection - embryo transfer (IVF-ICSI-ET) following controlled ovarian stimulation (COS) accompanied by gonadotropin-releasing hormone agonists (GnRH).

Methods: The study retrospectively examined a total of 2,517 patients treated with IVF. All patients underwent an oocyte pick-up (OPU) procedure, and subjects were included in the GnRH-agonist short protocol study upon a total of 140 fresh embryo transfers based on inclusion/exclusion criteria.

Findings: The hCG day P/E ratio of the patients that did not end in chemical pregnancy was found 0.7415 ± 0.0010285 , which was 2.4637 ± 0.0099075 for those ended in chemical pregnancy. The P/E ratio of patients with and without chemical pregnancy was not statistically significant ($p=0.718$).

Conclusion: In IVF patients subject to fresh embryo transfer and administered an agonist cycle, the ratio of serum P level to the E level on the same day does not seem to be an effective parameter in predicting the rate of chemical pregnancy. Further studies with wider series of patient populations are required to clarify this matter.

Keywords: Gonadotropin-releasing hormone agonist protocol, hCG-day, progesterone, progesterone/estradiol ratio.

INTRODUCTION

Regarding IVF cycles, the embryo implantation stage is still the most important stage that limits reproductive success [1]. Embryo implantation is the result of a perfect adjustment between the embryo and endometrium [2]. A fitting endometrium is needed for the blastocyst implantation and maintenance of pregnancy [3]. Ovarian steroids (estrogen and P) are required for a proper endometrial development. Endometrial development takes place with estrogen on the follicular phase and with P on the luteal phase. In the follicular phase, E plays a role in the epithelial, stromal and glandular proliferation of the endometrium [4]. P, on the other hand, is active in the luteal phase and involved in numerous functions including implantation [5]. In gonadotropin-induced cycles, by contrast to natural cycles, supra-physiological E and P levels in the early luteal phase cause an early endometrial development, leading to a disproportionate development with the embryo in the period of implantation [6].

Many IVF practitioners now prefer the short protocol for it is more convenient and more effective in

individuals with poor ovarian reserves [7]. GnRH agonist is highly important in determining the superior aspects of the treatment protocol and improving the outcomes [8,9]. In this context, the present study aimed to investigate the impact of P/E ratio on the day of ovulation induction on the pregnancy outcomes among the patients receiving IVF treatment subject to an agonist protocol.

MATERIALS AND METHODS

We examined the patients who referred to the IVF center at our hospital over a period of six years from March 2010 to November 2016. The study was approved by the Local Ethics Committee. Universal principles of the Helsinki Declaration were applied to the study. Of 2517 IVF patients in total, 140 patients that met the research criteria for this study were recorded subsequently. The database of our IVF department was scanned in detail in order to identify those patients who received GnRH agonist only with the short protocol and IVF-ICSI-ET for the treatment of infertility. Based on their medical history at the time of first referral, we included a group of 140 patients between 25 and 39 years of age, who underwent pelvic examination, and who were administered an IVF treatment due to tubal factor, polycystic ovary syndrome, unexplained infertility and mild-to-moderate malefactor. On days 2 and 3 of the cycle, baseline

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serum follicle-stimulating hormone (FSH), LH, E2, prolactin, thyroid stimulating hormone (TSH), and free T3 and T4 levels were measured for every patient subject to evaluation. Patients with serum FSH>12 IU/ml and E2>80 pg/ml, measured on days 2 and 3 of menstruation, were excluded from the study. Among them, patients with the following characteristics were excluded: those who underwent TESE (Testicular Sperm Extraction) due to azoospermia, cycles subject to embryo transfer and freezing-thawing cycles, and those with identified genetic anomalies. Also, those patients with a history of more than two unsuccessful applications of (COH) + assisted reproductive techniques (ART), uterine pathologies or autoimmune diseases were excluded as well.

Statistical Method

The data of the study were analyzed with Statistical Package for the Social Sciences (SPSS) 20 program (SPSS Inc., Chicago, IL, USA). A two-way P value <0.05 was accepted to be significant. Continuous variables are presented as mean, median, minimum-maximum value, sample size and standard deviation. The optimal threshold P/E values were analyzed using the Receiver Operating Characteristics (ROC) analysis.

The impact of P/E ratio on overall pregnancy rates was evaluated by logistic regression analysis. The logistic regression model was adjusted to age and the number of embryos transferred.

RESULTS

From March 2010 to November 2016, a total of 2517 patients were subject to the oocyte pick-up (OPU) procedure, and 140 agonist cycles with fresh embryo transfers were included in the study based on inclusion/exclusion criteria. Patients' baseline demographic, clinical and laboratory characteristics are shown in Table 1. COH, oocyte pick-up, embryo growth data and pregnancy outcomes of subject matter cycles are shown in Table 1. Chemical pregnancy and live pregnancy rates were found to be 19.3% and 8.8%, respectively. A ROC (Receiver Operating Characteristic) curve analysis was performed in order to determine a highly sensitive and specific P/E cutoff value that would predict post-cycle positivity of chemical pregnancy (Figure 1). The area under the curve (AUC) was found to be 0.512 (95% confidence interval: 0.407-0.638); however, it was not statistically significant ($p=0.718$).

Table 1: Baseline Demographic, Clinic and Laboratory Characteristics and COH, Oocyte Pick-Up, Embryo Growth and Pregnancy Outcomes of ICSI Patients at Agonist Cycles

Parameter	Value	Parameter	Value
Age, (year)	33.96±4.14	Stimulation time (day)	9.54±2.51
Body mass index, (kg/m ²)	24.48±4.29	Total FSH (IU)	3322.2±1192.3
Period of infertility, (year)	7.31±4.36	Total LH (IU)	1314.7±678.5
Number of cycles, (n)	1.98±1.16	hCG day ≥ 11 mm follicle, n	6.74±4.50
IVF indication, n (%)		hCG day ≥ 16 mm follicle, n	3.04±2.27
Unexplained	20 (16.1%)	hCG day endometrial thickness, (mm)	10.07±2.39
Low ovarian reserve	69 (55.6%)	hCG day E, (pg/mL)	1724.39±1367.63
Endometrioma	2 (1.6%)	Total number of oocytes, (n)	6.53±4.54
Polycysticovarysyndrome	7 (5.6%)	MII oocyte number, (n)	5.27±3.93
Tubal Factor	8 (6.5%)	Number of embryos transferred, (n)	1.40±0.51
Male Factor	14 (11.3%)	Embryo transfer day, n (%)	3.00±1.00
Others	4 (3.2%)	Pregnancy rate, n (%)	27 (19.3%)
		Clinical pregnancy rate, n (%)	18 (13.1%)
Number of baseline antral follicles, (n)	6.07±5.54	Ongoing pregnancy, n (%)	12 (8.8%)
Baseline FSH, (IU/L)	4.30±3.31	Live birth rate, n (%)	12 (8.8%)
P/E	0.0107±0.0044		
hCG day P value (ng/mL)	0.87±0.66		

Data are presented as mean ± SD, median [interquartile range] or number (percentage).

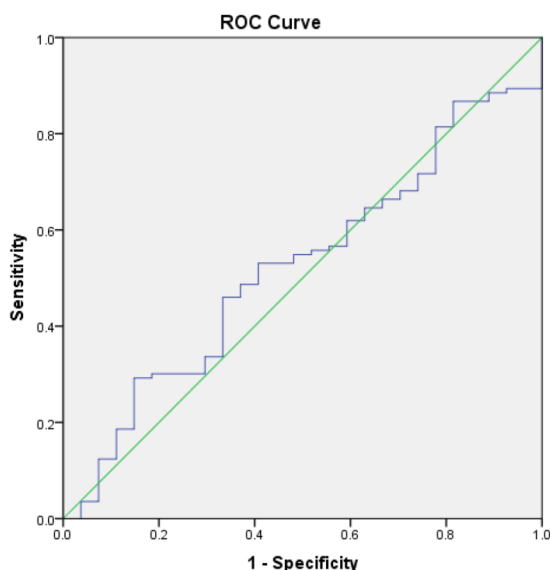


Figure 1: ROC (Receiver Operating Characteristic) curve for hCG day P/E ratio in predicting the chemical pregnancy rate.

*Area under ROC curve (AUC) = 0.522 (p=0.718).

The analysis comparing the characteristics of cycles with and without the outcome of chemical pregnancy are presented in Table 2. There was no significant difference between the two groups in terms of age, the period of infertility, IVF indication percentiles, baseline FSH or baseline E2 levels. Table 3 indicates a comparison of COH data, embryological results, hCG

Table 2: COH, Oocyte Pick-Up, Embryo Growth and Pregnancy Outcomes of ICSI Patients in Agonist Cycles

Parameter	Value
Stimulation time (day)	9.54±2.51
Total FSH (IU)	3322.2±1192.3
Total LH (IU)	1314.7±678.5
hCG day ≥ 11 mm follicle, n	6.74±4.50
hCG day ≥ 16 mm follicle, n	3.04±2.27
hCG day endometrial thickness, (mm)	10.07±2.39
hCG day E, (pg/mL)	1724.39±1367.63
Total number of oocytes, (n)	6.53±4.54
MII oocyte number, (n)	5.27±3.93
Number of embryos transferred, (n)	1.40±0.51
Embryo transfer day, n (%)	3.00±1.00
Pregnancy rate, n (%)	27 (19.3%)
Clinical pregnancy rate, n (%)	18 (13.1%)
Ongoing pregnancy, n (%)	12 (8.8%)
Live birth rate, n (%)	12 (8.8%)

Variables are shown in mean±SD or n (%).a. Mann-Whitney U-Test.

day P level and P/E ratios for the cycles with and without the outcome of a chemical pregnancy. It can be seen that mean embryo transfer days, the total number of oocytes picked up, and MII oocyte numbers are significantly higher in chemical pregnancy cycles (p values: <0.001; 0.028; 0.004, respectively). In cycles resulting in a chemical pregnancy, hCG day P level and hCG day P/E ratio were found higher than those without this outcome. This difference was not statistically significant among groups, (p=0.081 and p=0.718, respectively).

A logistic regression analysis performed for the impact of P/E ratio on overall pregnancy rates showed no significantly increased raw probability rate for the P/E ratio increased by 1 point (p=0.244). When the logistic regression model was adjusted to age and the number of embryos transferred, the adjusted probability rate for a 1-point increase in the P/E ratio was not statistically significant as well (p=0.293). Therefore, we did not reach a conclusion that the P/E ratio affected the overall conception rate.

As part of the ROC analysis, conducted in order to determine a cutoff value to predict chemical pregnancy rates based on our findings, the area under the curve (AUC) was found to be 0.522 (95% confidence interval: 0.407-0.638); however, it was not apparent statistically significant (p=0.718). Moreover, compared with the cycles without pregnancy, the cycles that resulted in chemical pregnancy presented a higher P value (0.93 ± 0.42 vs. 0.86 ± 0.71) and a higher P/E ratio (2.46 ± 0.0099 vs. 0.74 ± 0.00102) on the day of ovulation induction. However, both results did not attain statistical significance.

A logistic regression analysis on the impact of P/E ratio on overall pregnancy rates did not reveal a significantly increased raw probability rate for the P/E ratio increased by 1 point (p=0.244). When the logistic regression model was adjusted to age and the number of embryos transferred, the adjusted probability rate for a 1-point increase in the P/E ratio was not statistically significant as well (p=0.293). Thus, we could not reach a conclusion that the P/E ratio affected the overall conception rate.

DISCUSSION

P levels in the early luteal phase depend on the number of preovulatory follicles and the use of GnRH agonist [10,11]. P support is recommended in the luteal period for the IVF cycles through which a GNRH

Table 3: Demographic, Clinical and Laboratory Characteristics of Study Groups

Parameter	Chemical pregnancy (-) (n=116)	Chemical pregnancy (+) (n= 30)	P-value
Age, (year)	33.93±4.38	34.12±2.97	0.909 ^a
Body mass index, (kg/m ²)	24.65±4.20	23.72±4.69	0.196 ^a
Period of infertility, (year)	7.39±4.51	6.98±3.74	0.888 ^a
Number of cycles, (n)	1.96±1.22	2.04±0.90	0.358 ^a
IVF indication, n (%)			>0.05 ^b
Unexplained	14 (14.1%)	6 (24.0%)	-
Low ovarian reserve	58 (58.6%)	11 (44%)	-
Endometrioma	2 (2.0%)	0 (0.0%)	-
Polycystic ovary syndrome	6 (6.1%)	1 (4.0%)	-
Tubal Factor	8 (8.1)	0 (0.0%)	-
Male Factor	9 (9.1%)	5 (20.0%)	-
Others	2 (2.0%)	2 (8.0%)	-
Baseline FSH, (IU/L)	4.42±3.41	3.80±2.88	0.411 ^a
Baseline E2, (pg/mL)	21.59±32.28	11.08±6.42	0.158 ^a

Variables are presented as mean±SD or n (%).

a: Mann-Whitney U Test, b: Z-test (independent samples proportion test).

Table 4: A Comparison of COH Data, Embryological Results, hCG day P Level and P/E Ratios for the Cycles with and without the Outcome of Chemical Pregnancy

Parameter	Chemical pregnancy (-) (n=116)	Chemical pregnancy (+) (n=30)	P-value
Stimulation time (day)	9.58±2.63	9.41±1.97	0.930 ^a
Total FSH (IU)	3332.3±1147.2	3277.9±1396.2	0.470 ^a
Total LH (IU)	1337.8±709.3	1214.4±509.0	0.462 ^a
hCG day ≥ 11 mm follicle, n	6.47±4.44	7.89±4.68	0.125 ^a
hCG day ≥ 16 mm follicle, n	2.91±2.04	3.59±3.05	0.360 ^a
hCG day endometrial thickness, (mm)	9.92±2.34	10.69±2.57	0.165 ^a
hCG day E, (pg/mL)	1654.17±1362.95	2018.26±1373.43	0.114 ^a
Total number of oocytes, (n)	6.05±4.22	8.52±5.34	0.028 ^a
MII oocyte number, (n)	4.80±3.67	7.26±4.41	0.004 ^a
Number of embryos transferred, (n)	1.36±0.50	1.56±0.51	0.062 ^a
Average embryo transfer day, (n)	2.50±0.80	3.4±1.31	<0.001 ^a
			<0.001 ^b
Day 2 (%)	72 (63.7%)	9 (33.3%)	*
Day 3 (%)	34 (30.1%)	8 (29.6%)	-
Day 5 (%)	7 (6.2%)	10 (37.0%)	*
hCG day P level	0.86±0.71	0.93±0.42	0.081 ^a
hCG day P/E ratio	0.7415±0.0010285	2.4637±0.0099075	0.718 ^a

a: Mann-Whitney U Test, b: Z-test (independent samples proportion test).

*: groups with significant differences part of Z test.

agonist is utilized to prevent the adverse effects of luteal phase failure on early pregnancy, and it is reported to increase pregnancy rates [12].

The reason why P levels increase during IVF cycles is an ongoing debate. Recent studies indicate that a high P level can go along with low LH levels; however, no strong association is reported between the two [13,14]. In contrast to this, an increased P level was observed to be associated with increased numbers of follicles and the utilization of gonadotropins at a higher rate [14]. There is no consensus in the literature regarding the cutoff value of late follicular P increase. However, there are studies reporting that pregnancy rates decrease when hCG day serum P levels are higher, which is called premature luteinization. High serum P levels affect endometrial receptivity and implantation, thereby affecting pregnancy rates [15-18]. A study by Kolibianakis *et al.* [19] reports that a mid-cycle progesterone level higher than 1.5 mg/ml reduces implantation and they consider it is associated with reduced number and size of follicles, and the intensity of FSH stimulation. It is reported that a progesterone increase that is excessively above the normal level could be associated with the adrenal gland. In nowadays, IVF practitioners rely on the size and number of follicles to decide day of HCG. Furthermore, it may be necessary to consider the response of a patient to a particular treatment protocol. Unfortunately, there is a very limited body of data evaluating the proper induction time across different stimulation protocols and the P/E ratio on the day of induction. Kyrou *et al.* [20] report that, in preventing premature progesterone increase, it is practicable to induce those patients overreacting to the drug earlier. Another preventive measure consists of applying mild stimulation protocols. This approach will also be effective in preventing high E concentrations associated with progesterone increase in the follicular phase. Al-Azami *et al.* [21] report that increased mid-cycle E concentrations foreshadow a progesterone increase. Therefore, IVF practitioners recommend monitoring the E concentration and starting the induction procedure as soon as this concentration begins to bear a premature progesterone risk. Alternatively, if adrenal gland is the major cause of such an increase, one should also assess the effect of dexamethasone in preventing progesterone increase. Melo *et al.* [22] concluded that increased P does not cause adverse impact on ongoing pregnancy rates as part of the oocyte donation program. However, this picture concerns the negative effect of progesterone on endometrium, rather than oocyte/embryo quality.

Thus, alongside those studies defining the aforementioned premature luteinization with high P value, there are others suggesting that one must also take E and follicle numbers into account; and hCG day P/E2 ratio progesterone in COH cycles has come to the fore as a new prognostic parameter. In a prospective study investigating this matter, Elgindy *et al.* [16] examined the importance of P/E₂ in IVF cycles administered with a long agonist protocol. They showed that clinical pregnancy rate fell when hCG day p level is less than 1.5 ng/mL and P/E₂ rate exceeds 0.55 over the cycles with embryo transfers performed in the division-phase (days 2 and 3); however, those parameters failed to predict clinical pregnancy rate in cycles subject to a blastocyst transfer. In contradistinction to this, in a recent study that investigates the effects of P/E₂ ratio on treatment success as part of GnRH agonist cycles, it is reported that live birth rates decreased with p/E2 >0.48; nevertheless, P/E₂ ratio is shown to be a weak predictor of IVF outcomes in those cycles that are subject to a GnRH antagonist protocol [9]. On the other hand, Shalom-Paz *et al.* [23] as part of a study published in 2015, reported that in IVF cycles involving different stimulation protocols (long agonist, short agonist, and antagonist protocols) if P/E is higher than 0.45, it is considered as poor prognostic factor for live birth rate. Similarly, Mascarenhas *et al.* [21] published another study conducted with different stimulation protocols in 2015, in which they divided cycles p ≥1.5 ng/ml into >1 ng/ml and ≤1 ng/ml and compared those subgroups with cycles p <1.5 ng/ml. According to the findings of that study, poor prognostic effect of increased p level was only limited to those presenting a P/E2 ratio >1. As part of the present study, we evaluated GnRH agonist cycles and investigated the possibility of a threshold P/E2 level by ROC analysis instead of analyzing the impact of an arbitrarily defined level. In this study, the fact that AUC (0.522) remained within the interval of 0.5-1, and close to 0.5, might indicate that P/E ratio is not a very good testing tool in predicting pregnancy.

The findings of the present study have shown that, in IVF-ICSI-ET cycles that involve a GnRH analog, the P/E ratio is significant in terms of cycle success. Another inference from this study can be formulated as follows: The relevant practices must concentrate on the personalization of treatment protocols, the proper and effective observation of the endocrinological profile throughout the stimulation, which must be followed by an adjustment of the induction time according to

patient's response to treatment. The performance of further multi-centered studies may consolidate our findings.

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