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Effect of Serum Progesterone (P4) Level at the Day of Human Chorionic Gonadotropin (HCG) Administration on the Outcome of Intracytoplasmic Sperm Injection and Fresh Embryo Transfer

Yasmine El-Masry[1*], Ashraf Elmohamdy Gharib[1] and Manal Moustafa Abd Allah[1]

[1]Obstetrics and Gynecology Department, Faculty of Medicine, Tanta University, Tanta, Egypt.

Authors' contributions

This work was carried out in collaboration among all authors. Author YEM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AEG and MMAA managed the analyses of the study. Author YEM managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Our aim was to investigate the effect of different progesterone (P4) at day of triggering HCG on the outcomes of ICSI with fresh embryo transfer in cases who underwent controlled ovarian stimulation (COS). Pituitary desensitization done either with long agonist or antagonist pituitary desensitization protocols, then analyzing the effect of serum P4-hCG level on ICSI-fresh embryos transfer outcome including; number and quality of retrieved oocytes (OR), embryo number (ER) & quality and ongoing pregnancy outcomes. The cases are which continued their pregnancy till 12 weeks, aborted cases, ectopic pregnancy & cancelled cases (for different reasons).

Materials and Methods: This prospective cohort study was carried on 120 cases who underwent ICSI cycles for different causes and types of infertility. Controlled ovarian stimulation (COS) protocol and pituitary down-regulation either by; GnRH long agonist /antagonist protocols then,

**Corresponding author: E-mail: elmasryyasmine333@gmail.com;*

fertilization, embryo grading, embryo transfer and hormonal luteal support was done. Blood samples were taken on the day of hCG administration to measure P4 in all cases. All patients who got pregnant and continue till 12 weeks, they were categorized into 3 subgroups as regard serum P4 level: Group A: (P4< 0.5 ng/ml), Group B: (P4=O.5-I.5 ng/ml) & Group C: (P4 >I.5 ng/ml) and correlated with their ICSI outcome. The outcomes of ICSI-ET cycles in those cases were compared with 3 groups of P4 levels in the controlled ovarian stimulation with two protocols.

Results: P4 level had insignificant relation with number and quality of retrieved oocytes, fertilized embryo number and quality and endometrial thickness regardless the protocol of COS. The low and high levels of P4 both, had a detrimental effect on CPR, meanwhile, with no harmful impact on the ongoing pregnancy rate was noticed, regardless the protocol of ovarian stimulation. P4-hCG isn't considered to be the only predictive measure of ICSI outcome. Highest CRP was noticed in cases with P4 level (0.5-I.5 ng/ ml) regardless the type of protocol used.

Keywords: Progesterone level; PPR; GnRH Agonist/ antagonist; HCG; ICSI-ET; CPR.

1. INTRODUCTION

Infertility is common and the global burden remains high over the years. The *NICE in 2013* recommended ICSI as the definitive management for unresolved infertility after other treatments had failed. IVF may be used to manage female or male fertility issues. *In the 1980s*, was the 1st use of GnRH analogues that reduced the cancelation rate and improved the ICSI outcomes. Without this, premature progesterone rise (PPR) occurs in 20–25% cycles due to the positive feedback effect of high E_2 levels. Since the early 1990s, there was ongoing debate about the impact of preovulatory P4 on ICSI outcome. Its impact has been highly controversial for several years, with some studies reporting a negative effect on cycle outcome when premature progesterone rise. But the most important question is if this PPR are used, does it have any effect on pregnancy rate, abortion in assisted reproductive technique, ART, cycles or not? [1-6].

Recently, the ovarian response may be of great importance when considering the PPR; so ovarian response must be taken in consideration, rather than P4 level only, when considering the reasons for PPR [7]. Venetis et al. mentioned that PPR was associated with a significantly decreased pregnancy rate, regardless the GnRH analogue used [8,9]. Bosch et al. found in all protocol types a threshold of P4 > 1.5 ng/ ml deleterious on results, with levels of P4 recovered higher noticed in agonist protocol than antagonist [10].

Until now, not many previous trials have attempted to evaluate whether low progesterone levels may impair PR following IVF or not. The only trial with similar results (lower pregnancy rates in the low progesterone range) was performed by Levy et al., in 254 patients undergoing COS with GnRH-agonist pituitary suppression [11]. As oocyte quality in patients with low P4 values seems to be unaltered, one can postulate that the reduced live birth rate may be due to eitherreduced luteinization, altered transferred embryos or both. Finally, the low P4 levels may also be a confounding factor of another mechanism that hinders late follicular P4 production and pregnancy after IVF [12].

2. METHODS

This prospective, observational study had been conducted on 120 patients attended to the IVF clinic in obstetrics and gynecology department in Tanta University hospital and private centers for a period at 24 months, conducted on infertile couples for whom ICSI will be chosen as a line of treatment.

2.1 Inclusion Criteria

Female age was ranged from 20-30 years, BMI ranged from 20-28 kg/m^2. Patients who had primary or secondary types of infertility and/or male subfertility as regard of type & cause of infertility. Patients with previous failed trails of IVF/ICSI were included.

2.2 Exclusion Criteria

Patients suffering of uterine factor like Asherman syndrome and fibroids, Endometriosis, severe male infertility & Endocrine disorders such as abnormalities in thyroid function.

Detailed full history was taken. General examination like vital signs including blood pressure (mm hg), pulse (/min), temperature (c) height (cm), weight (kg) and demographic data had taken. Abdominal, chest and pelvic examinations had been done. Investigations like

Blood samples for hormonal profiles including basal FSH, LH and E2 level at D2 of the cycle, serum AMH level, TSH & prolactin level & Peak estradiol and P4 level on the day of triggering.

2.3 Controlled Ovarian Hyperstimulation Protocol

The use of long agonist protocol, antagonist protocol on each patient is usually based on the physician's decision. After Gonadotropin stimulation patients fall under 3 categories based on their response: high, intermediate and poor responders. Gonadotropin stimulation using recombinant FSH (R-FSH) or urinary HMG had been administrated on 2nd day of cycle. The dosages had been individualized by physician for each case as regard the age, body mass index, anti-mullerian hormone, FSH level and antral follicular count on 2nd or 3rd day of cucle. Cases were monitored by transvaginal ultrasound folliculometry & serum E2 assay.

2.4 Pituitary Down-Regulation

2.4.1 GnRH antagonist

It had been done either by GnRH antagonist, in form of daily administrations of either Cetrorelix or Ganirelix which had been started on D6 of ovarian stimulation & continued till HCG injection. TVS had been performed on day 7 of the cycle. Repeat scans had been performed every 1, 2 or 3 days according to follicular growth rate and blood samples for P4 assay had taken in the day of triggering.

2.4.2 GnRH agonist long protocol

The patients underwent down-regulation by receiving 0.1 mg Triptorelin during mid-luteal phase of the previous cycle (day 21). R-FSH and/or purified hMG had been used at doses according to BMI, age and the number of follicles in both ovaries. The FSH & hMG dose had been adjusted according to ovarian response. The criteria to determine the time for hCG triggering (5000 IU or 10,000 IU, (Choriomon or Pregnyl) was the presence > 2 follicles and which should be ≥l8 mm in diameter. Oocyte collections had been performed transvaginally, 36 hours, after triggering.

2.5 Grouping of Patients as Regard the P-HCG Level

Group A: low level (P4< 0.5 ng/ml). Group B: intermediate level (P4= 0.5- 1.5 ng/ml). Group C: high level (P4 > 1.5 ng/ml) [8,9,13,14,15,16]. We conducted ICSI and fresh embryos transfer. Oocyte pickup was done 36 hours after hCG administration. The fertilization was verified 16 hours later by microscopy. G1 & 2 embryos were transferred and only those ones will be frozen. ET was done under USG guidance on Days 3, 4 or 5 after OR. 2-3 embryos were transferred for each woman. Vaginal progesterone pessaries 400 mg twice daily (Cyclogest 400 mg or Prontogest 400 mg). Then, pregnancy test was done. If pregnancy test was positive, it was confirmed by hearing fetal heart sounds at 7 weeks by TVS, then we continued the observation of patients till 12 weeks of gestation. If pregnancy test was negative, it had been stopped.

2.6 Progesterone Hormone Assays

Serum P4-HCG level by using COBAS e 411 Fully automated electrochemiluminescence immunoassay analyzer (Roche Diagnostic, Germany). All cases in the study had a usual ICSI-ET treatment and no extra intervention or blood investigations had been done. Data were obtained from computerized databases.

No potential risks were considered while undergoing ICSI and taking samples for hormonal assay. And the potential risks of ICSI-ET were explained to all participants before starting of COH.

3. RESULTS

The sample of the selected patients ranged between 20-30 years old, and 20-28 kg/m2 for BMI. There was no significant relation between patients' demographics and different P-hCG levels.

The study cases divided into 3 groups as regard the P-HCG level (ng/ml)

There was no significant statistical relation between infertility conditions and different P-hCG levels (ng/ml) in both GnRH long agonist/ antagonist protocol (Tables 2,3).

In the cases of antagonist stimulation protocol, there was no significant statistical relation between the basal (FSH, LH, and E2) hormones and AMH hormone with different P-hCG levels, as shown from p-values (0.948, 0.249, 0.089 and 0.096) respectively (Table 4).

Table 1. The distribution of the causes, the type of infertility and the number of failed ICSI among the study cases

	Factors type	No. of cases	Percent %
Cause of Infertility	Male	49	40.80 %
	Female	41	34.20 %
	Combined	21	17.50 %
	Unexplained	9	7.50 %
Type of infertility	Primary type	87	72.50 %
	Secondary type	33	27.50 %
N. of failed ICSI	Zero	104	86.70 %
	once	13	10.80 %
	> twice	3	2.50 %

Table 2. The relation between factor of infertility, type & the number of failed ICSI and P-hCG levels (Group A, B and C) in antagonist stimulation protocols

	Antagonist protocol	Group A	Group B	Group C	Total	X_2	P-value
Factor of Infertility	Male	5 (31.3%)	17 (53.1%)	15 (39.5%)	37 (43%)	7.228	0.300
	Female	5 (31.3%)	10 (31.3%)	10 (26.3%)	25 (29.1%)		
	Combined	3 (18.8%)	5 (15.6%)	9 (23.7%)	17 (19.8%)		
	Unexplained causes	3 (18.8%)	Zero (%)	4 (10.5%)	7 (8.1%)		
Type of Infertility	Primary type	13 (81.3%)	21 (65.6%)	30 (78.9%)	64 (74.4%)	2.101	0.350
	Secondary type	3 (18.8%)	11 (34.4%)	8 (21.1%)	22 (25.6%)		
No. of failed ICSI	Zero	15 (93.8%)	25 (78.1%)	35 (92.1%)	75 (87.2%)	6.530	0.163
	once	zero	6 (18.8%)	3 (7.9%)	9 (10.5%)		
	twice	1 (50%)	1 (50%)	zero	2 (2.3%)		
Total N. (%)		16 (18.6%)	32 (37.2%)	38 (44.2 %)	86 (100%)		

P-hCG- progesterone level on day of triggering; X_2- Arithmetic mean value; P value- significance unit

Table 3. The relation between factor, type of infertility & the number of failed ICSI and P-hCG levels in long agonist stimulation protocols

	Long agonist protocol	Group A	Group B	Group C	Total	X^2	P-value
Factor of Infertility	Male	3 (60%)	5 (29.4%)	4 (33.3%)	12 (35.3%)	4.763	0.575
	Female	1 (20%)	8 (47.1%)	7 (58.3%)	16 (47.1)		
	Combined	1 (20%)	3 (17.6%)	Zero	4 (11.8%)		
	Unexplained	Zero	1 (5.9%)	1 (8.3%)	2 (5.9%)		
Type of Infertility	Primary type	4 (80%)	9 (52.9%)	10 (83.3%)	23(67.6 %)	3.378	0.185
	Secondary type	1 (20%)	8 (47.1%)	2 (16.7%)	11 (32.4%)		
N. of failed ICSI	Zero	5 (100%)	12 (70.6%)	12 (100%)	29 (85.3%)		
	Once	zero	4 (23.5%)	zero	4 (11.8%)		
	Twice	zero	1 (5.9%)	zero	1 (2.9%)		
Total N. (%)		5 (14.7%)	17 (50%)	12 (35.3%)	34 (100%)		

In the cases of long agonist group, no significant statistical relation between basal (FSH, LH, and E2) hormones and AMH hormone with different P-HCG levels, as shown from p-values (0.304, 0.927, 0.471 and 0.129) respectively (Table 4).

Table 4. Relation between the endocrinal profile of the study cases and P-hCG (ng/ml) in both protocols

Protocol	Hormones	Group A	Group B	Group C	F. test	P. value
Antagonist	Basal FSH (mliu/ml)	5.00+2.44	5.02+1.70	4.87+1.97	0.053	0.948
	Basal LH (mliu/ml)	4.43+1.89	5.02+1.60	5.43+2.34	1.415	0.249
	Basal E_2 (pg/ml)	42.75+4.52	44.03+3.92	45.45+4.38	2.486	0.089
	AMH (ng/ml)	2.01+ 1.13	2.86+1.27	2.54+1.31	2.416	0.096
Long agonist	Basal FSH (mlIU/ML)	4.00 + 2.00	5.41 + 2.73	4.33 + 1.27	1.239	0.304
	Basal LH (mliu/ML)	5.40 + 2.41	5.85+ 2.40	5.77 + 2.07	0.076	0.927
	Basal E_2 (ng/ml)	43.00+8.12	45.88 + 3.28	46.08 + 5.42	0.772	0.471
	AMH (ng/ml)	2.56+1.25	2.00+0.96	2.87+1.26	2.192	0.129

F test- Anova test

Table 5. The relation between the quality of OR among the different P-hCG groups, in long agonist/antagonist protocols

Protocol	Quality of OR	Group A	Group B	Group C	F. test	P. Value
Antagonist	M1	3.07+2.01	3.61+2.39	3.22+1.40	0.498	0.610
	M II	4.00+3.46	4.88+2.80	5.79+2.26	2.647	0.077
	GV	3.42+1.83	2.71+1.87	3.12+2.19	0.508	0.604
Long agonist	M1	1.750+0.96	2.06+1.29	3.08+1.88	1.984	0.156
	M II	4.25+2.63	5.53+3.24	5.50+3.10	0.288	0.752
	GV	4.00+1.87	3.42+2.07	3.42+1.24	0.235	0.792

MI- good quality of retrieved oocytes; MII- best quality of OR; GV- poor quality of OR.

Table 6. The relation between the qualities of embryos transferred among the different P-hCG groups in long agonist/antagonist protocols

	Quality of embryos transferred	Group A	Group B	Group C	F. test	P. Value
Antagonist	GA	4.09+1.92	3.73+2.19	3.76+2.01	0.130	0.878
	GB	2.25+1.29	2.11+1.28	2.47+1.25	0.464	0.631
	GC	1.00+0.01	1.25+0.46	1.90+1.10	1.240	0.316
Long agon	GA	3.50+1.29	4.00+2.33	3.83+1.69	0.102	0.904
	GB	3.33+1.52	2.75+1.48	2.67+1.49	0.243	0.786
	GC	1.00+0.01	1.29+0.49	1.63+0.74	1.074	0.368

GA- best quality of transferred embryos, GB- moderate type, GC- poor type

Table 7. Distribution of the high-quality OR (M II) & high-quality embryos transferred (GA) among the study cases in both stimulation protocols and their relation with the different P-hCG

Protocol	The high quality OR&ET	Group A	Group B	Group C	X^2	P. Value
Antagonist	M II (440)	64 (14.5%)	156 (35.5 %)	220 (50%)	29.70	0.195
	GA (300)	45 (15%)	112 (37.3%)	143 (47.7%)	19.70	0.350
Long agonist	M II (177)	17 (9.6%)	94 (53.1%)	66 (37.3%)	10.46	90.916
	GA (124)	14 (11.3%)	64 (51.6%)	46 (37.1%)	11.10	0.803

Regarding the quality of the OR and quality of embryos transferred in the work, there was no significant statistical relation OR and quality of embryos transferred and different P-hCG levels, despite of rise of number of OR with rise of P4 level, regardless the type of stimulation protocols (Tables 5,6).

As regard the relation between the high quality OR/ET and P-hCG levels, in the antagonist protocol group, the high quality OR (M II) was highest incidence in group C, 50%, also the high-quality ET, (GA) was highest in the same group, 47.7%. In the long agonist protocol group, the high quality OR (M II) was highest occurrence in group B, 53.1%, also the high-quality ET (GA) was highest occurrence in the same group, 51.6%, and there was no significant statistical relation between the high quality OR & the high-quality ET and different P-hCG levels, regardless the COS protocols (Table 7).

As regard relation between P-hCG and ICSI pregnancy outcomes in patients underwent COH with long agonist/ antagonist protocol, there was no significant statistical relation between ongoing PR (in cases who did/not get pregnant after ET) and different P-hCG levels (Tables 9,10).

Table 8. ICSI outcomes (CPR & ongoing pregnancy rate) among the study cases in both stimulation protocols

Protocol		Pregnant			Non-Pregnant		
		Pregnant continued till 12Ws	Abortion	Ectopic pregnancy	Negative pregnancy test	Cancelled cycles	Postponed as Freezing of Embryos
Antagonist	N (%)	24 (60%)	15 (40%)	Zero	18 (39.1%)	12 (26.1%)	16 (34.8%)
	Total	40 /86			46/86		
Long agonist	N (%)	10 (58.8%)	7 (41.2%)	Zero	4 (23.5%)	2 (11.8%)	11 (64.7%)
	Total	17/34			17/34		

Table 9. The relation between the ICSI outcomes (CPR & Ongoing pregnancy) and different P-hCG levels (in antagonist protocol)

Antagonist	Pregnant			Non-Pregnant		
	Pregnant continued till 12Ws	Abortion	Ectopic pregnancy	Negative pregnancy test	Cancelled cases	Postponed as Freezing
Group A	1 (33.3%)	2 (66.7%)	Zero %	4 (30.8%)	8 (61.5%)	1 (7.7%)
Group B	14 (56%)	11 (44%)	Zero %	4 (57.1%)	2 (28.6%)	1 (14.3%)
Group C	9 (75%)	3 (25%)	Zero %	10 (38.5%)	2 (7.7%)	14 (53.8%)
Total	40/86			46/86		
X_2	2.181			16.773		
P. value	0.336			0.002**		

Table 10. The relation between ICSI outcomes (CPR and ongoing PR) and different P-hCG levels (in long agonist protocol)

Long agonist	Pregnant			Non-Pregnant		
P-HCG Groups	Pregnant continued till 12Ws	Abortion	Ectopic pregnancy	Negative pregnancy test	Cancelled cases	Postponed as Freezing of embryos
Group A	1 (33.3%)	2 (66.7%)	Zero %	1 (50%)	1 (50%)	Zero %
Group B	8 (66.7%)	4 (33.3%)	Zero %	2 (40%)	1 (20%)	2 (40%)
Group C	1 (50%)	1 (50%)	Zero %	1 (10%)	Zero %	9 (90%)
Total	17/34			17/34		
X2	1.174			8.655		
P. value	0.556			0.070		

Table 11. The relation between CPR and P-HCG among the study cases in both stimulation protocols

		Group A	Group B	Group C
Antagonist	Total (86 case)	3/16	25/32	12/38
	CPR	18.8%	78.1%	31.6 %
	X^2	21.218		
	P. value	0.001**		
Long agonist	Total (34 case)	3/5	12/17	2/12
	CPR	60%	70.6%	16.7 %
	X^2	8.416		
	P. value	0.015*		

Table 12. The distribution of the study cases as regard the ovarian response to COH

Ovarian response Groups (no. of OR)	No. of cases	Percent %	Mean + SD	Range
Low Responders (<5 OR)	11	9.2%	3.36 + 1.03	1 – 4
Good Responders (5-15 OR)	83	69.2%	9.54 + 2.21	5 – 15
High Responders (>15 OR)	26	21.7 %	20.35 + 3.90	6 – 32

Table 13. Relation between the ovarian response in the study cases and CPR at different P-HCG levels (in antagonist protocol)

	Antagonist	Group A	Group B	Group C
Poor Responders	Total(10 Cases)	1/7	1/3	-----
	CPR	14.3 %	33.3 %	-----
	F. test	0.476		
	P. value	1.000		
Good Responders	Total (58 Cases)	2/8	22/27	11/23
	CPR	25 %	81.5 %	47.8 %
	F. test	10.723		
	P. value	0.005*		
High Responders	Total(18 cases)	Zero/1	2/2	1/15
	CPR	Zero %	100%	6.7 %
	F. test	11.280		
	P. value	0.004*		

Table 14. Relation between the ovarian response in the study cases and CPR at different P-hCG levels (in long agonist protocol)

	Long Agonist	Group A	Group B	Group C
Poor Responders	Total (one case)	Zero/1/1	-----	-----
	CPR	Zero %	--------	-----
	F. test	---------		
	P. value	--------		
Good Responders	Total (25 cases)	3/4	11/16	1/5
	CPR	75 %	68.8 %	20 %
	F. test	4.219		
	P. value	0.121		
High Responders	Total (8 cases)	Zero /Zero	1/1	1/7
	CPR	Zero %	100 %	14.3 %
	F. test	3.429		
	P. value	0.064		

Our study cases in group A, low P-hCG, had least CPR (18.8%), when compared with the other 2 groups, in antagonist protocol group. Also CPR was decreased (60%) in the same low P4 group, (group C), in cases used long agonist protocol. There was significant statistical relation between CPR & different P-hCG levels, in cases underwent ICSI, in both protocols. CPR was best in incidence in group B,78.1% in antagonist protocol and 70.6% in long agonist protocol if compared with other groups A&C. CPR were decreased in low, group A and also decreased in high, group C, regardless the COS used (Table 11).

There was no significant statistical relation presented between different P-HCG levels and CPR in this poor responder. In the good responders, CPR was (highest in group B), 81.5%. There was significant statistical relation presented between different P-HCG levels and CPR in good responders. Meanwhile, in the higher responders, CPR was (highest in group B), 100%. There was significant statistical relation presented between them, but it was with very little significance, in group A as there were no cases, P4 <0.5 ng/ml.

The cases in long agonist protocol, there was no cases belonged to in the poor responders group. In the good responders, CPR was highest in group B (68.6%). There was no significant statistical relation presented between them. And in the higher responders, CPR was highest in group B (100%). There was no significant statistical relation presented between them, in long agonist protocol (Table 14).

4. DISCUSSION

The debate whether this subtle PPR adversely affects ICSI outcome is still ongoing [17]. There was no significant statistical relation between infertility conditions, demographics of the study cases and different P-hCG levels (ng/ml) in both protocols in our study and that can be confirmed by recent clinical study carried by, Jawa Ashmita et al. in 2018, [18]. Also our results were matched with what Swati G et al. [19] P.C. Huang et al. in 2015, [20], Kinnari Vilaschandra et al, in 2018, all mentioned that, there was no significant correlation between age, BMI, hormonal profile of patients and type of infertility of patients and P4 levels among the study cases [21].

Abuzeid et al. [22], Fanchin et al. [23] Hajishafiha et al. [12] they reported, that there was no significant statistical relation was observed between the mean number of OR, ovum quality, number of ET and quality of embryo based on different P-hCG, regardless the GnRH analogues used.

In agreement to Griesinger et al. in 2013 and Xu et al, & Abuelghar et al, in 2013. [6] Reported that in spite of the number of retrieved oocytes raised with PPR, there was no significant relation between them. They suggested that P level don't affect oocytes quality [24-29].

Our results showed that the PPR didn't have a detrimental effect on embryo number or quality, and that result seemed comparable to those of previous study in 2016 by Lu et al., [30] & Elgindy et al, & Papanikolaou et al. [31]. In contrast to Hoffman et al., as they observed that in cases had ICSI with high or low P4-HCG and in patients who received oocytes donated from women with high or low P4, that P-HCG may affect it as an ovarian event, with adverse effects on oocyte number, quality & fertilization [32].

As regard the effect of P-hCG levels on CPR in both protocols, there was significant statistical relation between CPR & different P-hCG levels. CPR were decreased in low, group A and also decreased in high, group C, regardless COS protocol used. Our results showed that the low level was the same as the high level of P-hCG associated with detrimental consequences on ICSI outcomes and adverse effect on CPR. This was supported by clinical study done by, Li M et al [33].

Swati G et al, mentioned that CPR were inversely proportional to serum P4-hCG. our results were closely similar to those results, with discrepancies between them and ours due to diversities in P4 cut–off level and COS protocols [19]. On the other hand, the results were in contrast with the study by Abuzied et al. [22].

Melo et al, reported, that no significant differences in CPR in cases with or without an elevated P-hCG, [34] also, in disagreement with results of the study done by Schoolcraft MD. The final conclusion was made that P4 > O.5 ng/ml were associated with a significantly lesser CPR compared with <O.5 ng/ml [1].

Larcher SJM et al. mentioned that there was a significant difference in CPR between patients from the groups of low, intermediate and high P serum levels. That means CPR inversely

proportional to the rise in serum P4 levels, and these results were closely similar to ours [13].

In agreement with the findings reported by in 2013 and Kyrou et al, that the rise of P4 level is directly proportional with rise in ovarian response. They reported that premature rise of progesterone significantly decreased embryo implantation rate and CPR, showing that PPR may affect treatment outcomes of IVF-ET [35].

According to update studies evidenced by Wadha Mohawash et al, in 2018, from the issue entitled, there is no P-hCG value differentiating a good from a poor cycle success rate. They demonstrated that in their ICSI patient population there is no association between P-hCG & CPR & life birth rate after COH with GnH & GnRH analogues, either agonists or antagonists, our results contrasted with these findings [36].

In disagreement with the results of the study done by Saharkhiz et al., showed that significant rise in P-hCG didn't lead to decrease in pregnancy rate and implantation rate [37].

As regard relation between P-hCG and ICSI pregnancy outcomes in patients underwent COH with antagonist protocol, that there was no significant statistical relation between ongoing PR and different P-hCG levels. In long agonist protocol group, it was noticed that there was no significant statistical relation between ongoing PR (in cases who did/not get pregnant after ET) and different P-hCG levels.

In agreement with Hajishafiha et al. [12] Abuzeid et al. [22] as they mentioned that, there was no relationship between P-hCG and pregnancy events and ongoing PR. Meanwhile, in disagreement with results of Bosch et al., in 2010, he showed that adverse effect of PPR on ongoing PR is present whatever the type of ovarian response [8].

In agreement with prior meta-analysis conducted by Venetis et al, they mentioned in their meta-analysis there was no impact of P-HCG on implantation rates but one on miscarriages and LBR [38].

Abuelghar et al, in 2013 as they reported that, P-hCG, no significant effect on ICSI outcomes, including abortion and ectopic pregnancy in cases had ICSI. Regarding the incidence of abortion in the study; there was no relationship between P-hCG and pregnancy events. In terms of rates of pregnancy, abortion & Ectopic pregnancy at different P-hCG, no significant difference was observed [6].

The current research offered strong evidence that low P-HCG may be as detrimental as high P-HCG to pregnancy outcome in ICSI. Until now, a few previous trials have attempted to evaluate whether low P-hCG may impair pregnancy following ICSI or not.) Our study cases in group A, low P-hCG, had least CPR (18.8%), when compared with the other 2 groups, in antagonist protocol group. Also CPR was decreased (60%) in the same low P4 group, (group C), in cases used long agonist protocol. There was significant statistical relation between CPR & different P-hCG levels, in cases underwent ICSI, in both protocols. CPR was best in incidence in group B,78.1% in antagonist protocol and 70.6% in long agonist protocol if compared with other groups A&C. CPR were decreased in low, group A and also decreased in high, group C, regardless the COS used. (To the best of our knowledge, few trials with similar findings (lower CPR in the low P range), as what Levy et al. had reported in his study in 254 patients undergoing COS with GnRH-a, which confirming the same entitled issue, that we discussed before (Table 11).

Table 13 and 14 shows the relation between the ovarian response and CPR at different P-hCG levels, in both protocols. In antagonist protocol there was no significant statistical relation presented between different P-HCG levels and CPR in poor responder. In the good responders, CPR was highest in group B (81.5%). There was significant statistical relation presented between different P-HCG levels and CPR in good responders. Meanwhile, in the higher responders, CPR was highest in group B (100%).

Our previous results are approximately similar to the findings of the last recent update study, published in 2019. A retrospective, observational, single- cohort study carried on 2192 patients. For poor responders, the effect of P-hCG remains modest except for lowest P4, especially < 0.5 ng/ml where CPR strongly decreased. In poor responders, PPR may be neglected so avoiding unnecessary cancellation or embryo freezing. So, in high responders, the negative effect of PPR appears more obvious; suggesting that freeze- all policy should be carried more widely [14].

PE didn't cause a significant clinical impact on PR. Their results confirmed that the risk of PPR

increases with the ovarian response. ICSI outcomes aren't affected in high responders; (M. Cruz et al., suggested that in high responder women, P4 levels do not affect IVF results. And we agreed with these results.

In a recent retrospective cohort study in 2019, on 2971 fresh ICSI-ET cycles with GnRH agonist long protocol were analyzed to investigate whether the detrimental effect of PPR on CPR varies depending on the magnitude of ovarian response. They reported that, the progressive rise of serum P4 from the <0.5 to >4 ng/ml intervals caused a gradual and continuous decline in the CPR of all 3 types of ovarian response. High responders are not exempt from the detrimental effects of PPR but the threshold interval where the detrimental effect begins is higher in the high responders compared with the low and normal responders [15].

The current research offered strong evidence that low P-HCG may be as detrimental as high P-HCG to pregnancy outcome in ICSI. Until now, a few previous trials have attempted to evaluate whether low P-hCG may impair pregnancy following ICSI or not. Our study results showed that, cases in group A, low P-hCG, had least CPR (18.8%), when compared with the other 2 groups, in antagonist protocol group. Also CPR was decreased (60%) in the same low P4 group, (group C), in cases used long agonist protocol. There was significant statistical relation between CPR & different P-hCG levels, in cases underwent ICSI, in both protocols. CPR was best in incidence in group B,78.1% in antagonist protocol and 70.6% in long agonist protocol if compared with other groups A&C. CPR were decreased in low, group A and also decreased in high, group C, regardless the COS used. To the best of our knowledge, few trials with similar findings (lower CPR in the low P range), as what Levy et al. had reported in his study in 254 patients undergoing COS with GnRH-a, which confirming the same entitled issue [17].

This was confirmed by the update papers of recent study done by Santos-Ribeiro et al, he reported that, by comparing the ongoing PR of cases with high P >I.5 ng/ml, they were able to conclude that P ≤O.5 ng/ml were as detrimental to ongoing PR as high P. [16]

They reported that, the pathogenesis of impaired outcomes in cycles with very low level of P4 is not quite clear yet. Low P-HCG levels don't appear to be related to NO. of OR or fertilization rate, but to either decrease luteinization, altered ER or both, however other mechanisms might exit [16].

The recent update study published in 2019. That study gave evidence of an important harmful impact of P-HCG at lower & higher values, independent of OR & ET. No significant association between P-HCG and each covariate except with no. of OR; a significant association was present between no. of OR & P-hCG providing a non-linear effect on LBR. For higher values of OR, CPR & LBR rapidly increase, however LBR is more sensitive to P-HCG values. Higher CPR prognoses occur for optimal P-HCG, but strongly decreased for lower or higher P4 values [14].

5. CONCLUSION

Our study analysis on ICSI outcomes, showed that P4-HCG had relation to biochemical, clinical PR, with no relation to ongoing PR. In light of our results, the ovarian response will be better taken in consideration rather than just the serum P-HCG, so further researches needed to be done to estimate detrimental threshold for each group of ovarian responders. There was no significant difference between the number of OR, ovum quality, number & quality of ET based on different P-HCG in ICSI with different protocols.

Our study confirmed the detrimental effect of low P-HCG as well as the high one, as it is quite known, that few studies investigated that issue. Although, high and low level of P-HCG has adverse effect on CPR, there was no significant statistical relation between ongoing PR and different P-hCG level, in both protocols. There was no significant statistical relation between CPR & different P-hCG levels in high and low responders, so, it is better to take in consideration the ovarian response rather than the serum P4 levels alone. P4-hCG is a promising predictive factor determining the ICSI outcomes; meanwhile it is not the only factor determining the CPR & life birth rate.

CONSENT AND ETHICAL APPROVAL

Ethical committee approval-Faculty of Medicine, Tanta university was obtained to conduct this study. Any unexpected risks might occur during the research was been explained to the cases & the ethical committee on time. There were adequate provisions to keep privacy of cases & data confidentiality, the patient names were replaced by serial number & her address was

confidential. This research proposal conforms to the accepted ethical standard in research ethics committee and quality assurance unit, faculty of medicine, Tanta university. An informed consent had been obtained from all participants in this research.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Schoolcraft W, Sinton E, Schlenker T, Huynh D, Hamilton F and Meldrum DR. Lower pregnancy rate with premature luteinization during pituitary suppression with leuprolide acetate. Fertil Steril. 1991;55:563e6.
2. Kolibianakis EM, Venetis CA, Bontis J, Tarlatzis, BC. Significantly lower pregnancy rates in the presence of progesterone elevation in patients treated with GnRH antagonists and GnH: a systematic review and meta-analysis. Curr. Pharm. Biotechnol. 2012;13:464–470
3. Kolibianakis E, Bourgain C, Albano C, Osmanagaoglu K, Smitz J, Van Steirteghem A, Devroey P. Effect of ovarian stimulation with recombinant follicle-stimulating hormone, gonadotropin releasing hormone antagonists, and human chorionic gonadotropin on endometrial maturation on the day of oocyte pickup. Fertil. Steril. 2002;78:1025–1029.
4. Silverberg KM, Burns WN, Olive DL, Riehl RM and Schenken RS. Serum progesterone levels predict success of in vitro fertilization\ embryo transfer in patients stimulated with leuprolide acetate and human menopausal gonadotropins. Endocrinol Metab .1991;73:797-803.
5. Yovel I, Yaron Y, Amit A, Peyser MR, David MP and Kogosowski A. High progesterone levels adversely affect embryo quality and pregnancy rates in vitro fertilization and oocyte donation programs. Fertil Steril .1995;64:128-131.
6. Abuelghar WM, Elsaeed MM, Tamara TF, Ellaithy MI, Ali MS. Measurement of serum estradiol/progesterone ratio on the day of embryo transfer to predict clinical pregnancies in intra cytoplasmic sperm injection cycles. Is this of real clinical value? Middle East Fertil Soc J. 2013;18:31-37.
7. Venetis CA, Kolibianakis EM, Papanikolaou E, Bontis J, Devroey, Tarlatzis, BC. Is progesterone elevation on the day of human chorionic gonadotrophin administration associated with the probability of pregnancy in in vitro fertilization? A systematic review and meta-analysis. Hum. Reprod. Update. 2007;13:343–355.
8. Bosch, Ernesto, Iván Valencia, Ernesto Escudero, Juana Crespo, Carlos Simón, José Remohí, and Antonio Pellicer. "Premature luteinization during gonadotropin-releasing hormone antagonist cycles and its relationship with in vitro fertilization outcome." Fertility and sterility. 2003;80(6):1444-1449.
9. Venetis, Christos A, Efstratios M Kolibianakis, Julia K Bosdou, George T Lainas, Ioannis A Sfontouris, Basil C Tarlatzis, Tryfon G Lainas. Estimating the net effect of progesterone elevation on the day of hCG on live birth rates after IVF: a cohort analysis of 3296 IVF cycles." Human reproduction. 2015;30(3):684-691.
10. Bosch E, Labarta E, Crespo J. Circulating progesterone levels and ongoing pregnancy rates in controlled ovarian stimulation cycles for in vitro fertilization: analysis of over 4000 cycles. Hum Reprod. 2010;25: 2092-100.
11. Levy MJ, Smotrich DB, Widra EA, Sagoskin AW, Murray DL and Hall JL. The predictive value of serum progesterone and 17-OH progesterone levels on in-vitro fertilization outcome. J Assist Reprod Genet. 1995;12:161–166.
12. Hajishafiha Mahsomeh, Zahra Shahbazi, AbdolGhader Pakniyat, Sima Oshnouei, Nazila Kiarang. "Relationship between progesterone level on the day of human chorionic gonadotropin administration with outcomes of intra-cytoplasmic sperm

injection in infertile couples." Iranian journal of reproductive medicine 2015;13(7):397.

13. Larcher SJM, Ganzer LM, Maccari VM. Clinical pregnancy rates according to the serum progesterone level on the human chorionic gonadotropin day. Fertil Steril. 2016;106:e200.
14. Arvis P, Guivarch- Leveque A, Lehert P. The negative effect of progesterone levels on the day of HCG on LBR is not restricted to values above 1.5 ng/ml in IVF/ICSI cycles. Reproductive Bio Medicine. Online; 2019.
15. Ozgur Oktem, Kaykan Yakin, Sule Yildiz, Oguz, Aycan Isiklar. High responders are not exempt from detrimental effect of prematurely rising progesterone level in fresh embryo transfer. Reproductive Bio Medicine. Online. 2019;38:206-215.
16. Santos-Ribeiro S, Polyzos NP, Haentjens P, Smitz J, Camus M, Tournaye H, Blockeel C. Live birth rates after IVF are reduced by both low and high progesterone levels on the day of human chorionic gonadotrophin administration. Human Reproduction. 2014;29(8):1698-1705.
17. Silverberg, Kaylen M, Maxine Martin, David L Olive, William N. Burns, Robert S Schenken. Elevated serum progesterone levels on the day of human chorionic gonadotropin administration in in vitro fertilization cycles do not adversely affect embryo quality." Fertility and sterility 1994;61(3):508-513.
18. Jawa Ashmita, Swarankar Vikas and Garg Swati. The Impact of Progesterone Level on Day of hCG Injection in IVF Cycles on Clinical Pregnancy Rate. online.org on Friday; 2018.
19. Swati G, Surbhi TS, Deepa LM. Progestrone level on the day of hCG trigger and IVF outcomes: an observational study. IJBAMR. 2016;6(1):682-6.
20. Pei-Chen Huang, Ming-Jer Chen, Hwa-Fen Guu, Yu-Chiao Yi, Jason Yen-Ping Ho, Ya-Fang Chen, Li-Yu Chen, Min-Min Chou. Effect of premature serum progesterone rise on embryo transfer outcomes and the role of blastocyst culture and transfer in assisted reproductive technology cycles with premature progesterone rise. Taiwanese Journal of Obstetrics & Gynecology. 54 (2015): 640-646.
21. Kinnari Vilaschandra Amin, Purnima Nadkarni, Pooja Nadkarni Singh, Prabhakar Singh. Serum progesterone levels on the day of hCG trigger and ICSI outcome: a retrospective observational cohort study. Int J Reprod Contracept Obstet Gynecol. 2018;7(8):3194-3198
22. Abuzeid MI, Sasy MA. Elevated progesterone levels in the late follicular phase do not predict success of in vitro fertilization- embryo transfer. Fertil Steril.1996;65:981-985.
23. Fanchin R, Righini C, Olivennes F, de Ziegler D, Selva J, Frydman R. Premature progesterone elevation does not alter oocyte quality in in vitro fertilization. Fertil Steril. 1996;65:1178e83.
24. Xu B, Li Z, Zhang H, Jin L and Li Y. Serum progesterone level effects on the outcome of in vitro fertilization in patients with different ovarian response: an analysis of >10,000 cycles. Fertil Steril. 2012;97:1321e7.
25. Griesinger G, Mannaerts B, Andersen CY, Witjes H, Kolibianakis EM, Gordon K. Progesterone elevation does not compromise pregnancy rates in high responders: a pooled analysis of in vitro fertilization patients treated with recombinant follicle-stimulating hormone/gonadotropin-releasing hormone antagonist in six trials. Fertil Steril. 2013;100:1622.8.e1-3.
26. Ubaldi, Filippo, Carola Albano, Manfred Peukert, Hilde Riethmüller-Winzen, Michel Camus, Johan Smitz, André Van Steirteghem, and Paul Devroey. Endocrinology: subtle progesterone rise after the administration of the gonadotrophin-releasing hormone antagonist Cetrorelix in intracytoplasmic sperm injection cycles. Human reproduction 1996;11(7):1405-1407.
27. Fanchin R, Hourvitz A, Olivennes F, Taieb J, Hazout, A. and Frydman, R. Premature progesterone elevation spares blastulation but not pregnancy rates in in vitro fertilization with coculture. Fertil. Steril. 1997;68:648–652.
28. Hofmann GE, Bentzien F, Bergh PA, Garrisi GJ, Williams MC, Guzman I. Premature luteinisation in controlled ovarian hyperstimulation has no adverse effect on oocyte and embryo quality. Fertil Steril .1993;60:675-679.
29. Andersen AN, Devroey P, Arce, J-C. Clinical outcome following stimulation with highly purified hMG or recombinant FSH in patients undergoing IVF: a randomized

assessor-blind controlled trial. Hum. Reprod. 2006;21:3217–3227.
30. Lu, Xuefeng, Qiuju Chen, Yonglun Fu, Ai Ai, Qifeng Lyu, and Yan Ping Kuang. "Elevated progesterone on the trigger day does not impair the outcome of Human Menotrophins Gonadotrophin and Medroxyprogesterone acetate treatment cycles." Scientific reports. 2016;6:31112.
31. Papanikolaou EG, Kolibianakis EM, Pozzobon C, Tank P, Tournaye H, Bourgain C. Progesterone rise on the day of human chorionic gonadotropin administration impairs pregnancy outcome in Day 3 single-embryo transfer, while it has no effect on Day 5 single blastocyst transfer. Fertil Steril. 2009;91:949e52.
32. Hofmann, Glen E, Frauke Bentzien, Paul A. Bergh, G. John Garrisi, Maryanne C. Williams, Ida Guzman, and Daniel Navot. Premature luteinization in controlled ovarian hyperstimulation has no adverse effect on oocyte and embryo quality. Fertility and sterility. 1993;60(4):675-679.
33. Melo MAB, Marcos Meseguer, Nicolas Garrido, Ernesto Bosch, Antonio Pellicer, José Remohí. "The significance of premature luteinization in an oocyte-donation programme. Human Reproduction 2006;21(6):1503-1507.
34. Kyrou D, Kolibianakis EM, Fatemi HM, Camus M, Tournaye H, Tarlatzis BC, Devroey P. High exposure to progesterone between the end of menstruation and the day of triggering final oocyte maturation is associated with a decreased probability of pregnancy in patients treated by in vitro fertilization and ICSI. Fertil. Steril. 2011;96:884– 888.
35. Wadha Mohawash, Nayla Bushaqer, Fatemah Alrakaf, Meshael Algaffli, Haya Rawah, Nawal Dayoub, Hisham Ayoub, Nouf Alasmari. Progesterone level on the day of triggering and pregnancy outcome in long GnRH agonist protocol Middle East Fertility Society Journal. 2018;23:14–18.
36. Saharkhiz, Nasrin, Saghar Salehpour, Mahboobeh Tavasoli, Ali Aghighi. Premature progesterone rise at human chorionic gonadotropin triggering day has no correlation with intracytoplasmic sperm injection outcome. Iranian journal of reproductive medicine. 2015;13(2):79.
37. Lepage, Julien, Gwenola Keromnes, Sylvie Epelboin, Dominique Luton, and Chadi Yazbeck. Premature progesterone rise on day of hCG negatively correlated with live birth rate in IVF cycles: An analysis of 1022 cycles. Journal of gynecology obstetrics and human reproduction; 2018.
38. Wu Z, Li R, Ma Y, Deng B, Zhang X, Meng Y, Chen X, Liu P, Qiao J. Effect of HCG-day serum progesterone and oestradiol concentrations on pregnancy outcomes in GnRH agonist cycles. Reprod. Biomed. Online. 2012;24:511–520.

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